Effective Health Care Program

Comparative Effectiveness Review
Number 131

Pharmacologic Therapies for the Management of Crohn's Disease: Comparative Effectiveness

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Comparative Effectiveness Review

Number 131

Pharmacologic Therapies for the Management of Crohn's Disease: Comparative Effectiveness

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10061-I

Prepared by:
Johns Hopkins University Evidence-based Practice Center
Baltimore, MD

Investigators:
Susan Hutfless, Ph.D.
Sammy Almashat, M.D., M.P.H.
Zackary Berger, M.D., Ph.D.
Lisa M. Wilson, Sc.M.
Elizabeth Bonson, M.D., M.P.H.
Qi Chen, M.D., M.P.H.
Elie Donath, M.D.
Frank Herlong, M.D.
Milo A. Puhan, M.D., Ph.D.
Saranya Selvaraj
Anne Tuskey, M.D.
Alexandra Vasilescu, D.O.
Eric B. Bass, M.D., M.P.H.
Mark Worthington, M.D.
Ghanshyam Palamaner Subash Shantha, M.B.B.S., M.D.
Mark Lazarev, M.D.

AHRQ Publication No. 14-EHC012-EF
February 2014

This report is based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10061-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This report may periodically be assessed for the urgency to update. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at: www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Hutfless S, Almashat, S, Berger Z, Wilson LM, Bonson E, Chen Q, Donath E, Herlong F, Puhan MA, Selvaraj S, Tuskey A, Vasilescu A, Bass EB, Worthington M, Palamaner G, Lazarev M. Pharmacologic Therapies for the Management of Crohn's Disease: Comparative Effectiveness. Comparative Effectiveness Review No. 131. (Prepared by Johns Hopkins Evidence-based Practice Center under Contract No. 290-2007-10061-I.) AHRQ Publication No. 14-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard G. Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Christine Chang, M.D., M.P.H.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Acknowledgments

The Evidence-based Practice Center thanks Todd Noletto and Elisabeth Haberl for their assistance with reviewing articles and Eric Vohr for copy editing. We would also like to thank the Key Informants, Technical Expert Panel, Peer Reviewers, and Task Order Officer, as well as our Associate Editor, Kathleen N. Lohr, Ph.D., of RTI International.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:

Bob Diamond, M.D.
Centocor Ortho Biotech Inc.
Horsham, PA

Stephen B. Hanauer, M.D.
University of Chicago Medical Center
Chicago, IL

Edward Loftus, M.D.
Mayo Clinic College of Medicine
Rochester, MN

Logan Thornton, M.P.H., C.H.E.S.
Houston, TX

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

Bob Diamond, M.D.
Centocor Ortho Biotech Inc.
Horsham, PA

Stephen B. Hanauer, M.D.
University of Chicago Medical Center
Chicago, IL

Lisa Herrinton, Ph.D.
Kaiser Permanente
Oakland, CA

Melvin Heyman, M.D., M.P.H
University of California, San Francisco
San Francisco, CA

Logan Thornton, M.P.H., C.H.E.S.
Houston, TX

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Yngve Falck-Ytter, M.D., AGAF
Case Western Reserve University
Case and VA Medical Center
Cleveland, OH

Stephen B. Hanauer, M.D.
University of Chicago Medical Center
Chicago, IL

Lisa Herrinton, Ph.D.
Kaiser Permanente
Oakland, CA

Sunanda Kane, M.D.
Mayo Clinic
Rochester, MN

James Lewis, M.D., M.S.C.E.
Perelman School of Medicine at the
University of Pennsylvania
Philadelphia, PA

Pharmacologic Therapies for the Management of Crohn's Disease: Comparative Effectiveness

Structured Abstract

Objectives. The purpose of this review was to compare the efficacy and safety of biologics, immunomodulators, corticosteroids, and aminosalicylates in the treatment of Crohn's disease.

Data sources. We searched MEDLINE® (1966 through June 2011), Embase® (1974 through June 2011), and the Cochrane Central Register of Controlled Trials (Issue 2, 2011).

Review methods. Two reviewers independently reviewed titles, abstracts, and articles, and included English-language articles that reported on induction or maintenance of remission in placebo-controlled or head-to-head randomized controlled trials. We also included observational studies with a comparison group if they reported on the safety of treatment. Two reviewers extracted study information using standardized forms and independently assessed study quality. Efficacy was measured by induction and maintenance of remission. Remission was defined using the Crohn's Disease Activity Index, mucosal healing, the absence of Crohn's disease hospitalizations or surgeries, reduction of steroids, fistula healing, and patient-reported outcomes. A difference of 10 percentage points in the outcome between treatment groups was considered clinically meaningful. The safety outcomes of interest were mortality, occurrence of lymphomas and other cancers, infections, infusion- and injection-site reactions, and bone fractures for adults and children. Growth was an additional safety concern for children.

Results. We included 136 studies involving 148,733 patients. Twenty-three percent of trials directly compared different treatment strategies. The majority of trials excluded patients with mild disease and those with a history of surgical resection. The majority of trials allowed patients to take other Crohn's disease treatments during the trial. For adults, infliximab and 6-methyl-prednisolone were consistently favored over placebo across the induction and maintenance outcomes. Natalizumab and azathioprine were favored over placebo across the maintenance outcomes. Other comparisons either did not have more than one outcome reported or had inconsistent results. The quality of the safety evidence was poor due to poor reporting of the methods in trials and poor confounding control in observational studies, and no strong signals of harm were identified. For children, the strength of evidence was low or insufficient to support the efficacy of any medication to induce or maintain remission. No pediatric study reported on serious adverse events such as mortality, lymphoma, or other cancers.

Conclusions. Measuring the efficacy of medications using multiple outcomes, infliximab and 6-methyl-prednisolone induce and maintain remission in adults with Crohn's disease. Natalizumab and azathioprine maintain remission. Comparing Crohn's disease medications directly using pragmatic clinical trials will help to understand the effectiveness of medications in clinical practice using outcomes other than the Crohn's Disease Activity Index.

Contents

Executive Summary ES-1
Introduction 1
Background 1
Description of Disease 1
Interventions To Treat Crohn's Disease 1
Current Controversies in the Treatment of Crohn's Disease 5
Treatment Guidelines and Meta-Analyses on the Management of Crohn's Disease 5
Previous Systematic Reviews 6
Scope of the Evidence Report and Key Questions 6
Methods 9
Topic Development 9
Search Strategy 9
Study Selection 10
Data Abstraction 11
Quality Assessment 12
Applicability 13
Data Analysis and Synthesis 13
Grading the Strength of Evidence 14
Peer Review and Public Commentary 15
Results 16
Search Results 16
Key Question 1: Effectiveness of Therapies To Induce Remission in Adults 18
Natalizumab 24
TNF-Alpha Inhibitors 30
Thiopurines 47
Methotrexate 58
Corticosteroids 62
Aminosalicylates 74
Comparative Effectiveness of Therapies To Induce Remission in Adult Subgroups 79
Quality Assessment 79
Key Question 2: Effectiveness of Therapies To Maintain Remission in Adults 80
Natalizumab 85
TNF-Alpha Inhibitors 87
Thiopurines 99
Methotrexate 105
Corticosteroids 107
Aminosalicylates 117
Comparative Effectiveness of Therapies To Maintain Remission in Adult Subgroups 123
Quality Assessment 123
Key Question 3: Safety of Therapies in Adults 123
Key Points 124
Study Design and Population Characteristics 129
Mortality 130
Progressive Multifocal Leukoencephalopathy 143
Lymphoma 144

Hepatosplenic T-Cell Lymphoma 153
Cervical Cancer 155
Other Cancers 155
Infections 168
Tuberculosis 197
Infusion- and Injection-Site Reactions 199
Bone Fractures 208
Study Quality 210
Key Question 4: Effectiveness of Therapies Used To Prevent Post-Operative Recurrence as Pertains to Patient-Reported Outcomes 211
Studies Included 211
Study Design and Population Characteristics 211
Study Results 212
Study Quality and Limitations 212
Pediatric Results 212
Key Question 1: Effectiveness of Therapies To Induce Remission in Children 213
Key Question 2: Effectiveness of Therapies To Maintain Remission in Children 219
Key Question 3: Safety of Therapies in Children 223
Discussion 234
Key Findings and Clinical Implications 234
Summary of Key Findings for Adults 234
Summary of Key Findings for Pediatrics 235
Applicability of Remission Results for Adults 235
Populations 235
Intervention 236
Comparisons 236
Outcomes 236
Timing 236
Setting 236
Other – Conflict of Interest 236
Applicability of Safety Results for Adults 236
Pediatric Applicability 236
Comparison With Existing Guidelines and Systematic Reviews 237
Limitations 238
Limitations in the Data 238
Limitations in Our Review Method 240
Future Research Needs 241
Conclusions 241
References 243

Tables

Table A. Medications used for the treatment of Crohn's disease ES-2
Table B. Outcomes considered for each Key Question concerning the comparative effectiveness and safety of medications for the treatment of Crohn's disease ES-6
Table C. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to induce remission ES-12

Table D. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to maintain remission.....ES-17
Table E. Summary of the comparative safety of pharmacologic therapies for the management of Crohn's disease.....ES-22
Table 1. List of medications used for treatment of Crohn's disease.....3
Table 2. Black box warnings listed on the prescribing information sheets of medications to treat Crohn's disease.....4
Table 3. List of outcomes considered for each Key Question on the comparative effectiveness and safety of medications for treatment of Crohn's disease.....8
Table 4. List of disease activity indexes and disease-specific quality of life instruments.....8
Table 5. Inclusion and exclusion criteria for identifying eligible studies.....11
Table 6. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission.....19
Table 7. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating natalizumab to induce remission among patients with active Crohn's disease at randomization.....26
Table 8. Randomized controlled trials comparing the efficacy of natalizumab with placebo or another treatment to induce remission among patients with active Crohn's disease at randomization.....28
Table 9. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating TNF-alpha inhibitors to induce remission among patients with active Crohn's disease at randomization.....34
Table 10. Randomized controlled trials comparing the efficacy of TNF-alpha inhibitor therapy with placebo or another treatment to induce remission at week 2 among patients with active Crohn's disease at randomization.....40
Table 11. Randomized controlled trials comparing the efficacy of TNF-alpha inhibitor therapy with placebo or another treatment to induce remission at weeks 12 to 16 (or closest time point) among patients with active Crohn's disease at randomization.....42
Table 12. Randomized controlled trials comparing the efficacy of TNF-alpha inhibitor therapy with placebo or another treatment to induce remission (last reported time point) among patients with active Crohn's disease at randomization.....43
Table 13. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating thiopurines to induce remission among patients with active Crohn's disease at randomization.....50
Table 14. Randomized controlled trials comparing the effectiveness of thiopurines with placebo or another treatment to induce remission among patients with active Crohn's disease at randomization.....54
Table 15. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating methotrexate to induce remission among patients with active Crohn's disease at randomization.....60
Table 16. Randomized controlled trials comparing the efficacy of methotrexate with placebo or another treatment to induce remission among patients with active Crohn's disease at randomization.....62
Table 17. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating corticosteroids to induce remission among patients with active Crohn's disease at randomization.....65

Table 18. Randomized controlled trials comparing the efficacy of corticosteroids with placebo or another treatment to induce remission among patients with active Crohn's disease at randomization 69
Table 19. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating aminosalicylates to induce remission among patients with active Crohn's disease at randomization 76
Table 20. Randomized controlled trials comparing the efficacy of aminosalicylates with placebo to induce remission among patients with active Crohn's disease at randomization 78
Table 21. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to maintain remission 81
Table 22. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating natalizumab to maintain remission 86
Table 23. Randomized controlled trials comparing the efficacy of natalizumab with placebo to maintain remission at week 48 in patients with Crohn's disease who have at least achieved a response to a prior induction trial 87
Table 24. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating a TNF-alpha inhibitor to maintain remission 91
Table 25. Randomized controlled trials comparing the efficacy of TNF-alpha inhibitor therapy with placebo or another treatment to maintain remission in patients with Crohn's disease who had a response to the study medication prior to randomization 98
Table 26. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating a thiopurine to maintain remission 101
Table 27. Randomized controlled trials comparing the efficacy of thiopurines with placebo or another treatment to maintain remission in patients with inactive Crohn's disease 104
Table 28. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating methotrexate to maintain remission 106
Table 29. Remission rates reported in randomized controlled trials comparing the efficacy of methotrexate with placebo in patients with inactive Crohn's disease 107
Table 30. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating a corticosteroid to maintain remission 110
Table 31. Remission rates reported in randomized controlled trials comparing the efficacy of corticosteroids with placebo or another treatment in patients with inactive Crohn's disease 114
Table 32. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating an aminosalicylate to maintain remission 119
Table 33. Remission rates reported in randomized controlled trials comparing the efficacy of aminosalicylates with placebo in patients with inactive Crohn's disease 121
Table 34. Key findings and strength of the available evidence comparing pharmacologic therapies for the management of Crohn's disease in terms of safety-related outcomes 127
Table 35. Summary of reported mortality results in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease 131
Table 36. Summary of randomized controlled trials that reported no deaths when comparing the effectiveness of a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease 131

Table 37. Summary of reported mortality results in randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease 136
Table 38. Summary of reported mortality results in randomized controlled trials comparing prednisone alone or in combination with placebo or another treatment in patients with Crohn's disease 139
Table 39. Summary of reported mortality results in randomized controlled trials and observational studies comparing an aminosalicylate alone or in combination with placebo or another treatment in patients with Crohn's disease 142
Table 40. Summary of lymphoma risk in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease 145
Table 41. Summary of risk of lymphoma in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease 152
Table 42. Demographic and survival characteristics of patients with Crohn's disease who developed hepatosplenic T-cell lymphoma 154
Table 43. Medications used prior to diagnosis of hepatosplenic T-cell lymphoma in 37 unique patients with Crohn's disease 154
Table 44. Summary of the risk of other cancers in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease 156
Table 45. Summary of the risk of other cancers in randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease 161
Table 46. Summary of the risk of other cancers in randomized controlled trials and observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease 164
Table 47. Summary of the risk of other cancers in a randomized controlled trial comparing an aminosalicylate with placebo in patients with Crohn's disease 165
Table 48. Summary of the randomized controlled trials reporting no opportunistic infections when comparing the effectiveness of a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease 168
Table 49. Summary of other infections reported in observational studies comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease 176
Table 50. Summary of the risk of serious infections in observational studies comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease 184
Table 51. Summary of the risk of other infections in observational studies comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease 184
Table 52. Summary of the risk of serious infections in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease 190
Table 53. Summary of the risk of other infections in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease 190

Table 54. Summary of reported rates of tuberculosis in randomized controlled trials comparing the safety of therapies for the management of Crohn's disease 198
Table 55. Summary of the risk of bone fracture in studies comparing the safety of therapies for the management of Crohn's disease.....209
Table 56. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission in children.....215
Table 57. Summary of absolute disease activity scores in studies comparing the effectiveness of medications in inducing remission in children with Crohn's disease 217
Table 58. Key findings and strength of evidence comparing pharmacologic therapies for the management of children with Crohn's disease to maintain remission 220
Table 59. Key findings and strength of evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of safety 225
Table 60. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of serious infections.....227
Table 61. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of other infections.....228
Table 62. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of height change 231
Table 63. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of weight change.....232

Figures

Figure A. Treatment pyramid for patients with Crohn's disease.....3
Figure B. Analytic framework for assessing the comparative effectiveness and safety of pharmacologic therapies for Crohn's disease 5
Figure 1. Crohn's disease activity changes over time.....2
Figure 2. Treatment pyramid for patients with Crohn's disease.....5
Figure 3. Analytic framework for assessing the comparative effectiveness and safety of pharmacologic therapies for Crohn's disease 7
Figure 4. Summary of the literature search (number of articles).....17
Figure 5. Pooled relative risk of inducing remission as measured by a Crohn's Disease Activity Index less than 150 at weeks 2 to 4 comparing natalizumab with placebo 29
Figure 6. Pooled relative risk of inducing remission at week 2 comparing a TNF-alpha inhibitor with placebo 41
Figure 7. Pooled relative risk of inducing remission of Crohn's disease at week 8 comparing budesonide with another corticosteroid 72
Figure 8. Pooled relative risk of a remission of Crohn's disease at week 52 comparing budesonide with placebo.....116
Figure 9. Pooled relative risk of remission of Crohn's disease at weeks 48 to 54 comparing an aminosalicylate with placebo 122
Figure 10. Summary of Peto odds ratios of mortality among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease 132
Figure 11. Summary of Peto odds ratios of mortality among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease.....137

Figure 12. Summary of Peto odds ratios of mortality among observational studies comparing a corticosteroid alone or in combination with another treatment in patients with Crohn's disease 140
Figure 13. Summary of Peto odds ratios of lymphoma among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease 146
Figure 14. Summary of Peto odds ratios of lymphoma among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease 150
Figure 15. Summary of Peto odds ratios of cancer risk among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease 157
Figure 16. Summary of Peto odds ratios of cancer among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease 162
Figure 17. Summary of Peto odds ratios of serious infections among randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease 169
Figure 18. Summary of Peto odds ratios of other infections among randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease 170
Figure 19. Summary of Peto odds ratios of serious infections among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease 172
Figure 20. Summary of Peto odds ratios of serious infections among observational studies comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease 173
Figure 21. Summary of Peto odds ratios of opportunistic infections among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease 174
Figure 22. Summary of Peto odds ratios of other infections among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease 175
Figure 23. Summary of Peto odds ratios of other infections among randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease 185
Figure 24. Summary of Peto odds ratios of other infections among randomized controlled trials comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease 191
Figure 25. Summary of Peto odds ratios of other infections in a randomized controlled trial comparing an aminosalicylate alone or in combination with placebo or another treatment in patients with Crohn's disease 194
Figure 26. Summary of Peto odds ratios of infusion- and injection-site reactions among randomized controlled trials comparing natalizumab to placebo in patients with Crohn's disease 201

Figure 27. Summary of Peto odds ratios of infusion- and injection-site reactions among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with another treatment in patients with Crohn's disease 203
Figure 28. Summary of Peto odds ratios of infusion- and injection-site reactions among observational studies comparing a TNF-alpha inhibitor alone or in combination with another treatment in patients with Crohn's disease 204

Appendixes

Appendix A. Detailed Electronic Database Search Strategies
Appendix B. Forms
Appendix C. Excluded Articles
Appendix D. Evidence Tables
Appendix E. Additional Meta-Analyses
Appendix F. Summary of Studies Comparing the Safety of Pharmacologic Therapies Among Patients With Inflammatory Bowel Disease
Appendix G. Subgroup Analysis Tables

Executive Summary

Description of Crohn's Disease

Crohn's disease is a type of inflammatory bowel disease. Other types of inflammatory bowel disease include ulcerative colitis and indeterminate colitis. The medical community characterizes Crohn's disease as chronic full-thickness inflammation that can occur anywhere in the gastrointestinal tract but that most often affects the small bowel and colon. Typical symptoms of Crohn's disease include abdominal pain, chronic diarrhea, and gastrointestinal bleeding. Crohn's disease affects between 400,000 and 600,000 North Americans.[1] Ten percent of Crohn's disease patients are children aged 17 years or younger.[2]

The activity of Crohn's disease fluctuates over time, frequently leading to complications that require surgical intervention. One study estimated that during the first 7 years after diagnosis, 20 percent of Crohn's disease patients will have active disease at least once each year, 67 percent will fluctuate between years of active disease and years in remission, and 13 percent will have no relapses after the initial disease episode.[3]

The clinical management of Crohn's disease is complicated. Clinical practice guidelines for Crohn's disease recommend that clinicians take into account the disease location, severity, complications, and extraintestinal manifestations when choosing a treatment strategy. However, no universal treatment strategy exists for patients.[4] The lack of consensus about the best treatment strategy can result in confusion and frustration for both the clinicians who treat Crohn's disease patients and the patients themselves.

Interventions To Treat Crohn's Disease

Medical therapy in Crohn's disease targets intestinal inflammation with the intent of altering the natural history of the disease. Clinicians have prescribed corticosteroids and aminosalicylates such as sulfasalazine since the mid-1900s to treat Crohn's disease. Clinicians have prescribed immunomodulators (e.g., 6-mercaptopurine, azathioprine, and methotrexate) for the treatment of Crohn's disease since the 1970s, although they did not routinely prescribe these medications until the 1990s.[5] The biologics are a class comprised of four agents: three inhibit tumor necrosis factor-alpha (TNF-alpha) and one inhibits the cellular adhesion molecule alpha-4-integrin. The U.S. Food and Drug Administration (FDA) approved the first biologic TNF-alpha inhibitor, infliximab, for the treatment of Crohn's disease in adults in 1998. The FDA-approved TNF-alpha inhibitor biologics also include adalimumab and certolizumab pegol.[4] Natalizumab is another FDA-approved biologic for adults with Crohn's disease, which works by inhibiting the cellular adhesion molecule alpha 4-integrin (Table A).[6] Biologic treatments differ from other medication classes because they are synthesized using biologic, rather than chemical, processes.

When patients have active disease, clinicians prescribe medications to induce remission. After the patient is in remission (no longer has active disease), clinicians prescribe medications to maintain the remission. If a patient is in a state of remission and symptoms increase to an active state, clinicians refer to the symptom increase as a relapse. Clinicians recommend surgery to induce remission when Crohn's disease or its complications are resistant to medical therapy. Surgery is not a cure for disease, as recurrence is common.

Table A. Medications used for the treatment of Crohn's disease

Class	Generic Name	U.S. Trade Name	Route	Half-Life	Mechanism of Action	FDA Approved for CD in Adults	FDA Approved for CD in Children
Biologic	Adalimumab	Humira	Subcutaneous	10-18 days	TNF-alpha inhibitor	Yes	No
Biologic	Certolizumab pegol	Cimzia	Subcutaneous	~14 days	TNF-alpha inhibitor	Yes	No
Biologic	Infliximab	Remicade	Intravenous	7.7-9.5 days	TNF-alpha inhibitor	Yes	Yes
Biologic	Natalizumab	Tysabri	Intravenous	7-15 days	Prevents attachment of inflammatory immune cells to intestinal cell layers	Yes	No
Immunomodulator	Azathioprine	Azasan, Imuran	Oral, intravenous	5 hours	Purine synthesis inhibitor	No	No
Immunomodulator	6-Mercaptopurine	Purinethol	Oral	1-2 hours	Purine synthesis inhibitor	No	No
Immunomodulator	Methotrexate	Methotrexate	Intravenous, oral	3-15 hours	Dihydrofolate reductase inhibitor	No	No
Corticosteroid	Prednisone, prednisolone, 6-methyl-prednisolone, hydrocortisone, budesonide	Cortef, Entocort	Oral, topical, intravenous	8-54 hours	Binds glucocorticoid receptors in cytoplasm, where it upregulates anti-inflammatory genes	No*	No
Aminosalicylate	Mesalamine	Asacol, Canasa, Pentasa, Lialda, Rowasa	Oral, rectal	2-15 hours	Unknown	No	No
Aminosalicylate	Sulfasalazine	Azulfidine	Oral	5-10 hours	Unknown	No	No

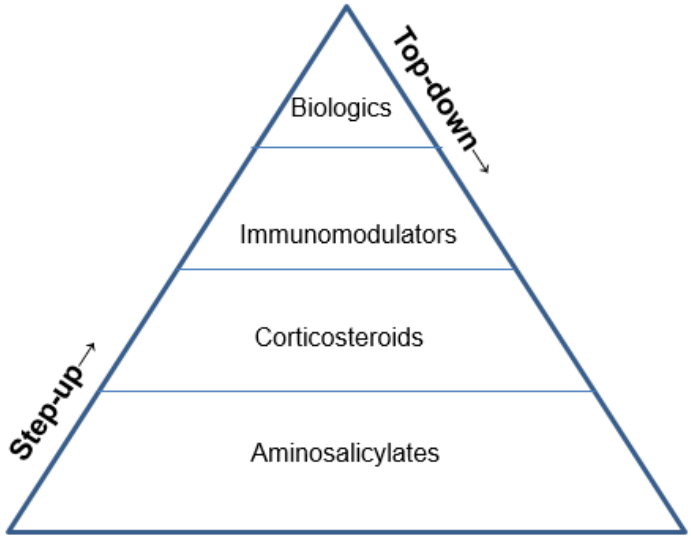
CD = Crohn's disease; FDA = U.S. Food and Drug Administration; TNF = tumor necrosis factor
*Budesonide is FDA approved for mild to moderate Crohn's disease.

Current Uncertainties and Controversies in the Treatment of Crohn's Disease

A 2009 report from the Institute of Medicine stated that a priority for comparative effectiveness research is the comparison of algorithms for treating Crohn's disease that introduce biologics at different time points in the disease course.[7] Some experts believe that patients have better long-term outcomes taking immunomodulators and biologics early ("top-down therapy"), as opposed to taking them after prolonged steroid use ("step-up therapy"). Experts have cautioned, however, that the long-term safety of these treatments, particularly when used in combination, remains unknown.[8,9] The disease treatment pyramid shown in Figure A summarizes the two treatment strategies from the onset of disease.[10]

The treatment guidelines point to controversial areas in need of future research. These areas include treatments to achieve long-term remission, the benefits and harms of step-up versus top-down treatment strategies, and how to optimize the use of biologic agents, given that many patients' disease can be managed without the use of biologics.[4]

Figure A. Treatment pyramid for patients with Crohn's disease



Purpose of This Report

The purpose of this review is to give clinicians involved in the care of patients with Crohn's disease a comprehensive comparison of the effectiveness and safety of biologics, immunomodulators, corticosteroids, and aminosalicylates in the treatment of Crohn's disease. The specific Key Questions (KQs) of interest are listed below.

KQ1. What is the comparative effectiveness of therapies, alone or in combination, used to induce remission in adults and children with active Crohn's disease?

Remission is a decrease in or absence of Crohn's disease symptoms. We define remission using the following markers: the Crohn's Disease Activity Index (CDAI), mucosal healing, the absence of Crohn's disease hospitalizations or surgeries, reduction of steroids, fistula healing, and patient-reported outcomes. We looked for data on remission rates at the following time points after randomization: 2–4 weeks, 2–16 weeks, and last reported time point (Table B).

KQ2. What is the comparative effectiveness of therapies, alone or in combination, used to maintain remission in adults and children with inactive Crohn's disease?

We looked for data on the maintenance of remission from inactive disease or response to a medication in a previous induction trial at the following time points after randomization: 48–54 weeks and last reported time point.

KQ3. What is the comparative safety of therapies, alone or in combination, used in adults and children with Crohn's disease in terms of minimizing short- and long-term adverse effects?

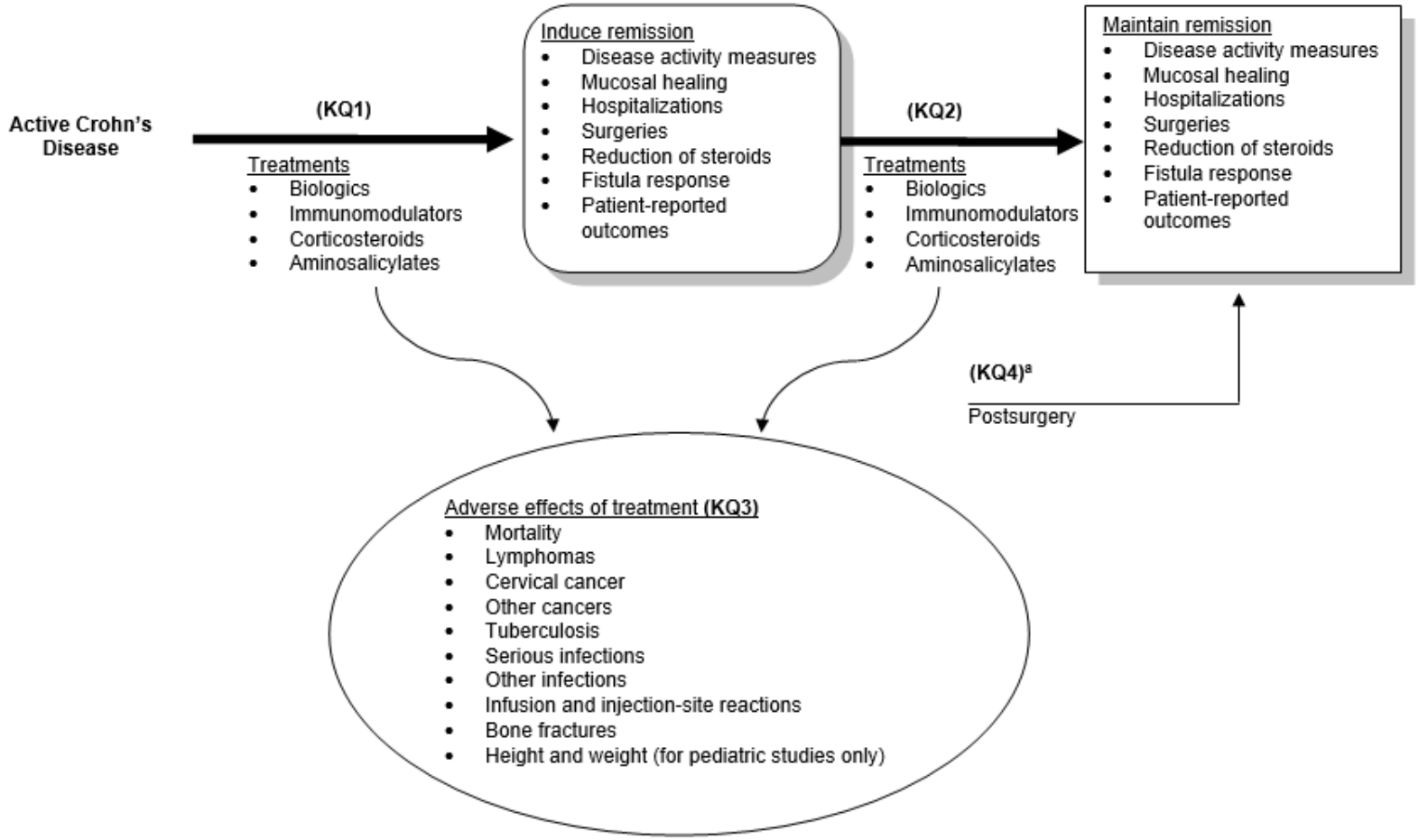
The safety outcomes of interest were mortality, occurrence of lymphomas and/or other cancers, infections, infusion- and injection-site reactions, bone fractures, and growth in children. We looked for data on these outcomes at the last reported time point. Short-term adverse effects are events that occur within 1 year of initiating a medication. Long-term adverse effects occur at least 1 year after initiating a medication.

KQ4. What is the comparative effectiveness of agents used to prevent postoperative recurrence in Crohn's disease as pertains to patient-reported outcomes?

The patient-reported outcomes of interest were standard quality-of-life indexes and specialty indexes (Inflammatory Bowel Disease Questionnaire [IBDQ], Short Inflammatory Bowel Disease Questionnaire), and days of work or school missed. We looked for data on patient-reported outcomes at the following time points after randomization: 48–54 weeks and last reported time point.

Figure B graphically depicts the KQs.

Figure B. Analytic framework for assessing the comparative effectiveness and safety of pharmacologic therapies for Crohn's disease



KQ = Key Question

Note: KQ1: comparative effectiveness in inducing remission; KQ2: comparative effectiveness in maintaining remission; KQ3: comparative safety; KQ4: comparative effectiveness of treatments for postsurgical patient-reported outcomes.

[a]For KQ4, the only examined endpoint is patient-reported outcomes.

Table B. Outcomes considered for each Key Question concerning the comparative effectiveness and safety of medications for the treatment of Crohn's disease

Key Question	Outcomes	Time Points
KQ1	• Disease activity measures (remission as measured by the CDAI, PCDAI, HBI, or other disease activity measurements) • Mucosal healing (presence of ulcers, CDEIS) • Hospitalizations • Surgeries • Reduction of steroids • Fistula response (complete or partial fistula closure or other measure of perianal disease) • Patient-reported outcomes (health-related quality of life, IBDQ, days of work or school missed)	• 2 to 4 weeks after randomization • 12 to 16 weeks after randomization • Last reported time point
KQ2	• Disease activity measures (relapse, CDAI, PCDAI, HBI, or other disease activity measurements) • Mucosal healing (presence of ulcers, CDEIS) • Hospitalizations • Surgeries • Reduction of steroids • Fistula response (fistula recurrence or other measure of perianal disease) • Patient-reported outcomes (health-related quality of life, IBDQ, days of work or school missed)	• 48 to 54 weeks after randomization • Last reported time point
KQ3	• Mortality • Lymphomas • Cervical cancer • Other cancers • Tuberculosis • Serious infections • Other infections • Infusion- and injection-site reactions • Bone fractures • Height and weight as indicators of growth (for pediatric studies only)	• Last reported time point
KQ4	• Patient-reported outcomes (health-related quality of life, IBDQ, days of work or school missed)	• 48 to 54 weeks after randomization • Last reported time point

CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity; HBI = Harvey-Bradshaw Index; IBDQ = Inflammatory Bowel Disease Questionnaire; KQ = Key Question; PCDAI = Pediatric Crohn's Disease Activity Index.

Note: KQ1: comparative effectiveness in inducing remission; KQ2: comparative effectiveness in maintaining remission; KQ3: comparative safety; KQ4: comparative effectiveness of treatments for postsurgical patient-reported outcomes.

Total scores for the CDAI range from 0 to 600, with higher scores indicating more severe disease activity. Total scores for the PCDAI range from 0 to 100, with higher scores indicating more severe disease activity. Total scores for the HBI range from 0 to 19, with higher scores indicating more severe disease activity. Total scores for the CDEIS range from 0 to 44, with higher scores indicating more severe disease activity. Total scores for the IBDQ range from 32 to 224, with higher scores indicating better quality of life.

Methods

Topic Development

The topic for this report was nominated in a public process. At the beginning of the project, we recruited a panel of Key Informants and Technical Experts to give input on the selection and refinement of the questions to be examined. In March 2010, we posted preliminary questions on the Effective Health Care Program Web site for public comment. With the Key Informants, Technical Experts, representatives of the Agency for Healthcare Research and Quality, and public comments, we finalized the KQs listed above.

Search Strategy

We searched the following databases for primary studies for the dates shown in parentheses: MEDLINE® (1966 through June 2011), Embase® (1974 through June 2011), and the Cochrane Central Register of Controlled Trials (Issue 2, 2011). We also reviewed the reference lists of each included article and relevant review articles. To assess the risk of two serious and rare complications that may be associated with the treatment for Crohn's disease, hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy, we supplemented our primary search strategy by also searching for cases reported to the FDA's Adverse Event Reporting System. To identify additional studies, we reviewed the Scientific Information Packets provided by the pharmaceutical manufacturers.

Study Selection

Two reviewers independently reviewed titles and abstracts. We excluded titles and abstracts when both reviewers agreed on exclusion. We resolved differences regarding article inclusion through consensus adjudication. A third reviewer audited a random sample of abstract and article reviews to ensure consistency in the reviewing process. We included relevant English-language studies evaluating nonpregnant patients with Crohn's disease.

For KQ1 and KQ2, on induction and maintenance of remission, we included only randomized controlled trials (RCTs). Both placebo-controlled and head-to-head trials were eligible. We did not include RCTs that examined only the same medication administered at different dosages. We did not include nonrandomized trials. We chose the outcomes of interest for KQ1 and KQ2 to represent important clinical and patient-reported outcomes.

For KQ3, on safety, we included RCTs and observational studies. We chose specific safety outcomes on the basis of the severity of the outcome, impact on quality of life, and potential for safety to differ by medication class. We selected clinical outcomes a priori for inclusion in the review. All RCTs that reported on safety-related outcomes were eligible. Observational studies were eligible if they reported: (1) clear comparison groups specified in the study aims or methods; (2) clear denominators (patients on groups of medications); and (3) clear numerators (patients who experienced the safety event of interest according to group of medication). We also included studies that reported an effect estimate or p-value for a safety outcome by medication use if they met the first criterion (clear comparison groups).

For KQ4, on postoperative outcomes, we focused on the comparative effectiveness of medications only in terms of patient-reported outcomes. We chose this approach because a rigorously conducted systematic review[11] recently assessed the other clinical outcomes

associated with the use of medications to maintain remission after intestinal resection in patients with Crohn's disease.

Data Abstraction

For all articles, reviewers extracted information on general study characteristics, study participants, study eligibility criteria, interventions, outcome measures and their method of ascertainment, and the results of each outcome (including measures of variability). We abstracted information on subgroup analyses to understand how disease characteristics could modify the relationship between medications and remission, including baseline C-reactive protein or elevated inflammatory markers, medication history, concomitant use of medications during the trial, disease duration, disease location, and prior surgery related to Crohn's disease.

Quality Assessment

We used study quality assessment to help us understand differences in results between studies. For RCTs, we based the dual independent review of article quality on the Cochrane Collaboration's Risk of Bias Tool.[12] For nonrandomized observational studies, we selected items from the Downs and Black quality checklist.[13] We supplemented both quality assessment tools with items from the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[14] The overall study quality was assessed as—

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.[14]

Applicability

We assessed the applicability of the bodies of evidence for each KQ in terms of the degree to which the study population, interventions, comparisons, outcomes, timing, and settings (PICOTS) were typical of the treatment of individuals with Crohn's disease.

Data Synthesis and Meta-Analysis

We synthesized the evidence for children separately from adults for all KQs. For each KQ, we created a set of detailed evidence tables containing the information we abstracted from eligible studies. We conducted meta-analyses when there were sufficient data (at least three studies) and when studies were sufficiently homogeneous with regard to study characteristics (PICOTS). For studies amenable to pooling for meta-analyses, we calculated pooled relative

risks using a DerSimonian and Laird random-effects model.[15] We looked for statistical heterogeneity between the studies in meta-analyses using: (1) a chi-squared test with a significance level of alpha less than or equal to 0.10 and (2) an I-squared statistic with a value of 50 percent or more, indicating substantial heterogeneity.[16] We did not report the pooled result if we found substantial heterogeneity.

We conducted sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimate. For all meta-analyses, we conducted formal tests for publication bias using Begg's[17] and Egger's tests;[18] including an evaluation of the asymmetry of funnel plots for each comparison of interest. We conducted all meta-analyses using Intercooled STATA 9.2 (College Station, TX).

When we were unable to pool studies for an outcome, we calculated and displayed absolute risk differences with 95-percent confidence intervals for the individual studies. For KQ1 and KQ2, we considered a difference to be clinically meaningful when there was an absolute difference of 10 percentage points in the outcome between the groups compared, even when the difference was not statistically significant at a p-value less than 0.05. For the IBDQ (the most commonly used patient-reported outcome), we considered a meaningful difference to be a between-group absolute difference of 17 points or greater in the change from baseline.[19]

In terms of adverse effects, when a study did not report an effect estimate, we calculated a Peto odds ratio if the combined number of events in each group was greater than 5.[20,21] We also calculated incidence rate ratios for person-time data when the authors did not report an effect estimate or when the reported effect estimate appeared to contradict the reported events per person-time. We did not specify a standard for a clinically meaningful difference in adverse events, because an absolute rate was rare for most of the adverse events. After performing the main analyses on adverse events, we carried out a sensitivity analysis with studies that evaluated patients with inflammatory bowel disease but did not report results separately for patients with Crohn's disease.

Grading the Strength of Evidence

At the completion of our review, we graded the strength of the evidence addressing the KQs by using the evidence-grading scheme recommended by the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[22] We based the strength-of-evidence grade on four domains: risk of bias, consistency, directness, and precision.

We classified the strength of evidence pertaining to KQs 1 through 4 into four grades:

- "High" grade, indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect
- "Moderate" grade, indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate
- "Low" grade, indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate
- "Insufficient" grade: evidence is unavailable; no studies observed

If the evidence grade or direction of the effect differed at two time points of interest, we reported the evidence grade separately for each time point.

Results

Search Results

We identified 136 studies involving 148,733 patients that met our inclusion criteria for one or more of the KQs. Combining KQ1 and KQ2 yielded 64 studies (94 publications) with 11,377 patients. For KQ3, we found 47 RCTs involving 9,884 Crohn's disease patients and 46 observational studies involving 121,649 Crohn's disease patients. We included an additional 15 studies with 14,934 patients with inflammatory bowel disease as a sensitivity analysis. For KQ4, we found one RCT with 78 patients with Crohn's disease. Five pediatric RCTs examined a total of 298 children, and five observational studies involving 397 children with Crohn's disease reported data for KQs 1-3 but not KQ4.

We reported the results of our systematic review first according to KQ and separated adult from pediatric results. When a study compared multiple medication classes, our report of the study begins with the first medication in our ordered list of medication classes, which we organized according to the top-down approach in the treatment pyramid (Figure A). The medication classes are: biologics (natalizumab, TNF-alpha inhibitor), immunomodulators (thiopurines, methotrexate), corticosteroids, and aminosalicylates.

Key Questions 1 and 2. Induction and Maintenance of Remission

Study Characteristics

The duration of the 64 RCTs ranged from 2 weeks to 4 years. Most RCTs were multicenter (76 percent) and located in Europe and North America, with fewer than 10 multicenter or single-center RCTs in Africa, Australia, Israel, or Asia.

Most patients with active disease (whom we considered in KQ1 on induction of remission) were identified using the CDAI (lower limit, 150 to 220; upper limit, 350 to 600; 43 studies). Most patients with inactive disease (whom we considered in KQ2 on maintenance of remission) were also identified using the CDAI (upper limit, 120 to 220; 23 studies). One study used the Harvey-Bradshaw Index. Twenty-two studies did not report a scoring system to identify disease activity.

Most studies allowed patients to use other medications during the RCT. Many specified that patients had to be on a stable dose at the time of randomization. These trials considered it a failure of treatment if patients made major dose changes during the trial.

Population Characteristics

A small percentage of RCTs reported on race. Of those studies, 84 to 100 percent of the patients were White. The largest non-White racial group in any individual study was 10 percent African American,[23] 8 percent Asian,[24] and 7 percent unspecified other race.[25] The mean or median disease duration ranged from 7 months to 14 years. The mean and median age at the time of randomization ranged from 26 to 47 years. The minimum age reported in any one study was 14 years,[26] and the maximum age was 78 years.[27]

Remission Results

Despite the large number of studies, we were able to perform very few meta-analyses because of the heterogeneity in the definition of the inclusion criteria and outcomes between

studies. Recently published studies tended to define remission using the CDAI, with scores below 150 indicating remission and scores of 150 or more indicating active disease. Older studies, including the study for which researchers developed the CDAI,[28] tended to use disease activity measures with or without clinical outcomes, such as the need for surgery or laboratory measures, to indicate remission status. We found very few studies that used measures of remission other than the CDAI (e.g., mucosal healing, hospitalizations, surgeries, reduction of corticosteroid use, fistula response, or patient-reported outcomes).

Key Question 1. Induction of Remission

Of the 78 comparisons with evidence, 4 resulted in high strength of evidence and 20 resulted in moderate strength of evidence (Table C). Most patient-reported outcomes were measured by the IBDQ. Total scores for the IBDQ range from 32 to 224, with higher scores indicating better quality of life.[29]

Key Question 2. Maintenance of Remission

Of the 55 comparisons with evidence, none resulted in high strength of evidence and 11 resulted in moderate strength of evidence (Table D).

Subgroup Analyses

Six trials reported a statistical interaction test on disease characteristics that might modify the relationship between medications and remission. No consistent relationship for a disease characteristic subgroup of interest was observed among the six comparisons.

Table C. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to induce remission*

Comparison Maximum Trial Duration	Disease Activity Measure: Weeks 2–4	Disease Activity Measure: Weeks 12–16	Disease Activity Measure: After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Natalizumab vs. placebo 12 weeks	Favors natalizumab; moderate SOE	Favors natalizumab; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 12:* Favors neither; moderate SOE
Natalizumab + infliximab vs. infliximab 10 weeks	Favors neither; low SOE	Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 10:* Favors neither; low SOE
Adalimumab vs. placebo 4 weeks	*>160 mg SC dose:* Favors adalimumab; high SOE *≤80 mg SC dose:* Favors neither; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 4:* Favors neither; low SOE	*Week 4:* Favors neither; high SOE
CP vs. placebo 26 weeks	Favors neither; low SOE	Favors neither; low SOE	*Week 26:* Favors CP; low SOE	Insufficient	Insufficient	Insufficient	*Week 26:* Favors neither; low SOE	*Week 12 and Week 26:* Favors neither; low SOE
Infliximab vs. placebo 12 weeks	Favors infliximab; moderate SOE	Favors infliximab; low SOE	Insufficient	*Week 4:* Favors infliximab; low SOE	Insufficient	Insufficient	*Week 6:* Favors infliximab; high SOE	*Week 4:* Favors infliximab; moderate SOE
Infliximab vs. azathioprine 26 weeks	Insufficient	Favors infliximab; moderate SOE	*Week 26:* Favors infliximab; moderate SOE	*Week 26:* Favors infliximab; low SOE	Insufficient	Insufficient	Insufficient	*Week 26:* Favors neither; moderate SOE
Infliximab + azathioprine vs. infliximab 26 weeks	Insufficient	Favors infliximab + azathioprine; moderate SOE	*Week 26:* Favors infliximab + azathioprine; moderate SOE	*Week 26:* Favors infliximab + azathioprine; low SOE	Insufficient	Insufficient	Insufficient	*Week 26:* Favors neither; moderate SOE

Table C. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 2–4	Disease Activity Measure Weeks 12–16	Disease Activity Measure After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire[†]
Infliximab + azathioprine vs. azathioprine 26 weeks	Insufficient	Favors infliximab + azathioprine; moderate SOE	*Week 26:* Favors infliximab + azathioprine; moderate SOE	*Week 26;* Favors infliximab + azathioprine; low SOE	Insufficient	Insufficient	Insufficient	*Week 26:* Favors neither; moderate SOE
Infliximab + azathioprine vs. steroids 104 weeks	Insufficient	Insufficient	*Week 104:* Favors neither; low SOE	*Week 104:* Favors infliximab + azathioprine; low SOE	Insufficient	Insufficient	Insufficient	*Week 10:* Favors infliximab + azathioprine; low SOE
Infliximab + methotrexate vs. infliximab 48 weeks	Favors infliximab + methotrexate; low SOE	Favors infliximab + methotrexate; low SOE	*Week 48:* Favors infliximab + methotrexate; low SOE	Insufficient	Insufficient	*Week 48:* Favors infliximab + methotrexate; low SOE	Insufficient	*Week 4 and Week 8:* Favors infliximab + methotrexate; low SOE
Thiopurines vs. placebo 104 weeks	Favors neither; low SOE	Insufficient	*Weeks 17-38:* Favors neither; low SOE *Week 104:* Favors 6-MP; low SOE	Insufficient	Insufficient	*Week 16:* Favors neither; low SOE	*Week 17:* Favors neither; low SOE *Week 104:* Favors 6-MP; low SOE	*Week 16:* Favors neither; low SOE[‡]
Thiopurines vs. oral methotrexate 38 weeks	Favors neither; low SOE	Favors neither; low SOE	*Week 38:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Thiopurines vs. steroids 17 weeks	Favors steroids; low SOE	Favors steroids; low SOE	*Week 17:* Favors steroids; low SOE	Insufficient	Insufficient	Insufficient	*Week 17:* Favors steroids; low SOE	Insufficient

Table C. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 2–4	Disease Activity Measure Weeks 12–16	Disease Activity Measure After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Thiopurines vs. ASA 30 weeks	Favors ASA; low SOE	Favors neither; low SOE	*Week 17:* Favors neither; low SOE *Week 30:* Favors 6-MP; low SOE	Insufficient	Insufficient	Insufficient	*Week 17:* Favors neither; low SOE	Insufficient
Thiopurines (IV, then oral) vs. thiopurines (oral) 16 weeks	Insufficient	Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Thiopurines + steroids vs. steroids 28 weeks	Insufficient	Favors thiopurines + steroids; low SOE	*Week 28:* Favors thiopurines + steroids; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Thiopurines + steroids vs. methotrexate (IV, then oral) + steroids 26 weeks	Insufficient	Favors neither; low SOE	*Week 26:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	*Week 26:* Favors methotrexate + steroids; low SOE	Insufficient
Methotrexate (oral) vs. placebo 38 weeks	Favors neither; low SOE	Favors neither; low SOE	*Week 38:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Methotrexate (oral) vs. ASA 30 weeks	Insufficient	Insufficient	*Week 30:* Favors methotrexate; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table C. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 2–4	Disease Activity Measure Weeks 12–16	Disease Activity Measure After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Methotrexate (IM) + prednisone vs. prednisone 16 weeks	Insufficient	Favors methotrexate; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 16:* Favors neither; moderate SOE
Budesonide vs. placebo 16 weeks	*≥9 mg daily:* Favors budesonide; moderate SOE *<9 mg daily:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 8:* No difference; low SOE
6-methyl-prednisolone or prednisone vs. placebo 104 weeks	*6-methyl-prednisolone:* Favors 6-methyl-prednisolone; low SOE *Prednisone* Favors neither; low SOE	Favors steroids; low SOE	*Week 104:* Favors steroids; low SOE	Insufficient	Insufficient	Insufficient	*Week 17:* Favors steroids; low SOE	Insufficient
Budesonide vs. other steroids 10 weeks	Favors neither; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 8:* Favors neither; moderate SOE
Steroids vs. ASA 104 weeks	Favors steroids; low SOE	Favors steroids; low SOE	*Week 104:* Favors steroids; low SOE	Insufficient	Insufficient	Insufficient	*Week 17:* Favors neither; low SOE	*Week 2:* Favors steroids; high SOE§ *Week 12:* Favors neither; moderate SOE§

Table C. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 2–4	Disease Activity Measure Weeks 12–16	Disease Activity Measure After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire[†]
6-methyl-prednisolone + sulfasalazine vs. placebo 104 weeks	Favors 6-methyl-prednisolone + sulfasalazine; low SOE	Favors 6-methyl-prednisolone + sulfasalazine; low SOE	*Week 104:* Favors 6-methyl-prednisolone + sulfasalazine; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. steroids 104 weeks	Favors neither; low SOE	Favors neither; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. sulfasalazine 104 weeks	Favors steroids + sulfasalazine; low SOE	Favors steroids + sulfasalazine; low SOE	*Week 104:* Favors steroids + sulfasalazine; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Mesalamine vs. placebo 17 weeks	Favors neither; low SOE	*≥3.2 g daily:* Favors mesalamine; low SOE *<3.2 g daily:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Sulfasalazine vs. placebo 104 weeks	Favors neither; low SOE	Favors sulfasalazine; low SOE	*Week 104:* Favors sulfasalazine; low SOE	Insufficient	Insufficient	Insufficient	*Week 17:* Favors sulfasalazine; low SOE	Insufficient

6-MP = 6-mercaptopurine; ASA = aminosalicylates; CP = certolizumab pegol; IM = intramuscular; IV = intravenous; SC = subcutaneous; SOE = strength of evidence; steroids = corticosteroids

Note: The strength of the evidence was defined as follows: high = high confidence that the evidence reflects the true effect; moderate = moderate confidence that the evidence reflects the true effect; low = low confidence that the evidence reflects the true effect; insufficient = evidence is unavailable.

*All other potential comparisons of therapies and outcomes were graded as insufficient because there were no eligible trials. The evidence for the last reported measure is provided for disease activity after 16 weeks, mucosal healing, hospitalizations and surgeries, reduction of steroids, fistula respons, and patient-reported outcomes.

[†]Patient-reported outcomes were measured by the Inflammatory Bowel Disease Questionnaire except where indicated by a footnote.

[‡]Outcome based on "feeling better" in 2 trials.

[§]Used McMaster University Quality of Life scale.

Table D. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to maintain remission*

Comparison Maximum Trial Duration	Disease Activity Measure: Weeks 48–54	Disease Activity Measure: After 54 Weeks	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Natalizumab vs. placebo 48 weeks	Favors natalizumab; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	*Week 48:* Favors natalizumab; moderate SOE	Insufficient	*Week 48:* Favors natalizumab; moderate SOE
Adalimumab vs. placebo 52 weeks	Favors adalimumab; low SOE	Insufficient	Insufficient	*Week 52:* Favors adalimumab for all-cause hospitalizations; favors neither for CD-related hospitalizations; moderate SOE	*Week 52:* Favors neither; moderate SOE	*Week 52:* Favors adalimumab; low SOE	Insufficient	*Week 52:* Favors neither; low SOE
CP vs. placebo 18 weeks	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 18:* Favors neither; low SOE
Infliximab vs. placebo 52 weeks	Favors neither among all randomized; favors infliximab among responders; low SOE	Insufficient	*Week 52:* Favors infliximab; low SOE	*Week 52:* Favors infliximab; moderate SOE	*Week 52:* Favors neither among patients with fistulizing disease; moderate SOE	*Week 52:* Favors infliximab; low SOE	*Week 40:* Favors infliximab; low SOE	*Week 52:* Favors infliximab; low SOE
Infliximab + azathioprine vs. infliximab 104 weeks	Insufficient	*Week 104:* Favors neither; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	*Week 104:* Favors neither; low SOE
Infliximab + azathioprine vs. infliximab + hydrocortisone 104 weeks	Favors neither; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table D. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to maintain remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 48-54	Disease Activity Measure After 54 Weeks	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Azathioprine vs. placebo 104 weeks	*≥1.7 mg/kg/day:* Favors azathioprine; low SOE *<1 mg/kg/day:* Favors neither; low SOE	*Week 104:* Favors azathioprine at ≥1.7 mg/kg/day; low SOE Favors neither at <1 mg/kg/day; low SOE	Insufficient	Insufficient	Insufficient	*Week 26:* Favors azathioprine; low SOE	Insufficient	Insufficient
Azathioprine vs. budesonide 52 weeks	Favors azathioprine; low SOE	Insufficient	*Week 52:* Favors azathioprine; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Azathioprine vs. prednisone 104 weeks	Favors azathioprine; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Azathioprine vs. sulfasalazine 104 weeks	Favors neither; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Methotrexate (IM) vs. placebo 40 weeks	*Week 40:* Favors methotrexate; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide vs. placebo 52 weeks	Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 52:* Favors neither; low SOE
Prednisone vs. placebo 104 weeks	Favors neither; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table D. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to maintain remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 48-54	Disease Activity Measure After 54 Weeks	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
6-methyl-prednisolone vs. placebo 104 weeks	Favors 6-methyl-prednisolone; low SOE	*Week 104:* Favors 6-methyl-prednisolone; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide vs. mesalamine 52 weeks	Favors budesonide; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 52:* Favors budesonide; moderate SOE
Steroids (6-methyl-prednisolone or prednisone) vs. sulfasalazine 104 weeks	Favors neither; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
6-methyl-prednisolone + sulfasalazine vs. placebo 104 weeks	Favors neither; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. steroids 104 weeks	Favors neither; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. sulfasalazine 104 weeks	Favors neither; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Mesalamine (controlled release) vs. placebo 52 weeks	Favors mesalamine; low SOE	*Week 104:* Favors neither; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 48:* Favors neither; low SOE

Table D. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to maintain remission* (continued)

Comparison Maximum trial duration	Disease activity measure Weeks 48-54	Disease activity measure After 54 weeks	Mucosal healing	Hospitalizations	Surgeries	Reduction of steroids	Fistula response	Inflammatory Bowel Disease Questionnaire†
Mesalamine (pH release) vs. placebo 208 weeks	Favors mesalamine; low SOE	*Week 104:* Favors placebo; low SOE *Week 208:* Favors mesalamine; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Olsalazine vs. placebo 52 weeks	Favors neither; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Sulfasalazine vs. placebo 104 weeks	Favors neither; low SOE	*Week 104:* Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

CD = Crohn's disease; CP = certolizumab pegol; IM = intramuscular; SOE = strength of evidence; steroids = corticosteroids

Note: The strength of the evidence was defined as follows: high = high confidence that the evidence reflects the true effect; moderate = moderate confidence that the evidence reflects the true effect; low = low confidence that the evidence reflects the true effect; insufficient = evidence is unavailable.

*All other comparisons and outcomes were graded as insufficient because there were no eligible trials.

†Patient-reported outcomes were measured by the Inflammatory Bowel Disease Questionnaire except where indicated by a footnote. Total scores for the Inflammatory Bowel Disease Questionnaire range from 32 to 224, with higher scores indicating better quality of life.[29]

Key Question 3. Safety

Study Characteristics of RCTs

Of 64 RCTs, 45 (70 percent) reported a safety outcome of interest according to treatment group. The only information on safety assessment for nearly all RCTs was that researchers ascertained unspecified safety outcomes at study visits. These RCTs made no mention of the ascertainment method (questionnaire, patient-initiated report) or blinding.

Study Characteristics of Observational Studies

Seven prospective cohort (n=26,973), 26 retrospective cohort (n=53,856), 11 case-control (n=40,040), 1 cross-sectional (n=207),[30] and 1 observational study of unclear study design (n=573)[31] reported safety outcomes. All of the prospective and case-control studies stated a specific safety outcome of interest. All of the retrospective studies aimed to assess safety, but about half of them did not specify the exact safety outcomes of interest. No observational study mentioned active ascertainment or blinded assessment of safety outcomes.

Most observational studies occurred at single study centers. Most single-center or multicenter studies took place in the United States, Europe, Canada, or Australia, with one study in Africa and no studies in Asia.

Population Characteristics of Observational Studies

The age distribution was very inclusive, with some studies including patients of all ages (from children up to 90 years). Twenty-eight studies reported results for inflammatory bowel disease patients without separately reporting results for Crohn's disease patients.

In contrast to the RCTs, most of the observational studies reporting safety included all activity levels and severities of Crohn's disease. Most of the observational studies had no restrictions on previous medication use. Sixteen studies included only patients who had used infliximab. These 16 studies compared the safety of infliximab alone or in combination with other medications. Two retrospective studies required azathioprine use because researchers designed the studies to compare the effectiveness of azathioprine with or without concomitant aminosalicylate.[32,33]

Safety Results

We did not perform meta-analyses because very few safety outcomes had more than three studies that contributed to any monotherapy or combination therapy comparison. Also, when more than three studies were available, the inclusion criteria and study duration were too heterogeneous. We summarized the safety results in Table E.

There was no obvious trend that any medication was more or less safe across the safety outcomes of interest. The ability to examine such trends was limited, as the strength of evidence (SOE) for nearly every comparison was insufficient or low. A few findings indicated effects with some confidence according to the SOE grading, although each finding was based on a single RCT. Two safety comparisons were graded as high SOE: one comparison favored oral azathioprine with placebo infusion over intravenous infliximab, and a second comparison favored placebo over intravenous azathioprine. Two safety comparisons were graded as moderate SOE: one comparison favored a combination of prednisone and sulfasalazine over

prednisone alone for infections, and a second comparison did not favor either budesonide or prednisolone for the development of bone fractures.

Subgroup Analyses

No study reported a statistical interaction test for a subgroup of interest for the safety outcomes.

Table E. Summary of the comparative safety of pharmacologic therapies for the management of Crohn's disease

Outcome (Incidence)	Strength of Evidence	Conclusion
Mortality (<1% in most observed comparisons)	Low	The only comparison for which mortality differed between groups was treatment with corticosteroids compared with treatment without corticosteroids. The RRs in observational studies ranged from 1.0 to 2.5 favoring no corticosteroids, with followup ranging from 6 weeks to 7 years.
Mortality (<1% in most observed comparisons)	Low	In comparisons not involving corticosteroids, mortality did not differ among groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, aminosalicylates, or combinations of these drugs. The RRs in observational studies compared with no treatment or another treatment ranged from 0.8 to 1.0 for TNF-alpha inhibitors, 0.7 to 1.3 for immunomodulators, and 0.7 for aminosalicylates, with followup ranging from 4 weeks to 12 years.
HSTCL (insufficient data to estimate incidence)	Insufficient	We identified 37 unique cases of HSTCL associated with treatment of Crohn's disease from research reports, case series, and the AERS. Of these cases, 95% used a thiopurine and 76% used at least 1 biologic, but we could not establish a causal relationship because of limitations in the available information.
Lymphoma (<1% in most observed comparisons)	Low	The risk of lymphoma did not differ among groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, corticosteroids, aminosalicylates, or combinations of these drugs. The observational RRs compared with no treatment or another treatment were 0.6 to 1.7 for TNF-alpha inhibitors, 0.3 to 5.3 for immunomodulators, 1.0 for corticosteroids, and 1.0 for aminosalicylates, with followup ranging from 4 weeks to 12 years.
Lymphoma (<1% in most observed comparisons)	Insufficient	RCTs of immunomodulators, corticosteroids, or aminosalicylates did not report lymphoma as an outcome.
Cervical cancer (insufficient data to estimate incidence)	Low	The risk of cervical cancer did not differ among groups that received TNF-alpha inhibitors, immunomodulators, corticosteroids, aminosalicylates, or combinations of these drugs, with followup ranging from 26 weeks to 3 years.
Cervical cancer (insufficient data to estimate incidence)	Insufficient	None of the studies of natalizumab reported on cervical cancer.
All cancers (insufficient data to estimate incidence)	Low	The risk of nonmelanoma skin cancer was higher with TNF-alpha inhibitors alone or with immunomodulators used recently (within 90 days) or persistently (within 90 days and greater than 365 days) than with no TNF-alpha inhibitors or no immunomodulators. The ORs in observational studies ranged from 2.1 to 6.8.
All cancers (insufficient data to estimate incidence)	Low	The risk of nonmelanoma skin cancer was higher with thiopurines used recently (within 90 days) or persistently (within 90 days and greater than 365 days) than with no thiopurines. The ORs in observational studies ranged from 3.8 to 4.3.
All cancers (insufficient data to estimate incidence)	Low	The risk of adenocarcinoma of the small bowel was higher with 6-mercaptopurine than with no 6-mercaptopurine. The OR in an observational study was 10.8; the study did not report length of followup.

Table E. Summary of the comparative safety of pharmacologic therapies for the management of crohn's disease (continued)

Outcome (Incidence)	Strength of Evidence	Conclusion
All cancers (insufficient data to estimate incidence)	Low	The risk of other cancers did not differ between treatment groups. The RRs compared with no treatment or another treatment from observational studies ranged from 0 to 10.8, with followup ranging from 4 weeks to 12 years.
Infections (<5% in most trials for serious infections; <5 out of every 100 person-years for opportunistic infections; 5 to 20% in most trials)	Low	The risk of infection did not differ among groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, or aminosalicylates. The RRs, HRs, or ORs from RCTs and observational studies, compared with no treatment or another treatment, were 0.3 to 1.3 for natalizumab, 0.3 to 11.1 for TNF-alpha inhibitors, 0.3 to 5.4 for immunomodulators, 0.4 to 3.4 for corticosteroids, and 0.9 to 1.8 for aminosalicylates, with followup ranging from 4 weeks to 9 years.
Infections (<5% in most trials for serious infections; <5 out of every 100 person-years for opportunistic infections; 5 to 20% in most trials)	Moderate	The risk of infection was lower with prednisone and sulfasalazine than with prednisone alone. The RR from one RCT was 0.3, with 8 weeks of followup.
Tuberculosis (insufficient data to estimate incidence)	Low	The risk of developing tuberculosis did not differ between treatment groups in 5 RCTs comparing TNF-alpha inhibitors with placebo, 1 RCT comparing a combination of infliximab and immunomodulators with infliximab, and 1 RCT comparing a combination of infliximab and immunomodulators with immunomodulators. The followup ranged from 4 to 52 weeks.
Infusion-site reactions (0 to 40% in most trials of biologics)	Low	The rate of infusion reactions did not differ between treatment groups in most comparisons. The RRs, HRs, or ORs from RCTs and observational studies were: natalizumab vs. placebo, RR ranged from 0.8 to 1.5; certolizumab pegol vs. placebo, RR ranged from 0.2 to 1.7; combinations with infliximab vs. infliximab alone, RR ranged from 0.3 to 1.5; infliximab combined with thiopurine vs. infliximab combined with methotrexate, RR ranged from 0.8 to 1.4.
Infusion-site reactions (0 to 40% in most trials of biologics)	Low	The rate of infusion reactions was higher with infliximab and adalimumab than with placebo. The RRs from RCTs ranged from 1.1 to 3.2.
Infusion-site reactions (0 to 40% in most trials of biologics)	High	The rate of infusion reactions was higher with infliximab than with azathioprine. The RR from one RCT was 3.0, with 1 year of followup.
Bone fractures (insufficient data to estimate incidence)	Moderate	The risk of bone fracture did not differ between treatment groups that received budesonide or prednisolone. The RR from one RCT with 2 years of followup was 1.0.
Bone fractures (insufficient data to estimate incidence)	Low	The risk of bone fracture did not differ between corticosteroid users and corticosteroid nonusers. The RR from observational studies ranged from 0 to 2.5, with 2 years of followup.

AERS = Adverse Event Reporting System; HR = hazard ratio; HSTCL = hepatosplenic T-cell lymphoma; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; TNF = tumor necrosis factor

Key Question 4. Patient-Reported Outcomes After Surgery

We identified only one study that met the inclusion criteria for KQ4. This RCT compared azathioprine with mesalamine and reported on the IBDQ among patients who had undergone ileocolonic anastomosis within 6 to 24 months prior to randomization. The strength of the evidence was high for no difference in the effect on the IBDQ between azathioprine and mesalamine.

Key Questions 1–4 for Pediatrics

Study Characteristics

Five studies were RCTs,[34-38] two were prospective cohort studies,[39,40] and three were retrospective cohort studies.[41-43] Studies were conducted in various countries, and five studies were multicentered. The length of followup ranged from 8 weeks to 18 months for RCTs and up to 3.6 years in an observational study.

Population Characteristics

The mean age of patients ranged from 12 to 14 years. In the RCTs, 55 to 69 percent of patients were male, more than 90 percent of patients were White, and mean disease duration ranged from 7 to 36 months. Individual studies restricted their patients in terms of disease location, disease duration, and/or medications allowed prior to and during the study.

Pediatric Results

Few studies examined the efficacy and safety of Crohn's disease treatments in the pediatric population (younger than 18 years old). Four RCTs compared the efficacy of therapies, alone or in combination, in inducing or maintaining remission in children with Crohn's disease. Eight studies reported the comparative safety of therapies, alone or in combination, in children with Crohn's disease. Of these eight studies, most used height or weight change as their primary outcomes of interest. No study reported patient-reported outcomes after surgical resection.

The SOE was graded as insufficient or low for all but two comparisons in the pediatric population. The SOE was graded as moderate for no difference in the effectiveness of budesonide versus prednisolone in inducing remission. The SOE was also graded as moderate that patients treated with prednisolone had fewer infections than patients treated with budesonide.

Discussion

Key Findings

We found that a number of medications were effective in inducing and maintaining remission in Crohn's disease, but no single medication or class of medications stood out as being most effective while also providing the highest quality of life and the best safety profile. Consistency of effect was based on a medication comparison having the same direction of effect for both disease activity (across evaluable time points) and at least one other outcome.

For KQ1, on induction of remission, infliximab was found to have the greatest consistency across the outcomes of disease activity, mucosal healing, fistula healing, and IBDQ when compared with placebo (based on two trials). It was also the only comparison that included a high SOE for a given outcome (fistula healing).

Other consistent comparisons that included at least one outcome with a moderate SOE included the following: infliximab was favored over azathioprine for disease activity and mucosal healing (based on one trial); the combination of infliximab and azathioprine was favored over azathioprine alone for disease activity and mucosal healing (based on two trials); and the combination of infliximab and azathioprine was favored over infliximab alone for

disease activity and mucosal healing (based on one trial). In all three of these comparisons, IBDQ was not different between treatment arms.

Several placebo-controlled trials were also found to be consistent across outcomes. However, all the individual outcomes were rated as low SOE. The following interventions were favored over placebo: prednisone/6-methyl-prednisolone for disease activity and fistula healing (based on two trials); sulfasalazine for disease activity and fistula healing (based on two trials); and thiopurine for disease activity and fistula healing (based on one trial). Thiopurines and placebo did not differ in corticosteroid reduction and IBDQ.

For head-to-head trails, the following comparisons were consistent across outcomes, with all individual outcomes rated as low SOE: combination of infliximab and methotrexate favored over infliximab alone for disease activity, steroid reduction, and IBDQ (based on one trial); and corticosteroids favored over thiopurines for disease activity and fistula healing (based on one trial).

For KQ2, on maintenance of remission, infliximab was found to have the greatest consistency across outcomes when compared with placebo for disease activity, mucosal healing, hospitalization, surgery, corticosteroid reduction, fistula healing, and IBDQ (based on three trials). Adalimumab was also favored over placebo for the outcomes of disease activity, hospitalization, surgery, and corticosteroid reduction (based on two trials); however, adalimumab was not favored over placebo for IBDQ.

Other consistent comparisons with at least one outcome rated as moderate SOE included: natalizumab favored over placebo for disease activity, steroid reduction, and IBDQ (based on one trial); azathioprine over budesonide for disease activity and mucosal healing (based on one trial); and budesonide over aminosalicylates for disease activity and IBDQ (based on one trial). Thiopurines were consistently favored over placebo for disease activity and corticosteroid reduction (based on four trials); however, all the outcomes were rated as low SOE.

For KQ3, on safety, the SOE for nearly every comparison was graded as insufficient or low for safety-related outcomes.

Applicability of Remission Results for Adults

Older populations and non-Whites were underrepresented. Additionally, the relevance of the study findings beyond the clinical trial setting may be limited due to the lack of routine reporting on outcomes other than the CDAI, which is not used in clinical practice. The applicability to newly diagnosed patients and comparisons of step-up versus top-down treatment were limited because almost all of the trials included patients with at least 10 years of Crohn's disease prior to randomization and no trial compared patients receiving their first treatment after diagnosis. Finally, very few trials had endpoints beyond a 1-year duration.

Applicability of Safety Results for Adults

Because they had fewer inclusion and exclusion criteria than RCTs, the observational studies likely apply to Crohn's disease patients of all disease activity and severity levels. Very few observational studies required disease activity or prior medication use for study entry. Despite the differences in inclusion and exclusion criteria between the RCTs and observational studies, we did not see meaningful differences in safety signals between the RCTs and observational studies. The studies that included all inflammatory bowel disease patients had safety findings similar to those of studies that included only Crohn's disease patients or that reported results for both Crohn's disease and all inflammatory bowel disease patients.

Pediatric Applicability

The applicability of the pediatric studies was limited because of the small number of studies, with few participants per study. Also, very few medications were compared. The longest RCT had only 18 months of followup, and the longest prospective study had less than 4 years of followup.

Limitations

The identified body of evidence had several limitations that restricted the ability to draw conclusions about the effectiveness of medications to treat Crohn's disease. Head-to-head studies were limited, especially with regard to maintenance of remission. Although much attention has been given to top-down therapy (starting TNF-alpha inhibitors and/or thiopurines early in the disease course), few studies have compared this strategy with more traditional step-up therapy (escalating therapy after treatment with aminosalicylates or corticosteroids fails) in an RCT setting. Additionally, data were lacking on measures of remission other than the CDAI, such as patient-reported outcomes, mucosal healing, steroid reduction, fistula healing, hospitalization, and surgical rates. Comparisons for safety outcomes almost always had low or insufficient SOE due to lack of details on their assessment in RCTs and poor control for confounding in nonrandomized studies. The scope of studies in pediatric patients was very limited, as there are no double-blind RCTs among this population. None of the studies directly addressed safety concerns relevant to children, who may have longer lifetime exposures to these medications. Safety concerns of particular interest are the risk of hepatosplenic T-cell lymphoma, which affects boys and young men more than other demographic groups.

Findings in Relation to What Is Known

The major difference in findings between this review and previous reviews[4,44-57] pertains to infliximab. Other reviews found that all TNF-alpha inhibitors are efficacious at inducing and maintaining remission. When the clinically meaningful threshold for a difference in treatment effects is considered for consistency of efficacy across the different outcomes of interest, infliximab is the only TNF-alpha inhibitor that is consistently favored over placebo at multiple time points and for multiple outcomes. Consistency was not found for adalimumab or certolizumab pegol because of inconsistency of efficacy between outcomes and absence of outcome information other than the CDAI.

Research Gaps

Multiple gaps in the literature on medical therapy for Crohn's disease were isolated:

- Studies underrepresented non-White patients, pediatric patients, and newly diagnosed populations.
- Few studies made direct comparisons of medications.
- Trials were not powered to compare safety, and observational studies did not account for confounders when comparing adverse events.
- Few studies evaluated outcomes other than the CDAI, such as mucosal healing, rates of hospitalization and surgery, fistula healing, and patient-reported outcomes.

- Maintenance therapy outcomes in RCTs have rarely extended beyond 1 year, while observational studies have been insufficiently long to capture adverse events that may not manifest for years.

Conclusions

Infliximab was the only medication that was found to be consistently effective compared with placebo across a number of outcomes for both induction and maintenance of remission. There was little consistency across outcomes for head-to-head trials. For most medication comparisons, data were lacking on outcomes other than disease activity indexes. In children, the evidence was insufficient to permit assessment of the consistency of medication efficacy across outcomes. The quality of the safety evidence was poor due to poor reporting of the methods in trials and poor confounding control in observational studies. No strong or previously unidentified signals of harm were identified. Comparing Crohn's disease medications directly using pragmatic clinical trials will help to understand the effectiveness of medications in clinical practice using outcomes other than the Crohn's Disease Activity Index.

References

1. Loftus EV Jr, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. Aliment Pharmacol Ther. 2002;16(1):51-60. PMID: 11856078.
2. Bousvaros A, Sylvester F, Kugathasan S, et al. Challenges in pediatric inflammatory bowel disease. Inflammatory Bowel Dis. 2006;12(9):885-913. PMID: 16954808.
3. Munkholm P, Langholz E, Davidsen M, et al. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol. 1995;30(7):699-706. PMID: 7481535.
4. Lichtenstein GR, Hanauer SB, Sandborn WJ, et al. Management of Crohn's disease in adults. Am J Gastroenterol. 2009;104(2):465-83. PMID: 7481535.
5. Korelitz BI. A history of immunosuppressive drugs in the treatment of inflammatory bowel disease: origins at The Mount Sinai Hospital. Mt Sinai J Med. 2000;67(3):214-26. PMID: 10828907.
6. U.S. Food and Drug Administration. New Drug Application & Biologic License Application Efficacy Supplements (Approved CY 2008) Web Page. www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/EfficacySupplementApprovals/UCM081900.pdf. Accessed June 2011.
7. Institute of Medicine. Initial National Priorities for Comparative Effectiveness Research. Web Page. www.iom.edu/Reports/2009/ComparativeEffectivenessResearchPriorities.aspx. June 2009.
8. Lin MV, Blonski W, Lichtenstein GR. What is the optimal therapy for Crohn's disease: step-up or top-down? Expert Rev Gastroenterol Hepatol. 2010;4(2):167-80. PMID: 20350264.
9. D'Haens GR. Top-down therapy for Crohn's disease: rationale and evidence. Acta Clin Belg. 2009;64(6):540-6. PMID: 20101879.
10. Lichtenstein GR, Hanauer SB, Kane SV, et al. Crohn's is not a 6-week disease: lifelong management of mild to moderate Crohn's disease. Inflamm Bowel Dis. 2004;10 Suppl 2:S2-10. PMID: 15475770.

11. Doherty G, Bennett G, Patil S, et al. Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst Rev. 2009;(4):CD006873. PMID: 19821389.

12. Higgins J. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.2.The Cochrane Collaboration; 2008.

13. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-84. PMID: 9764259.

14. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Pubication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2011. Chapters available at www.effectivehealthcare.gov.

15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88. PMID: 3802833.

16. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. PMID: 12958120.

17. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-101. PMID: 7786990.

18. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34. PMID: 9310563.

19. Irvine EJ. Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality-of-life instrument for adult patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1999;28(4):S23-7. PMID: 10204520.

20. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med. 2007;26(1):53-77. PMID: 16596572.

21. Hernandez AV, Walker E, Ioannidis JP, et al. Challenges in meta-analysis of randomized clinical trials for rare harmful cardiovascular events: the case of rosiglitazone. Am Heart J. 2008;156(1):23-30. PMID: 18585493.

22. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the effective health-care program. J Clin Epidemiol. 2010;63(5):513-23. PMID: 19595577.

23. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999;340(18):1398-405. PMID: 10228190.

24. Gordon FH, Lai CW, Hamilton MI, et al. A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 integrin in active Crohn's disease. Gastroenterology. 2001;121(2):268-74. PMID: 11487536.

25. Sands BE, Kozarek R, Spainhour J, et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. Inflamm Bowel Dis. 2007;13(1):2-11. PMID: 17206633.

26. Hunder GG, McDuffie FC. Effect of intra-articular hydrocortisone on complement in synovial fluid. J Lab Clin Med. 1972;79(1):62-74. PMID: 4621416.

27. O'Donoghue DP, Dawson AM, Powell-Tuck J, et al. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. Lancet. 1978;2(8097):955-7. PMID: 81986.

28. Winship DH, Summers RW, Singleton JW, et al. National Cooperative Crohn's Disease Study: study design and conduct of the study. Gastroenterology. 1979;77(4 Pt 2):829-42. PMID: 38175.

29. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989;96(3):804-10. PMID: 2644154.

30. Siffledeen JS, Siminoski K, Jen H, et al. Vertebral fractures and role of low bone mineral density in Crohn's disease. Clin Gastroenterol Hepatol. 2007;5(6):721-8. PMID: 17482522.

31. Orlando A, Colombo E, Kohn A, et al. Infliximab in the treatment of Crohn's disease: predictors of response in an Italian multicentric open study. Dig Liver Dis. 2005;37(8):577-83. PMID: 15886081.

32. Shah JA, Edwards CM, Probert CS. Should azathioprine and 5-aminosalicylates be coprescribed in inflammatory bowel disease? An audit of adverse events and outcome. Eur J Gastroenterol Hepatol. 2008;20(3):169-73. PMID: 18301295.

33. Campbell S, Ghosh S. Effective maintenance of inflammatory bowel disease remission by azathioprine does not require concurrent 5-aminosalicylate therapy. Eur J Gastroenterol Hepatol. 2001;13(11):1297-301. PMID: 11692054.

34. Levine A, Weizman Z, Broide E, et al. A comparison of budesonide and prednisone for the treatment of active pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2003;36(2):248-52. PMID: 12548062.

35. Markowitz J, Grancher K, Kohn N, et al. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. Gastroenterology. 2000;119(4):895-902. PMID: 11040176.

36. Escher JC. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multicentre trial. Eur J Gastroenterol Hepatol. 2004;16(1):47-54. PMID: 15095852.

37. Cezard JP, Munck A, Mouterde O, et al. Prevention of relapse by mesalazine (Pentasa) in pediatric Crohn's disease: a multicenter, double-blind, randomized, placebo-controlled trial. Gastroenterol Clin Biol. 2009;33(1 Pt 1):31-40. PMID: 19118966.

38. Ruemmele FM, Lachaux A, Cezard JP, et al. Efficacy of infliximab in pediatric Crohn's disease: a randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. Inflamm Bowel Dis. 2009;15(3):388-94. PMID: 19023899.

39. Issenman RM, Atkinson SA, Radoja C, et al.Longitudinal assessment of growth, mineral metabolism, and bone mass in pediatric Crohn's disease. J Pediatr Gastroenterol Nutr. 1993;17(4):401-6. PMID: 8145096.

40. Saha MT, Ruuska T, Laippala P, et al. Growth of prepubertal children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1998;26(3):310-4. PMID: 9523867.

41. Levine A, Broide E, Stein M, et al. Evaluation of oral budesonide for treatment of mild and moderate exacerbations of Crohn's disease in children. J Pediatr. 2002;140(1):75-80. PMID: 11815767.

42. Thayu M, Denson LA, Shults J, et al. Determinants of changes in linear growth and body composition in incident pediatric Crohn disease. Gastroenterology. 2010 Aug;139(2):430-8. PMID: 20417635.

43. Alemzadeh N, Rekers-Mombarg LT, Mearin ML, et al. Adult height in patients with early onset of Crohn's disease. Gut. 2002;51(1):26-9. PMID: 12077087.

44. Sadowski DC, Bernstein CN, Bitton A, et al. Canadian Association of Gastroenterology Clinical Practice Guidelines: the use of tumour necrosis factor-alpha antagonist therapy in Crohn's disease. Can J Gastroenterol. 2009;23(3):185-202. PMID: 19319383.

45. Mayberry JF, Lobo A, Ford AC, et al. NICE clinical guideline (CG152): the management of Crohn’s disease in adults, children, and young people. Aliment Pharmacol Ther. 2013;37(2):195-203. PMID: 23151246.

46. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J. Crohn's Colitis. 2010;4(1):28-62. PMID: 21122489.

47. MacDonald JK, McDonald JW. Natalizumab for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2007;(1):CD006097. PMID: 17253580.

48. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2008;(1):CD006893. PMID: 18254120.

49. Lim WC, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev. 2010;(12):CD008870. PMID: 21154400.

50. Prefontaine E, Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2010;(6):CD000545. PMID: 20556747.

51. Patel V, Macdonald JK, McDonald JW, et al. Methotrexate for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2009;(4):CD006884. PMID: 19821390.

52. Seow CH, Benchimol EI, Griffiths AM, et al. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2008;(3):CD000296. PMID: 18646064.

53. Benchimol EI, Seow CH, Otley AR, et al. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009;(1):CD002913. PMID: 19160212.

54. Benchimol EI, Seow CH, Steinhart AH, et al. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2008;(2):CD006792. PMID: 18425970.

55. Talley NJ, Abreu MT, Achkar J-P, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. Am J Gastroenterol. 2011;106 Suppl 1:S2-25; quiz S26. PMID: 21472012.

56. Kandiel A, Fraser AG, Korelitz BI, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut. 2005;54(8):1121-5. PMID: 16009685.

57. Masunaga Y, Ohno K, Ogawa R, et al. Meta-analysis of risk of malignancy with immunosuppressive drugs in inflammatory bowel disease. Ann Pharmacother. 2007;41(1):21-8. PMID: 17200426.

Introduction

Background

Description of Disease

Crohn's disease is a type of inflammatory bowel disease. Other types of inflammatory bowel disease include ulcerative colitis and indeterminate colitis. Current medical science defines Crohn's disease as chronic full thickness inflammation that can occur anywhere in the gastrointestinal tract, but most often affects the small bowel and colon. Typical symptoms of Crohn's disease include abdominal pain, chronic diarrhea, and gastrointestinal bleeding. Crohn's disease affects between 400,000 and 600,000 North Americans.[1] Ten percent of Crohn's disease patients are children under the age of 17.[2]

Crohn's disease is an inappropriate immune response to intestinal microbes that is genetic in origin.[3] Key symptoms include focal ulcerations or acute and chronic inflammation, detected through endoscopy and biopsy, respectively.

The activity of Crohn's disease fluctuates over time. One study estimated that during the first 7 years after diagnosis, 20 percent of Crohn's disease patients will have active disease at least once each year, 67 percent will fluctuate between years of active disease and years in remission, and 13 percent will have no relapses after the initial disease episode.[4]

Crohn's disease frequently leads to complications that require surgical intervention. One of the most common complications of Crohn's disease is fibrotic narrowing of the intestines (stricture), which can lead to obstruction, collections of pus in the abdomen or around the rectum (abscess), and spontaneous rupture of the bowel contents through the skin or other organs (fistula). In a study based on a cohort from Olmsted County, Minn., half of all patients had experienced at least one intestinal complication within 10 years of diagnosis.[5] Two studies based on the same cohort reported that half of patients required at least one surgical resection within 10 years of diagnosis.[5]

Interventions To Treat Crohn's Disease

Dr. Burrill Crohn's initial description of this disease suggested that it could be cured with wide surgical resection. Research has since proven this to be false.[6] The current accepted treatment is to administer medications designed to stop the intestinal inflammation and prevent further complications. Physicians refer to patients who no longer have inflammation as being in remission. To maintain remission, patients must continue to use these drugs. However, in spite of the success of this form of treatment, some patients relapse with renewed disease activity and an increase of symptoms. We show these disease states in Figure 1.

There are four major classes of medications physicians have used to induce and maintain remission: biologics, immunomodulators, corticosteroids, and aminosalicylates. The aminosalicylate, sulfasalazine, and corticosteroids emerged in the mid-1900s. Immunomodulators (such as 6-mercaptopurine, azathioprine, and methotrexate) came out in the 1970s, although the use of these medications was not routine until the 1990s.[7] The Food and Drug Administration (FDA) approved the first biologic tumor necrosis factor-alpha (TNF-alpha) inhibitor, infliximab, for Crohn's disease in 1998. Additional FDA-approved biologics include the TNF-alpha inhibitors adalimumab and certolizumab pegol, and the cellular adhesion molecule alpha-4 integrin inhibitor natalizumab.[8]

Table 1 summarizes the Crohn's disease medications (biologics, immunomodulators, corticosteroids, and aminosalicylates) their mechanisms of action, and FDA approval status. Table 2 summarizes the black box warnings for safety for these medications.

Figure 1. Crohn's disease activity changes over time

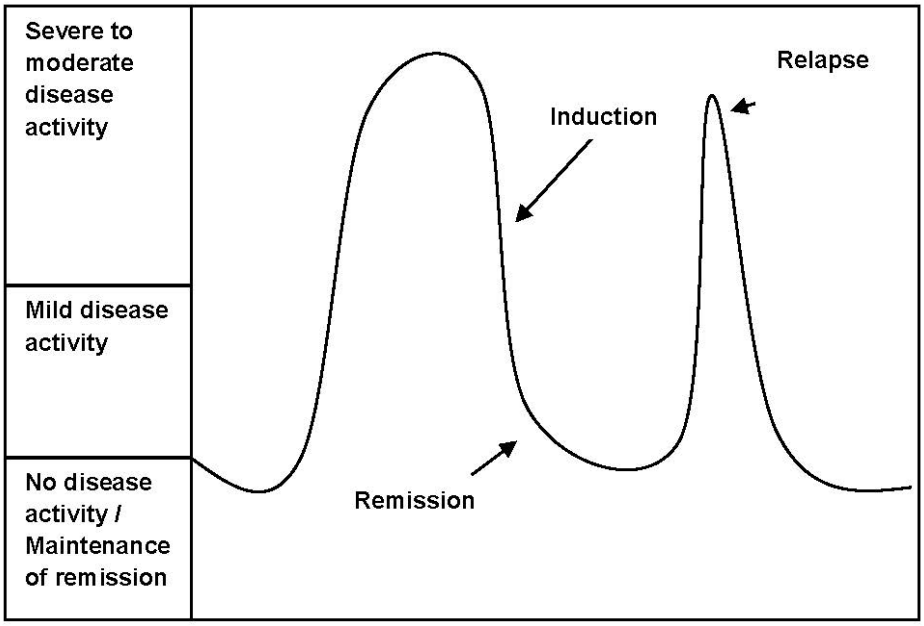


Table 1. List of medications used for treatment of Crohn's disease

Class	Generic Name	United States Trade Name	Route	Half-Life	Mechanism of Action	FDA Approved for CD in Adults	FDA Approved for CD in Children
Biologic	Adalimumab	Humira	Subcutaneous	10-18 days	TNF-alpha inhibitor	Yes	No
Biologic	Certolizumab pegol	Cimzia	Subcutaneous	~14 days	TNF-alpha inhibitor	Yes	No
Biologic	Infliximab	Remicade	Intravenous	7.7-9.5 days	TNF-alpha inhibitor	Yes	Yes
Biologic	Natalizumab	Tysabri	Intravenous	7-15 days	Prevents attachment of inflammatory immune cells to intestinal cell layers	Yes	No
Immunomodulator	Azathioprine	Azasan; Imuran	Oral, intravenous	5- hours	Purine synthesis inhibitor	No	No
Immunomodulator	6-mercaptopurine	Purinethol	Oral	1-2 hours	Purine synthesis inhibitor	No	No
Immunomodulator	Methotrexate	Methotrexate	Intravenous, oral	3-15 hours	Dihydrofolate reductase inhibitor	No	No
Corticosteroid	Prednisone, prednisolone, 6-methylpredisolone, hydrocortisone, budesonide	Cortef, Entocort	Oral, topical, intravenous	8-54 hours	Binds glucocorticoid receptors in cytoplasm, where it upregulates anti-inflammatory genes	No*	No
Aminosalicylate	Mesalamine	Asacol, Canasa, Pentasa, Lialda, Rowasa	Oral, rectal	2-15 hours	Unknown	No	No
Aminosalicylate	Sulfasalazine	Azulfidine	Oral	5-10 hours	Unknown	No	No

CD = Crohn's disease; FDA = Food and Drug Administration; TNF = tumor necrosis factor; U.S. = United States
*Budesonide is approved by the Food and Drug Administration for mild to moderate Crohn's disease.

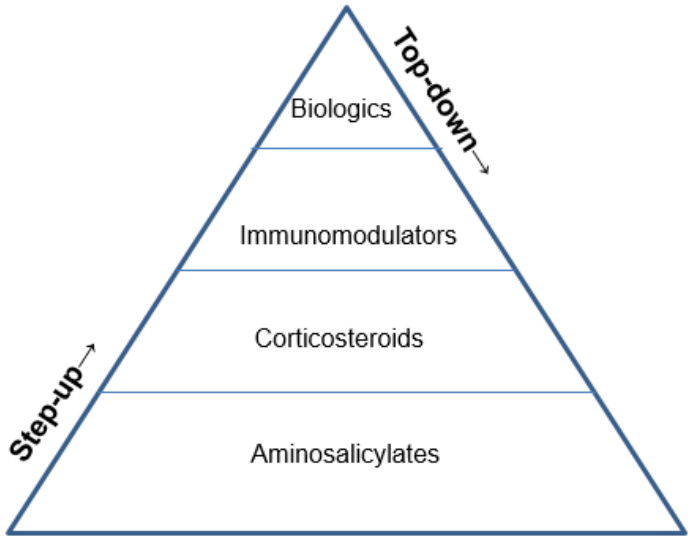
Table 2. Black box warnings listed on the prescribing information sheets of medications to treat Crohn's disease

Class	Generic Name	Boxed Warning
Biologic	Adalimumab	• Malignancies (lymphoma and other malignancies, some fatal) • Hepatosplenic T-cell lymphoma • Serious infections (hospitalization, death, tuberculosis, bacterial sepsis, invasive fungal infections, opportunistic infections)
Biologic	Certolizumab pegol	• Malignancies (lymphoma and other malignancies, some fatal) • Serious infections (hospitalization, death, tuberculosis, bacterial sepsis, invasive fungal infections, opportunistic infections)
Biologic	Infliximab	• Malignancies (lymphoma and other malignancies, some fatal) • Hepatosplenic T-cell lymphoma • Serious infections (hospitalization, death, tuberculosis, bacterial sepsis, invasive fungal infections, opportunistic infections)
Biologic	Natalizumab	• Progressive multifocal leukoencephalopathy
Immunomodulator	Azathioprine	• Malignancies (post-transplant lymphoma and hepatosplenic T-cell lymphoma)
Immunomodulator	Methotrexate	• Fetal death and/or congenital anomalies • Reduced elimination in patients with impaired renal function, ascites, or pleural effusions • Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity • Hepatotoxicity, fibrosis, and cirrhosis • Lung disease • Diarrhea and ulcerative stomatitis • Malignant lymphomas • Tumor lysis syndrome • Severe, occasionally fatal, skin reactions • Potentially fatal opportunistic infections • Soft tissue necrosis and osteonecrosis
Immunomodulator	6-mercaptopurine	No black box warnings
Corticosteroid	Prednisone, prednisolone, 6-methylpredisolone, hydrocortisone, budesonide	No black box warnings
Aminosalicylate	Sulfasalazine	No black box warnings
Aminosalicylate	Mesalamine	No black box warnings

Current Controversies in the Treatment of Crohn's Disease

One of the Institute of Medicine's priorities for comparative effectiveness research is to compare algorithms for Crohn's disease treatment that introduce biologics at different time points in the disease course.[9] Another treatment that warrants study is the use of biologics in combination with immunomodulators. Some research has suggested that improved long-term outcomes result from using immunomodulators and biologics early ("top-down therapy"), as opposed to using them after a patient has undergone prolonged steroid therapy ("step-up therapy") (Figure 2).[10] Science needs to weigh the benefits of this early treatment approach against the risks of increased immunosuppression, including lymphoma,[11] and the expense and harms of over-treating patients who will not receive an intestinal resection (40 percent) and patients who will not have aggressive, disabling disease (70 percent).[1] The major challenge and focus of current research is to arrest the natural progression of disease while minimizing adverse events and interventions, such as surgeries.[12]

Figure 2. Treatment pyramid for patients with Crohn's disease



Treatment Guidelines and Meta-Analyses on the Management of Crohn's Disease

When evidence-based research is sparse, treatment guidelines for the management of Crohn's disease often combine evidence-based medicine with expert panel review. In the United States, the American College of Gastroenterology, the American Gastroenterological Association, and the American Society of Colon and Rectal Surgeons publish management guidelines for Crohn's disease.[8 13-18] The treatment guidelines point to controversial areas in need of future research including: treatments to achieve long-term remission; the benefits and harms of step-up versus top-down treatment strategies; and optimizing the use of biologic agents, given that other treatments are effective at managing disease for large number of patients. This report addresses these aims.

Previous Systematic Reviews

Meta-analyses have compared individual medications with placebo but few have compared medications to each other. There are 43 high-quality meta-analyses for Crohn's disease that have compared biologics, immunomodulators, corticosteroids, and aminosalicylates with placebo. Eighteen of these are from the Cochrane Collaboration.

A recent high-quality meta-analysis of randomized control trials published through February 2009 examined the efficacy of treatments after surgical resection, but did not report on the quality of life effects.[19] Few meta-analyses reported quality of life, although quality of life remains a high priority topic for patients.

The central question for patients and their caretakers is the comparison of medications to each other at relevant time points in the natural progression of disease. This report focuses on these questions and includes the comparison of combinations of medications.

Scope of the Evidence Report and Key Questions

As displayed in Figure 3, the purpose of this review is to give clinicians a comprehensive comparison of the effectiveness and safety of biologics, immunomodulators, corticosteroids, and aminosalicylates in the treatment of Crohn's disease. The specific Key Questions (KQs) of interest are:

KQ1: What is the comparative effectiveness of therapies alone or in combination used to induce remission in adults and children with active Crohn's disease?

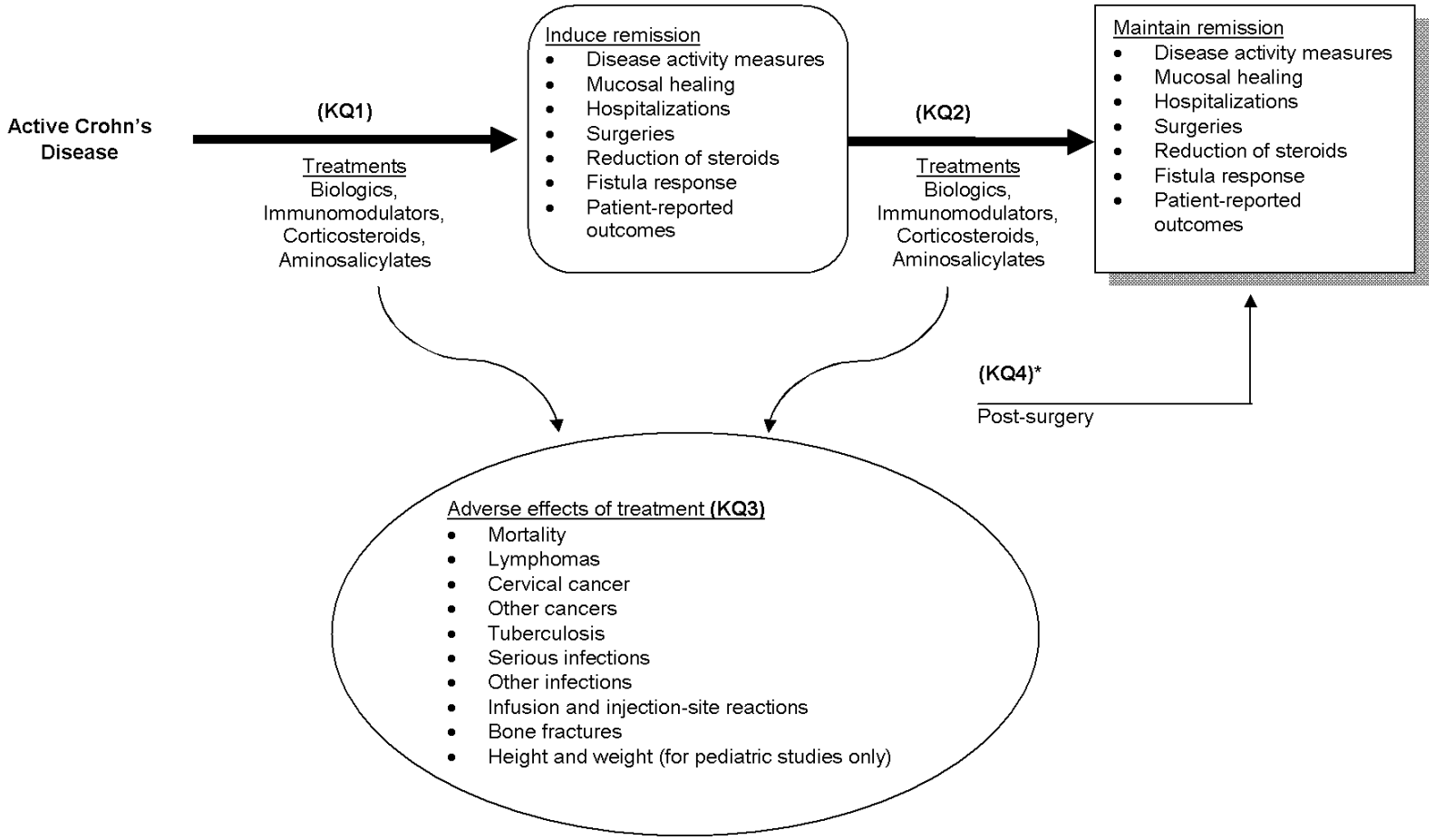
KQ2: What is the comparative effectiveness of therapies alone or in combination used to maintain remission in adults and children with inactive Crohn's disease?

KQ3: What is the comparative safety of therapies alone or in combination used in adults and children with Crohn's disease in terms of minimizing short- and long-term adverse effects?

KQ4: What is the comparative effectiveness of agents used to prevent post-operative recurrence in Crohn's disease as pertains to patient-reported outcomes?

For each KQ, we aimed to evaluate specific outcomes as listed in Table 3. Table 4 lists the disease activity indexes and disease-specific quality of life instruments the studies commonly used.

Figure 3. Analytic framework for assessing the comparative effectiveness and safety of pharmacologic therapies for Crohn's disease



KQ = Key Question
Note: KQ1: comparative effectiveness in inducing remission; KQ2: comparative effectiveness in maintaining remission; KQ3: comparative safety; KQ4: comparative effectiveness of treatments for post-surgical patient-reported outcomes
*For KQ4, the only examined endpoint is patient-reported outcomes.

Table 3. List of outcomes considered for each Key Question on the comparative effectiveness and safety of medications for treatment of Crohn's disease

Key Question	Outcomes
KQ1	• Disease activity measures (remission, CDAI, PCDAI, HBI, or other disease activity measurements) • Mucosal healing (presence of ulcers, CDEIS) • Hospitalizations • Surgeries • Reduction of steroids • Fistula response (complete or partial fistula closure or other measure of perianal disease) • Patient-reported outcomes (health-related quality of life, IBDQ, days of work or school missed)
KQ2	• Disease activity measures (relapse, CDAI, PCDAI, HBI, or other disease activity measurements) • Mucosal healing (presence of ulcers, CDEIS) • Hospitalizations • Surgeries • Reduction of steroids • Fistula response (fistula recurrence or other measure of perianal disease) • Patient-reported outcomes (health-related quality of life, IBDQ, days of work or school missed)
KQ3	• Mortality • Lymphomas • Cervical cancer • Other cancers • Tuberculosis • Serious infections • Other infections • Infusion- and injection-site reactions • Bone fractures • Height and weight (for pediatric studies only)
KQ4	• Patient-reported outcomes (health-related quality of life, IBDQ, days of work or school missed)

CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity; HBI = Harvey-Bradshaw Index; IBDQ = Inflammatory Bowel Disease Questionnaire; KQ = Key Question; PCDAI = Pediatric Crohn's Disease Activity Index

Note: KQ1: comparative effectiveness in inducing remission; KQ2: comparative effectiveness in maintaining remission; KQ3: comparative safety; KQ4: comparative effectiveness of treatments for post-surgical patient-reported outcomes

Table 4. List of disease activity indexes and disease-specific quality of life instruments

Measure or Instrument	Range of Total Scores	Higher Scores Indicate
Crohn's Disease Activity Index	0 to 600	More severe disease activity
Pediatric Crohn's Disease Activity Index	0 to 100	More severe disease activity
Harvey-Bradshaw Index	0 to 19	More severe disease activity
Crohn's Disease Endoscopic Index of Severity	0 to 44	More severe disease activity
Inflammatory Bowel Disease Questionnaire	32 to 224	Better quality of life

Methods

A patient with Crohn's disease nominated this topic because she was frustrated by the lack of consensus among physicians about her treatment options after surgical resection. Her experience reflects the general lack of consensus about pharmacologic therapies for the management of Crohn's disease. Our Evidence-based Practice Center established a team and a work plan to develop this evidence report. The project involved recruiting Key Informants and technical experts, formulating and refining the Key Questions (KQs), performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review and public comment.

Topic Development

At the beginning of the project, we recruited a panel of Key Informants to give input on the selection and refinement of the KQs. The Key Informants included a patient with Crohn's disease, clinician-investigators having experience in research on treatment of Crohn's disease, and a pharmaceutical company representative. Our draft KQs appeared on the Agency for Healthcare Research and Quality (AHRQ) Web site for public comment in March 2010.

Assessing input from Key Informants, representatives of AHRQ, and public comments, we developed the KQs that we listed in the Scope and Key Questions section of the Introduction. The final KQs focus on the comparative effectiveness and safety of individual and combined therapies for Crohn's disease (including biologics, immunomodulators, corticosteroids, and aminosalicylates) in terms of: (1) induction of remission, (2) maintenance of remission, (3) adverse effects, and (4) patient-reported outcomes after surgical resection.

We drafted a protocol to address our KQs. We then recruited a panel of technical experts, which included the Key Informants, an epidemiologist, and a pediatric gastroenterologist. With input from the Technical Expert Panel and representatives from AHRQ, we finalized the protocol.

Search Strategy

We searched the following databases for primary studies for the dates shown in parentheses: MEDLINE® (1966 through June 2011), Embase® (1974 through June 2011), and the Cochrane Central Register of Controlled Trials (Issue 2, 2011). We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject heading (MeSH) terms and text words of key articles identified a priori (Appendix A).

To identify additional studies, we reviewed the following material from the Evidence-based Practice Center's Program's Scientific Resource Center:

- Medical and/or statistical reviews of adalimumab, certolizumab pegol, infliximab, natalizumab, hydrocortisone, prednisone, prednisolone, and mesalamine from the Food and Drug Administration (FDA) Web site,
- Health Canada Product Monographs for adalimumab, certolizumab pegol, infliximab, natalizumab, azathioprine, 6-mercaptopurine, methotrexate, hydrocortisone, and 6-methylprednisolone,
- Public registries of clinical trials, including the Clinical Study Results Web site (www.clinicalstudyresults.org) and ClinicalTrials.gov (www.clinicaltrials.gov).

We also reviewed the reference lists of each included article and relevant review articles.

To assess the risk of two serious rare complications of treatment for Crohn's disease, hepatosplenic T-cell lymphoma and primary multifocal leukoencephalopathy, we supplemented the primary search strategy by also searching for cases reported to the FDA's Adverse Event Reporting System.

We downloaded the results of the searches and imported into ProCite® version 5 (ISI ResearchSoft, Carlsbad, Calif.). We scanned for exact article duplicates, author/title duplicates, and title duplicates using the duplication check feature in ProCite®. From ProCite, we uploaded the articles to DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based software package developed for systematic review data management. We used this database to track the search results at the levels of title review, abstract review, article inclusion/exclusion, and data abstraction.

Study Selection

Two independent reviewers conducted title scans. To eliminate the title at this level, both reviewers had to agree that it was ineligible (Appendix B, Title Review Form). If they disagreed, we promoted the article to the next level. We designed the title review to capture as many studies as possible that potentially reported on the efficacy or safety of therapies for the management of Crohn's disease.

Two investigators reviewed abstracts independently, and we excluded articles if both investigators agreed that the article met one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 5 and the Abstract Review Form in Appendix B). We resolved differences between investigators regarding abstract inclusion or exclusion through consensus adjudication.

When reviewers promoted articles on the basis of abstract review, additional independent investigators determined if they should be included for data abstraction (Appendix B, Article Review Form). We resolved differences regarding article inclusion through consensus adjudication. A third reviewer audited a random sample of abstract and article reviews to ensure consistency in the reviewing process.

To evaluate induction and maintenance of remission (KQ1 and KQ2), we included only randomized controlled trials (RCTs). Both placebo-controlled and head-to-head trials were eligible. We did not include trials that only examined the same medication administered at different time points or at different dosages. We chose clinically important and patient-centered outcomes of interest for KQ1 and KQ2.

To evaluate the safety of treatment (KQ3), we included RCTs and observational studies. We chose specific safety outcomes based on the severity of the outcome, impact on quality of life, and potential for safety to differ by medication class. We selected clinical outcomes a priori for inclusion. All RCTs that reported on safety were eligible. Observational studies were eligible if they reported a relevant comparison group with clear numerators and denominators for each group or an effect estimate or p-value for a safety outcome by medication use. Because of the rarity and severity of hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy, we included all study types (including case reports) for these outcomes.

A rigorously conducted systematic review[19] had recently assessed the efficacy and safety of medications to maintain remission of Crohn's disease after intestinal resection. Instead of duplicating that work, we limited the focus of KQ4 to the comparative effects of medications on patient-reported outcomes as reported in RCTs and observational studies. The previous review did not include these outcomes.

Table 5. Inclusion and exclusion criteria for identifying eligible studies

Category	Inclusion Criteria	Exclusion Criteria
Population and condition	• Included studies of human subjects of all ages with Crohn's disease • Sensitivity analysis for KQ3 included patients with any inflammatory bowel disease	• Excluded studies if they included only pregnant women
Interventions	• Included studies evaluating a Crohn's disease medication of interest (see Table 1) or combination of medications of interest compared with each other or with placebo	
Comparisons	• Included studies that had a comparison group, where the comparison was either a medication or combination of medications of interest or placebo	• Excluded studies that compared a medication of interest to a medication not of interest (such as antibiotics or fish oil supplements) • Excluded studies that only evaluated the same medication given at different times or at different doses
Outcomes	• Included the following outcomes for KQ1 and KQ2: Crohn's Disease Activity Index (CDAI), mucosal healing, hospitalizations, surgery, corticosteroid reduction, fistula response, and patient-reported outcomes representing quality of life • Included the following harms of medications for KQ3: mortality, lymphomas, cervical cancer, other cancers, tuberculosis, serious infections, other infections, infusion and injection-site reactions, bone fractures, and, in children, height and weight as indicators of growth • Included the following patient-reported outcomes for KQ4: generic and disease-specific quality of life indices (e.g., IBDQ), and days of work or school missed	• Excluded studies that did not apply to the KQs
Type of study	• Included studies with any sample size from any year that met all other criteria • Included only RCTS for KQ1 and KQ2 • Included all study designs with a comparison group, for KQ3 and KQ4, including: RCTs, prospective and retrospective cohorts, crossover studies, case-control studies and cross-sectional studies • Included all study types (including case reports) for hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy because these outcomes are very rare and frequently fatal	• Excluded articles not written in English, articles with no original data (reviews, editorials, comments, letters), and abstract-only publications

IBDQ = Inflammatory Bowel Disease Questionnaire; KQ = Key Question; RCT = randomized controlled trial

Data Abstraction

We used a systematic approach for extracting data to minimize the risk of bias in this process. We created and pilot tested standardized forms for data extraction. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

For all articles, reviewers extracted information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, sex, race/ethnicity, duration of Crohn's disease, smoking status, disease severity, and disease location), eligibility criteria,

interventions (e.g., route of administration and dosing), outcome measures and the method of ascertainment, and the results of each outcome (including measures of variability).

For KQ1, KQ2, and KQ4, we abstracted data on the following time points: (1) first time point after randomization or study start; (2) 12 to 16 weeks after randomization or study start; (3) 48 to 54 weeks after randomization or study start; and (4) last prespecified time point. For KQ3, we abstracted data for the last reported time point only.

We abstracted information on subgroup analyses to understand how disease characteristics could modify the relationship between medications and remission. We considered the following characteristics for subgroup analyses a priori because these characteristics are most clinically relevant: elevated baseline markers of inflammation (including C-reactive protein rates), baseline mucosal lesions, medications used at randomization (baseline), prior medication exposure, disease duration, disease location, and prior Crohn's disease-related surgery. We only reported on studies that performed and reported a statistical test for interaction.

Study investigators double reviewed each article for data abstraction. We abstracted all information into the DistillerSR database (Evidence Partners, Ottawa, Canada). The second reviewer confirmed the first reviewer's data abstraction within DistillerSR for completeness and accuracy. We formed reviewer pairs to include personnel with both clinical and methodological expertise. Reviewers abstracted relevant data from figures when they were not available in text or table format. Reviewers entered comments into the system whenever applicable. We used the DistillerSR database to maintain the data, as well as to generate Excel files, which we used to create detailed evidence tables and summary tables.

Quality Assessment

We used study quality assessment to help us understand differences in results between studies. We used different quality assessment tools for RCTs and observational studies. For RCTs, we based the dual independent review of article quality on the Cochrane Collaboration's Risk of Bias Tool[20] and supplemented with items from the Evidence-based Practice Center Program's "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[21] The quality assessment for RCTs included items on: (1) adequate allocation sequence generation, (2) adequate allocation concealment, (3) blinding, (4) incomplete outcome data, (5) other potential threats to validity, (6) pharmaceutical support, (7) company involvement in the design, conduct, or reporting of the study, (8) loss to followup, and (9) an overall rating of the quality assessment. We assessed the overall study quality in the following manner:

- **Good (low risk of bias).** These studies had the least bias, and we considered the results valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.

- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.[21]

For observational studies, we selected quality concepts from the Downs and Black quality checklist[22] and added items from the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[21] We assessed observational studies based on the following criteria: (1) clear description of main outcome to be measured, (2) clear description of patient characteristics, (3) clear description of interventions of interest, (4) clear description of the distributions of principal confounders, (5) recruitment of the different intervention groups from the same population, (6) handling of loss to followup, (7) adequate adjustment for confounding, (8) pharmaceutical support, (9) company involvement in the design, conduct, or reporting of the study, and (10) overall study quality. We assessed the overall study quality as "good" if the responses for items 1 to 7 were all "yes"; "fair" if most of the responses to items 1 to 4 were "yes" and all of the responses to items 5 to 7 were "yes"; and "poor" if none of the responses to items 1 to 4 were "yes" or any of the responses to items 5 to 7 were "no" or "unable to determine."

Reviewers resolved differences in study quality through consensus adjudication. We reported only the adjudicated quality scores.

Applicability

Throughout the report, we discuss the applicability of the bodies of evidence in terms of the degree to which the study population (e.g., age, race, disease severity), interventions (e.g., dosing, frequency, duration), comparisons, outcomes, timings, and settings are typical of the treatment of individuals with Crohn's disease.

Data Analysis and Synthesis

For each KQ, we created a set of detailed evidence tables containing all information abstracted from eligible studies. We conducted meta-analyses when there were sufficient data (at least three trials) and when studies were sufficiently homogenous with respect to the population characteristics, intervention, comparison, outcome, timing, and setting. When possible for KQ1 (induction of remission), we decided to conduct meta-analyses at the following clinically relevant time points:

- 2 to 4 weeks (using the earliest available time point)
- 12 to 16 weeks (using earliest available time point)
- Last reported time point

For KQ2 (maintenance of remission), we conducted meta-analyses at these time points:

- 48 to 54 weeks
- Last reported time point

For KQ3 (adverse effects), the meta-analyses used the last reported time point available from at least three studies.

For studies amenable to pooling with meta-analyses, we calculated pooled relative risks using a DerSimonian and Laird random effects model.[23] We identified heterogeneity among the

trials in all the meta-analyses using: (1) a chi-squared test with a significance level of alpha less than or equal to 0.10, and (2) an I-squared statistic with a value greater than 50 percent indicating substantial heterogeneity.[24] We did not report the pooled result if we found substantial heterogeneity. We conducted sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimate. For all meta-analyses, we conducted formal tests for publication bias using Begg's[25] and Eggers tests,[26] including an evaluation of the asymmetry of funnel plots for each comparison of interest. We conducted all meta-analyses using STATA (Intercooled, version 9.2, StataCorp, College Station, Texas).

When we were unable to pool trials for an outcome, we calculated and displayed risk ratios with 95 percent confidence intervals for the individual studies. For KQ1 and KQ2, we considered a difference to be clinically meaningful when there was an absolute difference of 10 percentage points in the outcome between the groups compared, even when the difference was not statistically significant (p-value less than 0.05). Similarly, we did not report statistically significant relationships unless there was a clinically meaningful difference. For the Crohn's Disease Endoscopic Index of Severity, we defined a clinically meaningful difference as an absolute difference in change from baseline of greater than 5 points.[27] For the Inflammatory Bowel Disease Questionnaire (the most commonly employed outcome for patient-reported outcomes), we used an absolute difference in change from baseline of 17 points or greater.[28] We considered a clinically significant reduction in corticosteroids to be a between-group difference of 10 mg in the average daily dose. Since there is no reference standard, we chose a 10 mg difference because it represents at least a 25 percent reduction in a typical steroid dose and patients are often tapered in 5 mg increments. In terms of adverse effects, when a study did not report an effect estimate, we calculated a Peto odds ratio if the combined number of events in each arm was greater than 5.[29,30] We also calculated incidence rate ratios for person-time data when the authors did not report an effect estimate, or when the reported effect estimate appeared to contradict the reported events per person-time. We did not specify a standard for a clinically meaningful difference in the adverse events because the absolute rate was rare for most of the adverse events.

Grading the Strength of Evidence

At the completion of our review, we graded the best available evidence addressing KQ1 through KQ4 by modifying the evidence grading scheme recommended by the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[31] We applied evidence grades to the bodies of evidence for each outcome of each intervention comparison by population (e.g., adult or pediatric). If necessary, we created separate evidence grades by time point.

We assessed the potential for bias by ranking study designs with RCTs higher than observational studies. We also evaluated the consistency, directness, and precision of the effects. We rated the body of evidence as "consistent" if most of the studies showed the same direction of effect. We rated the consistency of a single study as "unknown," without downgrading the strength of evidence. We rated the body of evidence as "direct" if most studies directly measured the outcome of interest. We based our evaluation of precision on the clinically meaningful difference.

We classified the strength of evidence pertaining to KQ1 through KQ4 into four grades:

- "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect)

- "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate)
- "low" grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate)
- "insufficient" grade (evidence is unavailable; no studies observed)

We gave a high grade for strength of evidence to comparisons that included RCTs and a moderate grade to studies that did not include RCTs. For each domain (risk of bias, consistency, directness, precision, and other limitations) that was not optimal (moderate/high risk of bias, inconsistent, indirect, imprecise, or other limitations), we downgraded strength of evidence one level.

Peer Review and Public Commentary

We invited experts in adult and pediatric gastroenterology and individuals representing stakeholder and user communities to provide external peer review of this comparative effectiveness review. AHRQ and an associate editor also provided comments. AHRQ posted the draft report on its Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a "disposition of comments report" that will be made available 3 months after AHRQ posts the final comparative effectiveness review on the AHRQ Web site.

Results

Search Results

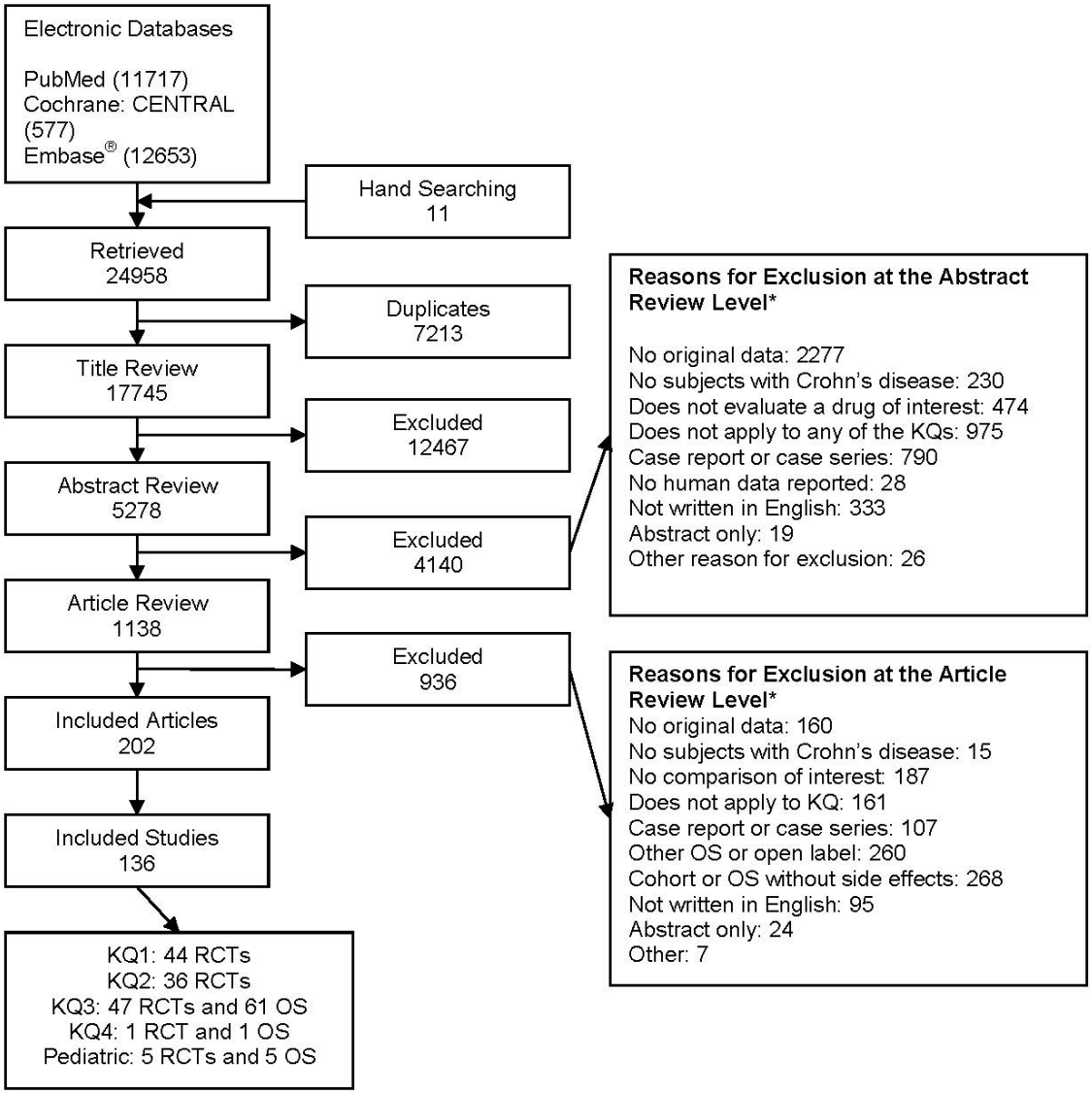
From our searches, we retrieved 17,745 articles after removing duplicates (Figure 4). After title and abstract review, we decided 1,138 articles were potentially relevant to review, and we retrieved the full articles. We included a total of 136 studies in this review (see Appendix C for list of articles excluded at the full text level).

We reported the results of our systematic review according to Key Question, and separated adults from children. For the efficacy results, we organized the results for each Key Question by medication class--natalizumab, TNF-alpha inhibitor, thiopurines, methotrexate, corticosteroids, or aminosalicylates. When a study compared multiple medication classes, we began with the first medication in our list of medication classes, which we organized according to the top-down approach in the treatment pyramid (Figure 2).

Within each medication class, we reported the study design, population characteristics, key points, strength of evidence (SOE) grading, and the outcomes results. We created key points for each comparison that had at least moderate SOE or a clinically meaningful difference. In the key points we presented the conclusion, the pooled relative risk or the range of risk differences, the placebo rates, and the SOE. We also presented the relative risk and risk differences in the SOE tables. We arranged the outcomes results by comparison. We presented the monotherapy placebo-controlled trials first, followed by monotherapy head-to-head comparisons, combination therapy placebo-controlled trials, combination therapy versus monotherapy comparisons, and combination therapy head-to-head comparisons. We reported the results of those meta-analyses for which we were able to combine clinically homogenous studies. When we were unable to pool the results, we presented the data in tables.

We organized the safety results by outcome then by medication class. We reported the subgroup analyses at the end of each Key Question. Detailed evidence tables are found in Appendix D.

Figure 4. Summary of the literature search (number of articles)



CENTRAL = Central Register of Controlled Trials; KQ = Key Question; OS = observational study; RCT = randomized controlled trial

*The total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.

Key Question 1: Effectiveness of Therapies To Induce Remission in Adults

In order for trials to qualify for KQ1, patients had to have active disease at the time of randomization so that we could identify the effect of treatments to induce remission. In the Methods we describe induction of remission as occurring within 16 weeks of treatment for active disease. From a clinical perspective, later time points are better measures of maintenance of remission after induction. Regardless, the trials that reported on outcomes after 16 weeks are included in this section rather than in KQ2 because we distinguished KQ1 from KQ2 based on the disease activity at randomization.

Table 6 summarizes the evidence grades and specific conclusions for each comparison. Details of the evidence grades are included in the Results and in Appendix D, Table 1.

Table 6. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission*

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 2-4	Disease Activity Measure Weeks 12-16	Disease Activity Measure After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Natalizumab vs. placebo 12 weeks	Favors natalizumab; Moderate SOE	Favors natalizumab; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 12* Favors neither; Moderate SOE
Natalizumab + infliximab vs. infliximab 10 weeks	Favors neither; Low SOE	Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 10* Favors neither; Low SOE
Adalimumab vs. placebo 4 weeks	*>160 mg sc dose* Favors adalimumab; High SOE *≤80 mg sc dose* Favors neither; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 4* Favors neither; Low SOE	*Week 4* Favors neither; High SOE
CP vs. placebo 26 weeks	Favors neither; Low SOE	Favors neither; Low SOE	*Week 26* Favors CP; Low SOE	Insufficient	Insufficient	Insufficient	*Week 26* Favors neither; Low SOE	*Week 12 and Week 26* Favors neither; Low SOE
Infliximab vs. placebo 12 weeks	Favors infliximab; Moderate SOE	Favors infliximab; Low SOE	Insufficient	*Week 4* Favors infliximab; Low SOE	Insufficient	Insufficient	*Week 6* Favors infliximab; High SOE	*Week 4* Favors infliximab; Moderate SOE
Infliximab vs. azathioprine 26 weeks	Insufficient	Favors infliximab; Moderate SOE	*Week 26* Favors infliximab; Moderate SOE	Week 26 Favors infliximab; Low SOE	Insufficient	Insufficient	Insufficient	*Week 26* Favors neither; Moderate SOE
Infliximab + azathioprine vs. infliximab 26 weeks	Insufficient	Favors infliximab + azathioprine; Moderate SOE	*Week 26* Favors infliximab + azathioprine; Moderate SOE	*Week 26* Favors infliximab + azathioprine; Low SOE	Insufficient	Insufficient	Insufficient	*Week 26* Favors neither; Moderate SOE

Table 6. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 2-4	Disease Activity Measure Weeks 12-16	Disease Activity Measure After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Infliximab + azathioprine vs. azathioprine 26 weeks	Insufficient	Favors infliximab + azathioprine; Moderate SOE	*Week 26* Favors infliximab + azathioprine; Moderate SOE	*Week 26* Favors infliximab + azathioprine; Low SOE	Insufficient	Insufficient	Insufficient	*Week 26* Favors neither; Moderate SOE
Infliximab + azathioprine vs. steroids 104 weeks	Insufficient	Insufficient	*Week 104* Favors neither; Low SOE	*Week 104* Favors infliximab + azathioprine; Low SOE	Insufficient	Insufficient	Insufficient	*Week 10* Favors infliximab + azathioprine; Low SOE
Infliximab + methotrexate vs. infliximab 48 weeks	Favors infliximab + methotrexate; Low SOE	Favors infliximab + methotrexate; Low SOE	*Week 48* Favors infliximab + methotrexate; Low SOE	Insufficient	Insufficient	*Week 48* Favors infliximab + methotrexate; Low SOE	Insufficient	*Week 4 and Week 8* Favors infliximab + methotrexate; Low SOE
Thiopurines vs. placebo 104 weeks	Favors neither; Low SOE	Insufficient	*Week 17-38* Favors neither; Low SOE *Week 104* Favors 6-MP; Low SOE	Insufficient	Insufficient	*Week 16* Favors neither; Low SOE	*Week 17* *Favors neither; Low SOE* *Week 104* Favors 6-MP; Low SOE	*Week 16* Favors neither; Low SOE‡
Thiopurines vs. oral methotrexate 38 weeks	Favors neither; Low SOE	Favors neither; Low SOE	*Week 38* Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Thiopurines vs. steroids 17 weeks	Favors steroids; Low SOE	Favors steroids; Low SOE	*Week 17* Favors steroids; Low SOE	Insufficient	Insufficient	Insufficient	*Week 17* Favors steroids; Low SOE	Insufficient

Table 6. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 2-4	Disease Activity Measure Weeks 12-16	Disease Activity Measure After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Thiopurines vs. ASA 30 weeks	Favors ASA; Low SOE	Favors neither; Low SOE	*Week 17* Favors neither; Low SOE *Week 30* Favors 6-MP; Low SOE	Insufficient	Insufficient	Insufficient	*Week 17* Favors neither; Low SOE	Insufficient
Thiopurines (IV + oral) vs. thiopurines (oral) 16 weeks	Insufficient	Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Thiopurines + steroids vs. steroids 28 weeks	Insufficient	Favors thiopurines + steroids; Low SOE	*Week 28* Favors thiopurines + steroids; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Thiopurines + steroids vs. methotrexate (IV, oral) + steroids 26 weeks	Insufficient	Favors neither; Low SOE	*Week 26* Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	*Week 26* Favors methotrexate + steroids; Low SOE	Insufficient
Methotrexate (oral) vs. placebo 38 weeks	Favors neither; Low SOE	Favors neither; Low SOE	*Week 38* Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Methotrexate (oral) vs. ASA 30 weeks	Insufficient	Insufficient	*Week 30* Favors methotrexate; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table 6. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 2-4	Disease Activity Measure Weeks 12-16	Disease Activity Measure After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire[†]
Methotrexate (IM) + prednisone vs. prednisone 16 weeks	Insufficient	Favors methotrexate; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 16* Favors neither; Moderate SOE
Budesonide vs. placebo 16 weeks	*≥9 mg daily* Favors budesonide; Moderate SOE *<9 mg daily* Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 8* No difference; Low
6-methyl-prednisolone or prednisone vs. placebo 104 weeks	*6-methyl-prednisolone* Favors 6-methylprednisolone; Low SOE *Prednisone* Favors neither; Low SOE	Favors steroids; Low SOE	*Week 104* Favors steroids; Low SOE	Insufficient	Insufficient	Insufficient	*Week 17* Favors steroids; Low SOE	Insufficient
Budesonide vs. other steroids 10 weeks	Favors neither; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 8* Favors neither; Moderate SOE
Steroids vs. ASA 104 weeks	Favors steroids; Low SOE	Favors steroids; Low SOE	*Week 104* Favors steroids; Low SOE	Insufficient	Insufficient	Insufficient	*Week 17* Favors neither; Low SOE	*Week 2* Favors steroids; High SOE[§] *Week 12* Favors neither; Moderate SOE[§]

Table 6. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 2-4	Disease Activity Measure Weeks 12-16	Disease Activity Measure After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
6-methyl-prednisolone + sulfasalazine vs. placebo 104 weeks	Favors 6-methyl-prednisolone + sulfasalazine; Low SOE	Favors 6-methyl-prednisolone + sulfasalazine; Low SOE	*Week 104* Favors 6-methyl-prednisolone + sulfasalazine; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. steroids 104 weeks	Favors neither; Low SOE	Favors neither; Low SOE	*Week 104* Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. sulfasalazine 104 weeks	Favors steroids + sulfasalazine; Low SOE	Favors steroids + sulfasalazine; Low SOE	*Week 104* Favors steroids + sulfasalazine; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Mesalamine vs. placebo 17 weeks	Favors neither; Low SOE	*≥3.2 g daily* Favors mesalamine; Low SOE *<3.2 g daily* Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Sulfasalazine vs. placebo 104 weeks	Favors neither; Low SOE	Favors sulfasalazine; Low SOE	*Week 104* Favors sulfasalazine; Low SOE	Insufficient	Insufficient	Insufficient	*Week 17* Favors sulfasalazine; Low SOE	Insufficient

6-MP = 6-mercaptopurine; ASA = aminosalicylates; CP = certolizumab pegol; g = grams; IM = intramuscular; IV = intravenous; mg = milligrams; SC = subcutaneous; SOE = strength of evidence; Steroid = corticosteroids; vs = versus

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

*All other potential comparisons of therapies and outcomes were graded as insufficient because there were no eligible trials. The evidence for the last reported measure is provided for disease activity after 16 weeks, mucosal healing, hospitalizations and surgeries, reduction of steroids, fistula response and patient-reported outcomes.

†Patient-reported outcomes were measured by the Inflammatory Bowel Disease Questionnaire except where indicated by a footnote.

‡Outcome based upon "feeling better" in 2 trials

§Used McMaster University Quality of Life scale

Natalizumab

Four trials randomized 1,523 participants to compare the efficacy of natalizumab with placebo to induce remission among patients with active Crohn's disease at randomization. Three trials[32-34] evaluated natalizumab versus placebo, while one trial[35] evaluated the combination of natalizumab and infliximab versus infliximab and placebo.

Study Design

The trials defined active disease as a CDAI greater than 150 or 220 (Appendix D, Evidence Table 2).[32-35] All trials used randomized double-blind designs. The treatment group received 300 mg natalizumab administered intravenously three times at baseline, 4 and 8 weeks in three trials,[32,33,35] whereas one trial[34] evaluated a single 3 mg/kg baseline dose of intravenous natalizumab. One trial took place at multiple centers in the United States,[35] another occurred in two centers in the United Kingdom,[34] and the others were multinational.[32,33] All trials except one[34] reported the starting year of enrollment, with the first year of enrollment ranging from 2001 to 2004.[32,33,35] The outcome definition was consistent in all trials; CDAI less than 150 was the definition of remission. Inclusion criteria were generally consistent including the exclusion of patients with abscesses and obstructive symptoms consistent with strictures in three trials.[32,33,35] Medication exclusions included previous treatment with a TNF-alpha inhibitor within three months[32,33] and treatment with methotrexate, cyclosporine, or tacrolimus within 3 to 4 months of enrollment.[34] Elevated C-reactive protein ([CRP] > 2.7 mg/L) was an inclusion criteria in one trial[32] based on subgroup analysis findings from a previous trial.[33] All trials permitted patients to use aminosalicylates, antibiotics, corticosteroids, and thiopurines during the trial if they had been on a stable dose of the medication prior to baseline.

Population Characteristics

The populations tended to be similar across trials with the exception of sex, disease location, and concomitant medication use (Appendix D, Evidence Table 3). The proportion of male participants in each trial group ranged from 3 to 63 percent. Three trials reported on race[32,34,35] with white patients comprising between 85 and 95 percent of participants. Two trials[32,33] reported smoking status, with smokers comprising 19 and 24 percent of participants. Mean age at enrollment was between 34 and 39 years. The mean duration of disease was between 8.5 and 12.5 years. All trials[32-35] reported disease location including ileal location (ranging between 15 and 40 percent), ileocolonic location (ranging between 28 and 56 percent), and colonic location (ranging between 22 and 30 percent). One trial[34] also reported that 30 percent of patients had perianal disease at baseline. All trials reported baseline CDAI, with mean CDAI ranging from 244 to 330 points. Concurrent medication use during the trial was as follows: aminosalicylates use ranged between 37 and 75 percent,[32-35] antibiotic use ranged from 5 to 19 percent,[32,33,35] corticosteroids use ranged between 27 and 75 percent, methotrexate use ranged from 3 to 4 percent,[33,35] and thiopurine use ranged between 17 and 33 percent.[33-35] Two trials[32,33] reported prior use of TNF-alpha inhibitors in 38 and 50 percent of participants. In the trial of combination therapy, all patients were unresponsive to infliximab as part of the inclusion criteria.[35]

Key Points

Table 7 summarizes the strength of evidence for the trials evaluating natalizumab in terms of remission induction. We found at least moderate strength of evidence or a clinically meaningful difference for the following comparisons and outcomes:

- Natalizumab was more effective than placebo in inducing a remission at weeks 2 to 4 (pooled relative risk [RR], 1.5; 95% confidence interval [CI], 1.1 to 2.0; placebo rate, 8 to 16 percent). (Strength of evidence [SOE]: Moderate)
- Natalizumab was more effective than placebo in inducing a remission at week 12 (absolute risk difference [RD], 9 to 13 percent; placebo rate, 0 to 31 percent). (SOE: Low)
- Natalizumab (300 mg intravenous every 4 weeks) and placebo did not differ in improving patient-reported outcomes at week 12 (absolute between-group difference in change in mean Inflammatory Bowel Disease Questionnaire [IBDQ] from baseline, 12 points; placebo change in IBDQ, 15 points). (SOE: Moderate)

Table 7. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating natalizumab to induce remission among patients with active Crohn's disease at randomization

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Natalizumab vs. placebo – wks 2-4	Disease activity measures	3 (1444)[32-34]	Medium	Consistent	Direct	Precise	Favors natalizumab Pooled RR, 1.5; 95% CI 1.1 to 2.0; placebo rate, 8% to 16% SOE: Moderate
Natalizumab vs. placebo–wk 12	Disease activity measures	3 (1444)[32-34]	Medium	Consistent	Direct	Imprecise	Favors natalizumab RD range, 9% to 13%; placebo rate, 0% to 31% SOE: Low
Natalizumab vs. placebo–wk 12	Patient-reported outcomes	2 (539)[32 34]	Medium	Consistent	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 12 pts; placebo change in IBDQ, 15 pts SOE: Moderate
Natalizumab + infliximab vs. infliximab–wks 2 and 10	Disease activity measures	1 (79)[35]	Low	Unknown (single trial)	Indirect Combination no longer used in clinical practice	Imprecise	Favors neither RD across time points, 7% to 8%; infliximab rate, 7% to 30% SOE: Low
Natalizumab + infliximab vs. infliximab–wk 10	Patient-reported outcomes	1 (79)[35]	Low	Unknown (single trial)	Indirect Combination no longer used in clinical practice	Imprecise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 2 pts; infliximab change in IBDQ, 17 pts SOE: Low

CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; pts = points; RD = absolute risk difference; RR = relative risk; SOE = strength of evidence; vs. = versus; wk = week

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

Scores for the Inflammatory Bowel Disease Questionnaire range from 32 to 224, with higher scores indicating better quality of life.[36]

Monotherapy Versus Placebo

Three trials randomized 1,444 participants and compared the efficacy of natalizumab with placebo to induce remission among patients with active Crohn's disease at randomization.[32-34]

Natalizumab Versus Placebo

Disease Activity Measures

Table 8 summarizes the efficacy of each treatment in inducing remission for the 2- to 4-week and 12- to 16-week time periods of interest (see also Appendix D, Table 4).

When we pooled the week 2 to 4 data, natalizumab was more likely to induce remission compared with placebo (pooled RR, 1.5; 95% CI, 1.1 to 2.0) (Figure 5). The RDs ranged from 4 percent to 31 percent. The small trial was the only trial to meet our clinically meaningful threshold when examined alone.[34] The largest trial was the only trial to be statistically significant, but did not meet the clinically meaningful threshold when examined alone.[32] There was no statistical heterogeneity across the three trials (I-squared, 0) and no trial significantly influenced results. At week 12, natalizumab was more likely to induce remission than placebo according to our clinically meaningful threshold in two of the three trials,[32,34] and one of these trials reported a statistically significant result.[32] A meta-analysis was not performed for week 12 because the dose was 3 mg/kg delivered at baseline only in one trial,[34] compared with 300 mg delivered 3 times in 8 weeks in the other two trials.[32,33]

Patient-Reported Outcomes

Two of the trials[32,34] reported the IBDQ score for 539 participants. In one trial of 509 participants, mean IBDQ rose from 124 to 151 points in the natalizumab group and from 123 to 138 points in the placebo group at week 12 ($P < 0.001$); which did not meet our clinically meaningful threshold of a 17-point difference between groups.[32] The other trial reported a 19-point change from baseline to week 4 in the natalizumab group, but did not report the corresponding difference in the placebo patients other than to say that the placebo group did not have a statistically significant change over time.[34]

Combination Therapy Versus Monotherapy

Natalizumab and Infliximab Versus Infliximab Alone

Disease Activity Measures

One trial of 79 participants compared a combination of natalizumab and infliximab with infliximab and placebo among patients who had an elevated CDAI (greater than 150) despite initial infliximab.[35] There was not a clinically meaningful added benefit of the combination of intravenous natalizumab with infliximab compared with infliximab alone to induce remission at 2 or 10 weeks. Table 8 summarizes the efficacy of each treatment in inducing remission for the time periods of interest (see also Appendix D, Table 4).

Patient-Reported Outcomes

At 10 weeks, the mean IBDQ rose from 138 to 157 points in the group receiving a combination of infliximab and natalizumab, and from 133 to 150 points in the group receiving

infliximab and placebo.[35] The 2-point difference between groups did not meet the clinically meaningful threshold.

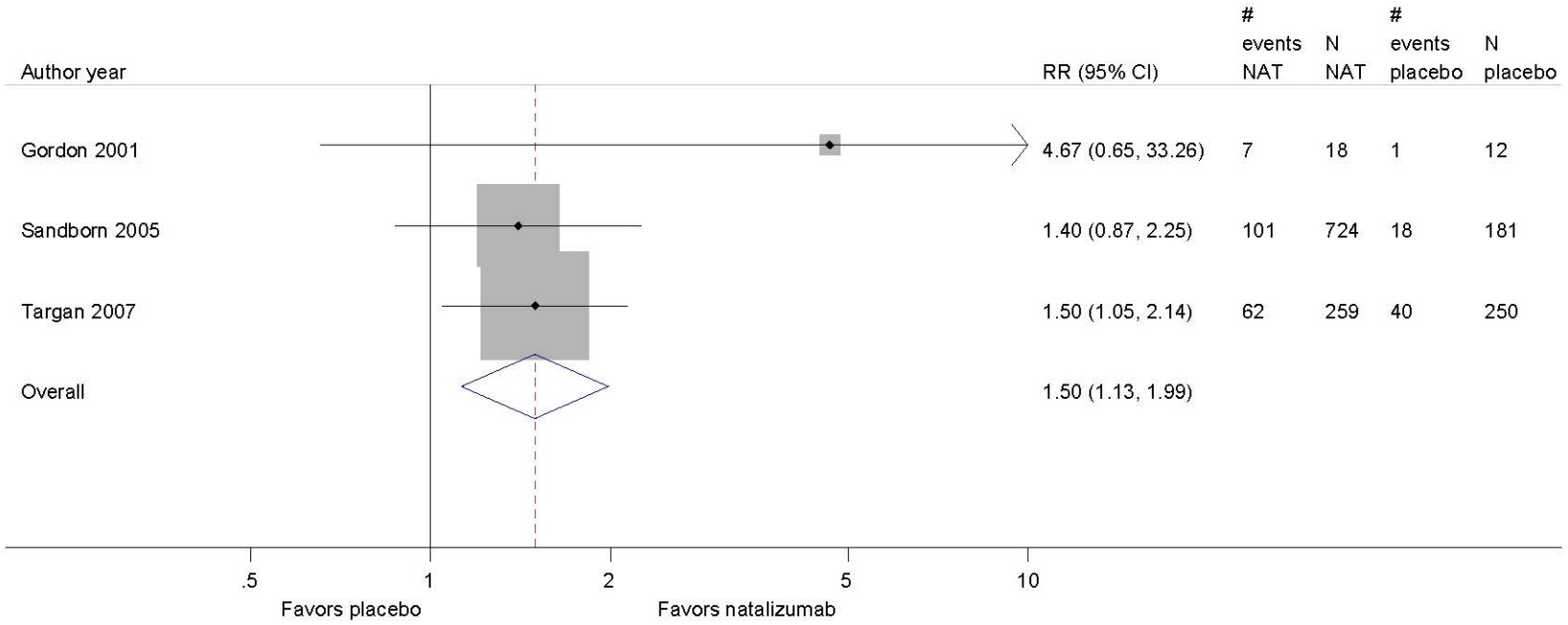
Table 8. Randomized controlled trials comparing the efficacy of natalizumab with placebo or another treatment to induce remission among patients with active Crohn's disease at randomization

Author, Year	Followup (Weeks)	Main Intervention (Dose), n	Comparison (Dose), n	Remission Rate (%) (CDAI<150)
Gordon, 2001[34]	2	Natalizumab (3 mg/kg IV once), 18	Placebo, 12	39% vs. 8%
	12	Natalizumab (3 mg/kg IV once), 18	Placebo, 12	11% vs. 0%
Sandborn, 2005[33]	2	Natalizumab (300 mg IV every 4 wks until wk 8), 724	Placebo, 181	14% vs. 10%
	12	Natalizumab (300 mg IV every 4 wks until wk 8), 724	Placebo, 181	40% vs. 31%
Targan, 2007[32]	4	Natalizumab (300 mg IV every 4 wks until wk 8), 259	Placebo, 250	24% vs. 16%*
	12	Natalizumab (300 mg IV every 4 wks until wk 8), 259	Placebo, 250	38% vs. 25%*
Sands, 2007[35]	2	Natalizumab (300 mg IV at wks 0, 4, 8) + infliximab (5 mg/kg IV at wk -2 and 6), 52	Infliximab (5 mg/kg IV at wk -2 and 6), 27	15% vs. 7%
	10	Natalizumab (300 mg IV at wks 0, 4, 8) + infliximab (5 mg/kg IV at wk -2 and 6), 52	Infliximab (5 mg/kg IV at wk -2 and 6), 27	37% vs. 30%

CDAI = Crohn's Disease Activity Index; IV = intravenous; mg = milligrams; mg/kg = milligrams per kilogram; vs. = versus; wk = week

*Trial reported $P < 0.01$.

Figure 5. Pooled relative risk of inducing remission as measured by a Crohn's Disease Activity Index less than 150 at weeks 2 to 4 comparing natalizumab with placebo



CI = confidence interval; NAT = natalizumab; RR = relative risk

Note: Boxes indicate individual trial point estimates. The box size denotes the weight of the trial, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each trial. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q=1.36 with 2 degrees of freedom (p=0.51)

I-squared statistic = 0%

TNF-Alpha Inhibitors

Twelve trials evaluated the effectiveness of a TNF-alpha inhibitor as monotherapy or in combination with another drug to induce remission. Seven trials compared TNF-alpha inhibitor monotherapy with placebo: two evaluated adalimumab,[37,38] four evaluated certolizumab pegol,[39-42] and two evaluated infliximab.[43,44] One trial compared infliximab with azathioprine.[45] Four trials compared TNF-alpha inhibitor combination therapy with another therapy: two trials[45,46] compared a combination of infliximab and a thiopurine with thiopurine alone, while one trial[45] compared a combination of infliximab and azathioprine with infliximab alone. Schroder et al. studied the combination of infliximab and methotrexate versus infliximab alone.[47] Another trial compared the combination of infliximab and azathioprine with corticosteroids.[48] One trial compared a TNF-alpha inhibitor as an early treatment prior to using a thiopurine with TNF-alpha inhibitor treatment after the use of a thiopurine and corticosteroids, which is often called a top-down versus step-up approach.[48]

Study Design

All 12 trials were RCTs, although two did not blind investigators or patients (Appendix D, Evidence Table 2).[47,48] The design characteristics and inclusion criteria were not homogeneous, with the exception of the trial locations. Ten trials were multinational, one was a multicenter European trial[46] and one took place at a single center in Europe.[47] Enrollment started between 1995 and 2008. The median time under trial per participant was 12 weeks (range, 4 weeks to 104 weeks). All trials included adults, although one trial enrolled patients as young as 16[48] rather than 18 years of age. Disease activity inclusion criteria included a minimum CDAI of 150 to 220 and no greater than 450,[37-43,45,46,48] steroid dependency,[46,47] thiopurine resistance or intolerance,[47] or at least one active abdominal or perianal fistula.[44] Other common disease activity related exclusions included abscess,[39,40,42,44-46] symptomatic strictures,[37-46,48] and previous surgery within 6 months.[37,38,42,45] Remission was defined as a CDAI less than 150, with three trials using an even more stringent definition of remission including a CDAI less than 150 combined with the absence of corticosteroids.[45,46,48]

Medication inclusion criteria were common. One trial aimed to enroll recently diagnosed patients by restricting the population to people with a disease duration of 4 years or less who had not been treated with corticosteroids, thiopurines, or biologics.[48] Another trial allowed prior corticosteroid use but excluded patients with prior thiopurine or biologic use.[45] Six trials allowed prior corticosteroid and thiopurine use but excluded previous users of biologics.[37,42-44,46,47] Lack of response or dependency on corticosteroids was required in two trials[46,47] while failure to respond to thiopurines was required in at least some of the patients in these trials.[46,47] Previous response followed by loss of response or intolerance to infliximab was required in one trial.[38] Patients who had an adverse reaction or no response to TNF-alpha inhibitor were excluded in two trials.[39,40] All trials that did not restrict patients based on the following medications permitted patients to use aminosalicylates, antibiotics, corticosteroids, and thiopurines during the trial if they had been on a stable dose of the medication prior to baseline.

Population Characteristics

The trials randomized 2,932 patients (Appendix D, Evidence Table 3). The participants of trials were demographically similar except for the disease duration at randomization, disease location, and use of other medications during the trial. By trial group, males comprised 0[41] to

63[35] percent of the participants. Only two trials[45,48] commented on race; the percentage of whites ranged from 84 to 99 percent. Smoking was reported in five trials[37-39,45,48] and ranged from 31 to 43 percent. Mean age at enrollment ranged from 29 to 40 years. Mean or median duration of disease ranged between 2 weeks and 13.6 years. In terms of disease location, ileal only location ranged between 7 and 68 percent, ileocolonic location between 5 and 68 percent, and colonic location between 9 and 36 percent. All but one trial[40] reported baseline CDAI. Mean CDAI ranged from 251 to 330 points. Among trials that did not exclude or require prior use of the medications or randomize patients to the medication, concomitant medication use included the following ranges, as recorded at baseline in at least one group of a trial: aminosalicylate use between 0[41] and 75[34] percent, antibiotic use between 5[32] and 19[44] percent, budesonide or corticosteroid use between 11[45] and 88[47] percent, and methotrexate or thiopurine between 0[41] and 56[38] percent.

Key Points

Table 9 summarizes the strength of evidence for the trials evaluating TNF-alpha inhibitors to induce remission. We found at least moderate strength of evidence or a clinically meaningful difference for the following areas:

- TNF-alpha inhibitors (infliximab, adalimumab, and certolizumab pegol) were more effective than placebo in inducing a remission at week 2 (pooled RR, 1.8; 95% CI, 1.4 to 2.4; placebo rate, 4 to 16 percent). (SOE: Moderate)
- One dose of adalimumab (at 160 mg) was more effective than placebo in inducing a remission at week 2 (absolute RD, 10 to 15 percent; placebo rate, 6 to 14 percent). (SOE: High)
- One dose of adalimumab (at 80 mg or less) did not differ from placebo in inducing a remission at week 2 (absolute RD, 0 to 6 percent; placebo rate, 14 percent). (SOE: High)
- Adalimumab and placebo did not differ in improving patient-reported outcomes at week 4 (absolute between-group difference in change in mean IBDQ from baseline, 2 to 15 points; placebo change in IBDQ, 15 points). (SOE: High)
- Certolizumab pegol was more effective than placebo in inducing a remission at week 26 (absolute RD, 11 percent; placebo rate, 18 percent). (SOE: Low)
- One dose of infliximab was more effective than placebo in inducing a remission at week 2 (absolute RD, 16 to 34 percent; placebo rate, 4 percent). (SOE: Moderate)
- One dose of infliximab was more effective than placebo in inducing a remission at week 12 (absolute RD, 10 to 22 percent; placebo rate, 8 percent). (SOE: Low)
- Infliximab was more effective than placebo in achieving mucosal healing at week 4 (absolute between-group difference in the change from baseline in Crohn's Disease Endoscopic Index of Severity [CDEIS] score, 7.7; placebo difference, 0.9). (SOE: Low)
- Infliximab was more effective than placebo in healing fistulas at week 6 in patients with actively draining fistulas (absolute RD in fistula closure, 25 to 42 percent; placebo rate, 13 percent). (SOE: High)
- Infliximab was more effective than placebo in improving patient-reported outcomes at week 4 (absolute between-group difference in change in mean IBDQ from baseline, 31 points; placebo change in IBDQ, 5 points). (SOE: Moderate)
- Infliximab (5 mg/kg induction and maintenance) was more effective than azathioprine (2.5 mg/kg/day) in inducing a steroid-free remission at weeks 10 and 26 (absolute RD

across time points, 13 to 14 percent; azathioprine rate, 24 to 30 percent). (SOE: Moderate)

- Infliximab (5 mg/kg induction and maintenance) was more effective than azathioprine (2.5 mg/kg daily) in achieving mucosal healing at week 26 (absolute RD in percentage of patients who achieved absence of mucosal ulcers, 13 percent; azathioprine rate, 17 percent). (SOE: Low)
- Infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5 mg/kg/day) did not differ in improving patient-reported outcomes at 26 weeks (absolute between-group difference in change in mean IBDQ from baseline, 9 points; azathioprine change in IBDQ, 31 points). (SOE: Moderate)
- A combination of infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5 mg/kg/day) was more effective than infliximab (5 mg/kg induction and maintenance) alone in inducing a steroid-free remission at weeks 10 and 26 (absolute RD across time points, 10 to 13 percent; infliximab alone rate, 37 to 44 percent). (SOE: Moderate)
- A combination of infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5 mg/kg daily) was more effective than infliximab (5 mg/kg induction and maintenance) and placebo in achieving mucosal healing at week 26 (absolute RD in percentage of patients who achieved absence of mucosal ulcers, 14 percent; infliximab and placebo rate, 30 percent). (SOE: Low)
- The combination of infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5 mg/kg/day) and the combination of infliximab (5 mg/kg induction and maintenance) and placebo did not differ in improving patient-reported outcomes at 26 weeks (absolute between-group difference in change in mean IBDQ from baseline, 5 points; infliximab change in IBDQ, 40 points). (SOE: Moderate)
- A combination of infliximab (5 mg/kg induction and maintenance) and a thiopurine (azathioprine or 6-mercaptopurine) was more effective than a thiopurine alone in inducing a steroid-free remission at weeks 10 to 12 and weeks 24 to 26 (absolute RD across time points, 12 to 30 percent; azathioprine rate, 24 to 44 percent). (SOE: Moderate)
- A combination of infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5 mg/kg daily) was more effective than azathioprine (2.5 mg/kg daily) and placebo in achieving mucosal healing at week 26 (absolute RD in percentage of patients who achieved absence of mucosal ulcers, 27 percent; azathioprine and placebo rate, 17 percent). (SOE: Low)
- The combination of infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5 mg/kg/day) and the combination of azathioprine (2.5 mg/kg/day) and placebo did not differ in improving patient-reported outcomes at 26 weeks (absolute between-group difference in change in mean IBDQ from baseline, 14 points; azathioprine change in IBDQ, 31 points). (SOE: Moderate)
- A combination of infliximab (5 mg/kg induction only) and azathioprine (2-2.5 mg/kg/day) was more effective than corticosteroids alone in achieving mucosal healing at week 104 (absolute RD in percentage of patients with no ulcers, 43 percent; corticosteroid rate, 30 percent). (SOE: Low)
- A combination of infliximab (5 mg/kg induction only) and azathioprine (2-2.5 mg/kg/day) was more effective than corticosteroids alone in improving patient-reported

outcomes at week 10 (absolute between-group difference in change in mean IBDQ from baseline, 22 points; corticosteroid change in IBDQ, 37 points). (SOE: Low)

- A combination of infliximab (5 mg/kg at weeks 0 and 2) and methotrexate (intravenous weekly to week 5, then oral) was more effective than infliximab (5 mg/kg at weeks 0 and 2) alone in inducing a remission at weeks 2, 12, and 48 (absolute RD across time points, 17 to 39 percent; infliximab rate, 25 to 50 percent). (SOE: Low)
- A combination of infliximab (5 mg/kg at weeks 0 and 2) and methotrexate (intravenous weekly to week 5, then oral) was more effective than infliximab (5 mg/kg at weeks 0 and 2) alone in being able to discontinue steroids (reduction in prednisolone dose from baseline, 17 mg vs. 6 mg). (SOE: Low)
- A combination of infliximab (5 mg/kg at weeks 0 and 2) and methotrexate (intravenous weekly to week 5, then oral) was more effective than infliximab (5 mg/kg at weeks 0 and 2) alone in improving patient-reported outcomes at 4 and 8 weeks (absolute between-group difference in change in mean IBDQ from baseline, 22 points; infliximab alone change in IBDQ, 28 points). (SOE: Low)

Table 9. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating TNF-alpha inhibitors to induce remission among patients with active Crohn's disease at randomization

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
TNF vs. placebo–wk 2	Disease activity measures	7 (2208)[37-43]	Medium	Consistent	Direct	Precise	Favors TNF Pooled RR, 1.8; 95% CI, 1.4 to 2.4; placebo rate, 4 to 16% SOE: Moderate
Adalimumab vs. placebo (160 mg x 1) –wk 2	Disease activity measures	2 (475)[37 38]	Low	Consistent	Direct	Precise	Favors adalimumab RD, 10% to 15%; placebo rate, 6% to 14% SOE: High
Adalimumab vs. placebo (≦ 80 mg x 1) –wk 2	Disease activity measures	2 (223)[37]	Low	Unknown (single trial)	Direct	Imprecise	Favors neither RD, 0% to 6%; placebo rate, 14% SOE: Moderate
Adalimumab vs. placebo–wk 4	Fistula response	1 (32)[37]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD, -17% to 58%; placebo rate, 17% SOE: Low
Adalimumab vs. placebo–wk 4	Patient-reported outcomes	2 (624)[37 38]	Low	Consistent	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 2 to 15 pts; placebo change in IBDQ, 15 pts SOE: High
Certolizumab pegol vs. placebo–wk 2, 12-16	Disease activity measures	4 (1478)[39-42]	Medium	Inconsistent	Indirect IV formulation not presently approved[41]	Imprecise	Favors neither RD, -19% to 31%; placebo rate, 8% to 32% SOE: Low
Certolizumab pegol vs. placebo–wk 26	Disease activity measures	1 (331)[39]	High	Unknown (single trial)	Direct	Precise	Favors certolizumab pegol RD, 11%; placebo rate, 18% SOE: Low
Certolizumab pegol vs. placebo–wk 26	Fistula response	1 (107)[39]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD, -1%; placebo rate, 31% SOE: Low

Table 9. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating TNF-alpha inhibitors to induce remission among patients with active Crohn's disease at randomization (continued)

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Certolizumab pegol vs. placebo–wks 12, 26	Patient-reported outcomes	2 (954)[39 40]	High	Consistent	Indirect Single dose for induction not presently used in practice[40]	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline across time points, 5 to 11 pts; placebo change in IBDQ, 18 to 21 pts SOE: Low
Infliximab vs. placebo–wk 2	Disease activity measures	1 (106)[43]	Medium	Unknown (single trial)	Direct	Precise	Favors infliximab RD, 16% to 34%; placebo rate, 4% SOE: Moderate
Infliximab vs. placebo–wk 12	Disease activity measures	1 (106)[43]	High	Unknown (single trial)	Indirect Single dose for induction not presently used in practice	Imprecise	Favors infliximab RD, 10% to 22%; placebo rate, 8% SOE: Low
Infliximab vs. placebo–wk 4	Mucosal healing	1 (30)[49]	High	Unknown (single trial)	Direct	Precise	Favors infliximab Absolute between-group difference in the change from baseline in CDEIS, 7.7; placebo difference, 0.9 SOE: Low
Infliximab vs. placebo–wk 6	Fistula response	1 (94)[44]	Low	Unknown (single trial)	Direct	Precise	Favors infliximab RD, 25% to 42%; placebo rate, 13% SOE: High
Infliximab vs. placebo–wk 4	Patient-reported outcomes	1 (83)[43]	Medium	Unknown (single trial)	Direct	Precise	Favors infliximab Absolute between-group difference in change in mean IBDQ from baseline, 31 pts; placebo change in IBDQ, 5 pts SOE: Moderate

Table 9. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating TNF-alpha inhibitors to induce remission among patients with active Crohn's disease at randomization (continued)

Comparison	Outcome	Number of trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Infliximab vs. azathioprine–wks 10, 26	Disease activity measures	1 (339)[45]	Medium	Unknown (single trial)	Direct	Precise	Favors infliximab RD across time points, 13% to 14%; azathioprine rate, 24% to 30% SOE: Moderate
Infliximab vs. azathioprine–wk 26	Mucosal healing	1 (202)[45]	High	Unknown (single trial)	Direct	Precise	Favors infliximab RD in percentage of patients who achieved absence of mucosal ulcers, 13%; azathioprine rate, 17% SOE: Low
Infliximab vs. azathioprine–wk 26	Patient-reported outcomes	1 (339)[45]	Medium	Unknown (single trial)	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 9 pts; azathioprine change in IBDQ, 31 pts SOE: Moderate
Infliximab + azathioprine vs. infliximab–wks 10, 26	Disease activity measures	1 (338)[45]	Medium	Unknown (single trial)	Direct	Precise	Favors infliximab + azathioprine RD across time points, 10% to 13%; infliximab alone rate, 37% to 44% SOE: Moderate
Infliximab + azathioprine vs. infliximab–wk 26	Mucosal healing	1 (200)[45]	High	Unknown (single trial)	Direct	Precise	Favors infliximab + azathioprine RD in percentage of patients who achieved absence of mucosal ulcers, 14%; infliximab rate, 30% SOE: Low
Infliximab + azathioprine vs. infliximab–wk 26	Patient-reported outcomes	1 (338)[45]	Medium	Unknown (single trial)	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 5 pts; infliximab change in IBDQ, 40 pts SOE: Moderate

Table 9. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating TNF-alpha inhibitors to induce remission among patients with active Crohn's disease at randomization (continued)

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Infliximab + azathioprine vs. azathioprine–wks 10-12, 24-26	Disease activity measures	2 (393)[45 46]	Medium	Consistent	Direct	Precise	Favors infliximab + azathioprine RD across time points, 12% to 30%; azathioprine rate, 24% to 44% SOE: Moderate
Infliximab + azathioprine vs. azathioprine–wk 26	Mucosal healing	1 (216)[45]	High	Unknown (single trial)	Direct	Precise	Favors infliximab + azathioprine RD in percentage of patients who achieved absence of mucosal ulcers, 27%; azathioprine rate, 17% SOE: Low
Infliximab + azathioprine vs. azathioprine–wk 26	Patient-reported outcomes	1 (508)[45]	Medium	Unknown (single trial)	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 14 pts; azathioprine change in IBDQ, 31 pts SOE: Moderate
Infliximab + azathioprine vs. steroids–wk 104	Disease activity measures	1 (129)[48]	High	Unknown (single trial)	Indirect Single dose for induction not presently used in practice	Imprecise	Favors neither RD, 6%; corticosteroid rate, 49% SOE: Low
Infliximab+ azathioprine vs. steroids–wk 104	Mucosal healing	1 (49)[48]	High	Unknown (single trial)	Indirect Single dose for induction not presently used in practice	Precise	Favors infliximab + azathioprine RD in percentage of patients with no ulcers, 43%; steroid rate, 30% SOE: Low
Infliximab + azathioprine vs. steroids–wk 10	Patient-reported outcomes	1 (129)[48]	High	Unknown (single trial)	Indirect Single dose for induction not presently used in practice	Precise	Favors infliximab + azathioprine Absolute between-group difference in change in mean IBDQ from baseline, 22 pts; steroids change in IBDQ, 37 pts SOE: Low

Table 9. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating TNF-alpha inhibitors to induce remission among patients with active Crohn's disease at randomization (continued)

Comparison	Outcome	Number of Rrials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Infliximab + methotrexate vs. infliximab–wks 2, 12, 48	Disease activity measures	1 (19)[47]	High	Unknown (single trial)	Direct	Imprecise	Favors infliximab + methotrexate RD across time points, 17% to 39%; infliximab rate, 25% to 50% SOE: Low
Infliximab + methotrexate vs. infliximab–wk 48	Reduction of steroids	1 (13)[47]	High	Unknown (single trial)	Direct	Imprecise	Favors infliximab + methotrexate Reduction in prednisolone dose from baseline, 17 mg vs. 6 mg SOE: Low
Infliximab + methotrexate vs. infliximab–wk 4 and 8	Patient-reported outcomes	1 (19)[47]	High	Unknown (single trial)	Direct	Imprecise	Favors infliximab + methotrexate Absolute between-group difference in change in mean IBDQ from baseline, 22 pts; infliximab change in IBDQ, 28 pts SOE: Low

CDEIS = Crohn's Disease Endoscopic Index of Severity; CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; pts = points; RD = absolute risk difference; RR = relative risk; SOE = strength of evidence; TNF = tumor necrosis factor-alpha inhibitor; TPMT = thiopurine methyltransferase; vs. = versus; wk = week

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

Scores for the Inflammatory Bowel Disease Questionnaire (IBDQ) range from 32 to 224, with higher scores indicating better quality of life.[36] Scores for the Crohn's Disease Endoscopic Index of Severity (CDEIS) range from 0 to 44, with higher scores indicating more severe disease.

Monotherapy Versus Placebo

TNF-Alpha Inhibitor Versus Placebo

Disease Activity Measures

Seven RCTs compared a TNF-alpha inhibitor versus placebo and reported the percent of participants who achieved a CDAI less than 150 as the indicator of remission.[37-43] Combining the week 2 results for infliximab, adalimumab, and certolizumab pegol in a meta-analysis, TNF-alpha inhibitor was favored over placebo (RR, 1.8; 95% CI, 1.4 to 2.4; $P < 0.001$) (Table 10 and Figure 6). The RD ranged from 0 to 34 percent. No one trial significantly influenced results and there was not substantial statistical heterogeneity (I-squared, 19 percent). Previous use or response to a TNF-alpha inhibitor may explain the wide range of observed RD and this possibility was examined in separate meta-analyses. Among the four trials that allowed prior TNF-alpha inhibitor use, the RR was 2.1 (95% CI, 1.5 to 3.0) (Appendix E). An elevated RR of 1.5 (95% CI, 1.1 to 2.2; $P=0.03$) was observed in the three trials that excluded patients who previously received TNF-alpha inhibitor, and the finding was statistically significant (Appendix E).[37,42,43] The trial[38] that included only patients with a previous response to infliximab, found that 21 percent of adalimumab patients were in remission at week 2 compared with 6 percent of controls (RR, 3.6; 95% CI, 1.8 to 6.9) (Figure 6).

The adalimumab trials did not report results beyond week 4. For the 12 to 16 week analysis, only certolizumab pegol and infliximab had available data (Table 11). The initial remission was not sustained at 12 weeks in these trials. Placebo met the threshold for having a clinically meaningful difference compared with certolizumab pegol in one trial,[41] although the trial did not report that the difference was statistically significant. Infliximab met the standard for a clinically meaningful difference compared with placebo, but that finding was also not reported as statistically significant.[43] One reason for the lack of sustained remission from that observed at 2 weeks may be that infliximab and certolizumab pegol were given only at baseline in three of the four trials. However, the single trial that gave doses of certolizumab pegol beyond baseline did not find a clinically meaningful difference between certolizumab pegol and placebo at week 12 (RD, 6 percent), but certolizumab pegol had a 11 percent higher remission rate at week 26 (Table 12).[39]

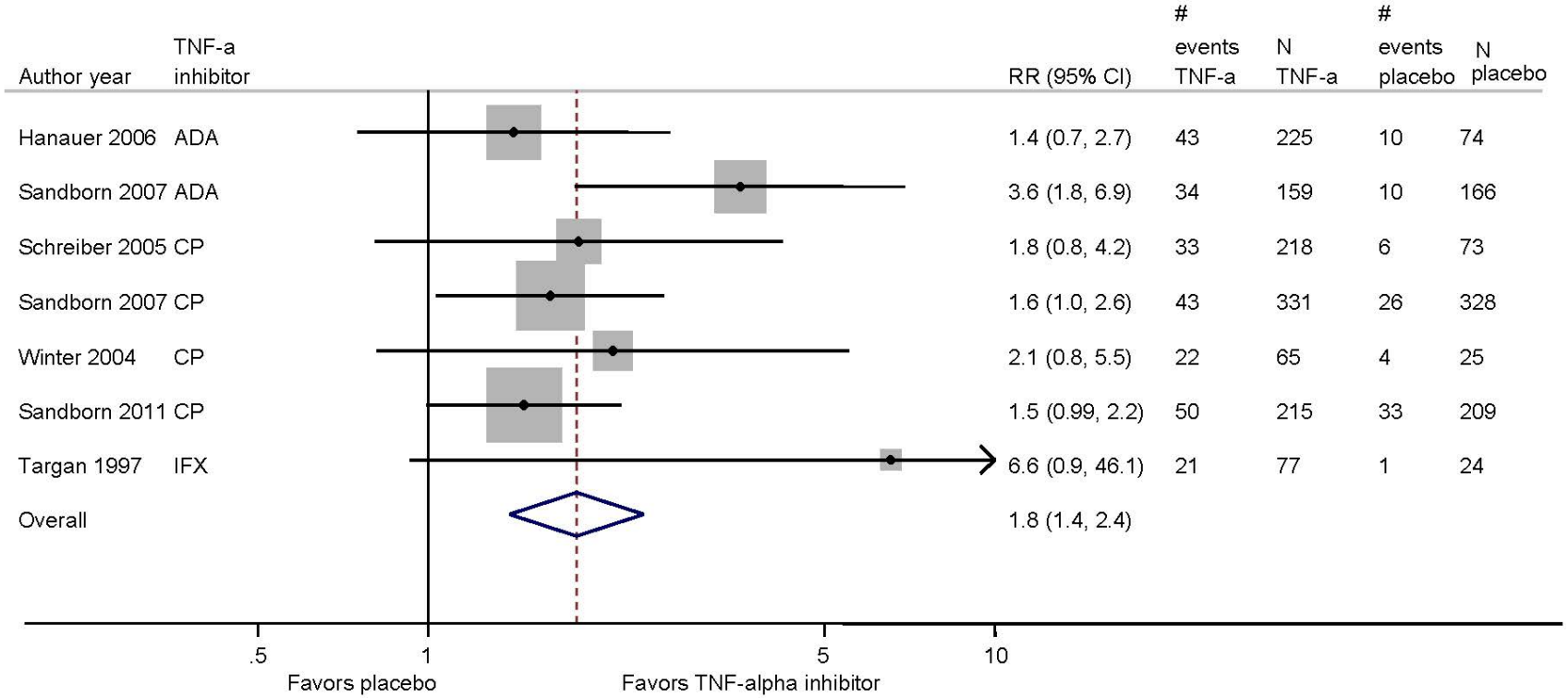
Table 10. Randomized controlled trials comparing the efficacy of TNF-alpha inhibitor therapy with placebo or another treatment to induce remission at week 2 among patients with active Crohn's disease at randomization

Author, Year	Main Intervention (Dose), n	Comparison (Dose), n	Remission Rate (%) (CDAI<150)
Hanauer, 2006[37]	Adalimumab (40 mg sc at week 0), 74	Placebo, 74	14% vs. 14%
	Adalimumab (80 mg sc at week 0), 75	Placebo, 74	20% vs. 14%
	Adalimumab (160 mg sc at week 0), 76	Placebo, 74	24% vs. 14%
Sandborn, 2007[38]	Adalimumab (160 mg sc at week 0), 159	Placebo, 166	21% vs. 6%*
Winter, 2004[41]	Certolizumab pegol (5 mg/kg IV once), 25	Placebo, 25	35% vs. 16%
	Certolizumab pegol (10 mg/kg IV once), 17	Placebo, 25	47% vs. 16%*
	Certolizumab pegol (20 mg/kg IV once), 23	Placebo, 25	20% vs. 16%
Schreiber, 2005[40]	Certolizumab pegol (100 mg sc at week 0), 74	Placebo, 73	18% vs. 8%
	Certolizumab pegol (200 mg sc at week 0), 72	Placebo, 73	10% vs. 8%
	Certolizumab pegol (400 mg sc at week 0), 72	Placebo, 73	18% vs. 8%
Sandborn, 2007[39]	Certolizumab pegol (400 mg sc at week 0), 331	Placebo, 328	13% vs. 8%
Sandborn, 2011[42]	Certolizumab pegol (400 mg sc at week 0), 223	Placebo, 215	23% vs. 16%*
Targan, 1997[43]	Infliximab (5 mg/kg IV once), 26	Placebo, 24	38% vs. 4%
	Infliximab (10 mg/kg IV once), 23	Placebo, 24	20% vs. 4%
	Infliximab (20 mg/kg IV once), 28	Placebo, 24	20% vs. 4%
Schroder, 2006[47]	Infliximab (5 mg/kg IV at week 0) + methotrexate (20 mg IV weekly for weeks 0-1), 11	Infliximab (5 mg/kg IV week 0), 8	64% vs. 25%

CDAI = Crohn's Disease Activity Index; IV = intravenous infusion; mg = milligrams; mg/kg = milligrams per kilogram; sc = subcutaneous injections; vs. = versus

*Trial reported $P < 0.05$

Figure 6. Pooled relative risk of inducing remission* at week 2 comparing a TNF-alpha inhibitor with placebo



Pooled Relative Risk and 95% Confidence Intervals of Remission at Week 2

ADA = adalimumab; CI = confidence interval; CP = certolizumab pegol; IFX = infliximab; RR = relative risk; TNF-a = tumor necrosis factor-alpha inhibitor

*In all trials, remission was defined as a Crohn's Disease Activity Index less than 150.

Boxes indicate individual trial point estimates. The box size denotes the weight of the trial, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each trial. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q=7.41 with 6 degrees of freedom (p=0.29)

I-squared statistic = 19%

Table 11. Randomized controlled trials comparing the efficacy of TNF-alpha inhibitor therapy with placebo or another treatment to induce remission at weeks 12 to 16 (or closest time point) among patients with active Crohn's disease at randomization

Author, Year	Followup (Weeks)	Main Intervention (Dose), n	Comparison (Dose), n	Remission Rate (%) (CDAI<150)
Winter, 2004[41]	12	Certolizumab pegol (5 mg/kg IV once), 25	Placebo, 25	32% vs. 32%
		Certolizumab pegol (10 mg/kg IV once), 17	Placebo, 25	24% vs. 32%
		Certolizumab pegol (20 mg/kg IV once), 23	Placebo, 25	13% vs. 32%
Schreiber, 2005[40]	12	Certolizumab pegol (100 mg sc once), 74	Placebo, 73	27% vs. 23%
		Certolizumab pegol (200 mg sc once), 72	Placebo, 73	19% vs. 23%
		Certolizumab pegol (400 mg sc once), 72	Placebo, 73	26% vs. 23%
Sandborn, 2007[39]	16	Certolizumab pegol (400 mg sc at 0, 2, 4 weeks, then every 4 weeks), 331	Placebo, 328	26% vs. 20%
Targan, 1997[43]	12	Infliximab (5 mg/kg IV once), 27	Placebo, 24	30% vs. 8%
		Infliximab (10 mg/kg IV once), 27	Placebo, 24	18% vs. 8%
		Infliximab (20 mg/kg IV once), 28	Placebo, 24	25% vs. 8%
Colombel, 2010[45]	10	Infliximab (5 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks), 169	Azathioprine (2.5 mg/kg orally daily), 170	37% vs. 24%*†
Colombel, 2010[45]	10	Infliximab (5 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks) + azathioprine (2.5 mg/kg orally daily),169	Azathioprine (2.5 mg/kg orally daily), 170	47% vs. 24%*†
Lemann, 2006[46]	12	Infliximab (5 mg/kg IV at 0, 2, and 6 weeks) + azathioprine (2-3 mg/kg/day orally) or 6-mercaptopurine (1-1.5 mg/kg/day orally), 25	Azathioprine (2-3 mg/kg/day orally) or 6-mercaptopurine (1-1.5 mg/kg/day orally), 29	64% vs. 34%*†
D'Haens, 2008[48]	14	Infliximab (5 mg/kg IV at 0, 2, 6 weeks) + azathioprine (2–2.5 mg/kg orally daily), 65	Methylprednisolone (32 mg orally daily with taper), or budesonide (9 mg orally daily with taper), 64	65% vs. 32%*†
Colombel, 2010[45]	10	Infliximab (5 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks) + azathioprine (2.5 mg/kg orally daily), 169	Infliximab (5 mg/kg IV at 0, 2, and 6 weeks), 169	47% vs. 37%*
Schroder, 2006[47]	12	Infliximab (5 mg/kg IV at 0 and 2 weeks) + methotrexate (20 mg IV weekly for weeks 0-5; then 20 mg orally weekly), 11	Infliximab (5 mg/kg once), 8	82% vs. 50%

CDAI = Crohn's Disease Activity Index; IV = intravenous infusion; mg = milligrams; mg/kg = milligrams per kilogram; NR = not reported; pt = point; sc = subcutaneous injections; vs. = versus

*Steroid-free remission

†Trial reported $P < 0.05$

Table 12. Randomized controlled trials comparing the efficacy of TNF-alpha inhibitor therapy with placebo or another treatment to induce remission (last reported time point) among patients with active Crohn's disease at randomization

Author, Year	Followup (weeks)	Main Intervention (Dose), n	Comparison (Dose), n	Remission Rate (%) (CDAI<150)
Sandborn, 2007[39]	26	Certolizumab pegol (400 mg sc at 0, 2, 4 wks, then every 4 wks), 331	Placebo, 328	29% vs. 18%*
Colombel, 2010[45]	26	Infliximab (5 mg/kg IV at 0, 2, 6 wks, then every 8 wks), 169	Azathioprine (2.5 mg/kg orally daily), 170	44% vs. 30%*†
Colombel, 2010[45]	26	Infliximab (5 mg/kg IV at 0, 2, 6 wks, then every 8 wks) + azathioprine (2.5 mg/kg orally daily),169	Azathioprine (2.5 mg/kg orally daily), 170	57% vs. 30%*†
Lemann, 2006[46]	24	Infliximab (5 mg/kg IV at 0, 2, 6 wks) + azathioprine (2-3 mg/kg/day orally) or 6-mercaptopurine (1-1.5 mg/kg/day orally), 24	Azathioprine (2-3 mg/kg/day orally) or 6-mercaptopurine (1-1.5 mg/kg/day orally), 27	50% vs. 26%†
D'Haens, 2008[48]	104	Infliximab (5 mg/kg IV at 0, 2, 6 wks) + azathioprine (2–2.5 mg/kg orally daily), 65	Methylprednisolone (32 mg orally daily with taper), or budesonide (9 mg orally daily with taper), 64	55% vs. 49%
Colombel, 2010[45]	26	Infliximab (5mg/kg IV at 0, 2, 6 wks, then every 8 wks) + azathioprine (2.5 mg/kg orally daily), 169	Infliximab (5 mg/kg IV at 0, 2, 6 wks, then every 8 wks), 169	57% vs. 44%*†
Schroder, 2006[47]	48	Infliximab (5 mg/kg IV at 0, 2 wks) + methotrexate (20 mg IV weekly for weeks 0-5; then 20 mg orally weekly), 11	Infliximab (5 mg/kg IV once), 8	45% vs. 25%

CDAI = Crohn's Disease Activity Index; IV = intravenous infusion; mg = milligrams; mg/kg = milligrams per kilogram; NR = not reported; pt = point; sc = subcutaneous injections; vs. = versus; wk = week
*Trial reported $P < 0.05$
†Steroid-free remission

Mucosal Healing

The infliximab trial[43] reported on mucosal healing for a subset of 30 participants.[49] The 4-week Crohn's Disease Endoscopic Index of Severity (CDEIS), which is measured on a scale of 0 to 44 with higher scores indicating more severe disease, decreased in all doses of infliximab compared with baseline indicating less severe disease (mean change of 7.7 compared with 13.0 at baseline; within group $P < 0.001$). The mean change in CDEIS for placebo was 0.9 compared with an 8.4 score at baseline (within group P=NS). Infliximab was favored over placebo according to the clinically meaningful threshold of a 5-point difference between groups. The trial did not report the statistical significance of the change from baseline in infliximab compared with placebo.

Fistula Response

Two trials reported on subsets of participants with draining fistulas at baseline[37,39] and one trial required a draining fistula at baseline for inclusion with fistula healing the primary goal of the trial.[44] The trials considered three different comparisons: adalimumab at three different doses versus placebo at 4 weeks (N=32),[37] certolizumab pegol (400 mg subcutaneous every 4 weeks) versus placebo at 26 weeks (N=107),[39] and infliximab (5 mg/kg or 10 mg/kg) versus placebo administered at 0, 2, and 6 weeks (N=94).[44]

We did not find a class effect of TNF-alpha inhibitor on fistula response. Three of 26 adalimumab patients had closure of all draining fistula at two consecutive visits at week 4 compared with one of six placebo patients.[37] Similarly, no difference was seen in complete

fistula closure for certolizumab pegol versus placebo at week 26 (30 versus 31 percent).[39] However, infliximab decreased the number of draining fistulas over two consecutive visits according to the clinically meaningful and statistically significant thresholds for each dose of infliximab: with 55 percent of those receiving 5 mg/kg, 38 percent of 10 mg/kg having no draining fistulas compared with a 13 percent fistula closure rate by 18 weeks in placebo (P=0.001 and P=0.04 compared with placebo).[44] The infliximab trial also reported the Perianal Disease Activity Index (PDAI), which is measured on a scale of 0 to 20 with higher scores indicating more severe disease. Although changes in the PDAI from baseline were not compared between infliximab and placebo, there was a 4- to 5-point decrease in PDAI score at 18 weeks in the infliximab groups compared with a 2-point decrease in placebo.[44]

Patient-Reported Outcomes

Six trials with 1,675 total participants reported the IBDQ.[37-40,42,43] We did not see a class effect of TNF-alpha inhibitor on the IBDQ. Adalimumab and certolizumab pegol did not lead to increases in the IBDQ that met our clinically meaningful criterion of a 17-point between group change in the score from baseline. Two trials compared adalimumab with placebo and did not meet the clinically meaningful threshold compared with placebo at week 4.[37,38] Three trials compared certolizumab pegol with placebo; certolizumab pegol did not meet the clinically meaningful threshold compared with placebo at week 6, 12, or 26.[39,40,42] Infliximab was both clinically and statistically superior to placebo at week 4.[43] Mean IBDQ rose from 118 to 154 in the infliximab groups and from 128 to 133 in the placebo group (P=0.001). The week 12 results were not reported for all randomized patients in the infliximab trial.

Monotherapy Versus Monotherapy

Infliximab Versus Azathioprine

Disease Activity Measures

One trial, of 338 patients with relatively short median disease duration of 2 years who had not received thiopurines or TNF-alpha inhibitors,[45] found infliximab to be clinically and statistically superior to azathioprine for the induction of steroid-free remission at weeks 10 and 26 (Tables 10 and 11). The finding at 26 weeks is particularly meaningful because a response to azathioprine is not expected until at least 12 weeks based on its pharmacokinetics.[50] The exclusion of homozygous mutant and heterozygous thiopurine methyltransferase phenotypes is also unlikely to explain the difference between infliximab and azathioprine at 26 weeks. Notably, patients were followed out to 52 weeks, but starting at week 30 patients were given the choice of continuing with the assigned therapy; this extension period did not meet our inclusion criteria.

Mucosal Healing

At baseline, 63 percent of patients (n=214) had mucosal lesions.[45] At 26 weeks, 30 percent (28 out of 93) of the infliximab group had no mucosal ulcers compared with 17 percent (18 out of 109) of the azathioprine group (P=0.02). This finding is clinically meaningful and statistically significant. The patients who did not have ulcerations were excluded as well as the 12 patients with an unclear video or no colonoscopy at 26 weeks.

Patient-Reported Outcomes

The change in IBDQ score from baseline was not different for infliximab and azathioprine at 2, 10, or 26 weeks according to our between-group difference threshold of a 17-point change from baseline between groups (Appendix D, Evidence Table 4).

Combination Therapy Versus Monotherapy

Infliximab and Azathioprine Versus Infliximab Alone

Disease Activity Measures

One trial of 338 patients[45] found a combination of infliximab and azathioprine was clinically superior to infliximab and placebo at weeks 10 and 26, although the results were only statistically significant at week 26. This is consistent with azathioprine generally taking 12 weeks to have an effect based on its pharmacokinetics (Tables 10 and 11).

Mucosal Healing

In the above trial,[45] 210 patients for this comparison had mucosal lesions. The trial evaluated these patients again after the primary endpoint. Rates of mucosal healing (no ulcers) at 26 weeks were 47 out of 107 (44 percent) for the combination of infliximab and azathioprine and 28 out of 93 (30 percent) for infliximab and placebo (P=0.06). Ten patients did not have a colonoscopy at week 26 or the quality of the video was insufficient for inclusion.

Patient-Reported Outcomes

The absolute difference in mean IBDQ change from baseline at week 26 was not clinically significant.[45]

Infliximab and Thiopurine Versus Thiopurine Alone

Disease Activity Measures

Two trials randomized 393 patients to a combination of infliximab and a thiopurine or thiopurine alone (with a placebo for infliximab).[45,46] In the smaller study[46] patients were divided into two strata – thiopurine naïve patients and those that had previously failed thiopurines. The thiopurine naïve stratum included a mix of patients with CDAI less than and greater than 150, while all patients in the thiopurine failure stratum had a CDAI greater than 150. By contrast, the larger study[45] excluded any prior thiopurine use. The larger trial of 339 patients[45] found the combination of infliximab and azathioprine clinically and statistically superior to azathioprine for the induction of steroid-free remission at weeks 10 and 26 (Tables 10 and 11). Among the thiopurine failure stratum of the smaller trial,[46] the combination of infliximab and a thiopurine (azathioprine or 6-mercaptopurine) was clinically and statistically significant compared with a thiopurine alone at 12 weeks, but was clinically meaningful but not statistically significant at 24 weeks. Among all randomized patients in this trial, the findings were clinically meaningful and statistically significant at both time points.[46]

Mucosal Healing

Both trials reported on mucosal healing. In the larger trial,[45] 226 patients (67 percent) for this comparison had mucosal lesions at baseline. At 26 weeks, 47 out of 107 (44 percent) combination of infliximab and azathioprine patients had no ulcers compared with 18 out of 109

(17 percent) for azathioprine patients ($P < 0.001$). Of the 20 patients in the other trial[46] who underwent colonoscopy at baseline and at 24 weeks, the number of patients with no ulcers at week 24 was neither clinically nor statistically significantly different between the two groups (27 versus 33 percent).

Patient-Reported Outcomes

The absolute difference in mean IBDQ change from baseline was not clinically significant at week 2, 10, or 26.[45]

Infliximab and Thiopurine Versus Corticosteroids in a Top-Down Versus Step-Up Trial

Disease Activity Measures

One trial[48] sought to compare top-down therapy with step-up therapy. At entry, patients were newly diagnosed, and were naïve to corticosteroids, thiopurines, and TNF-alpha inhibitor therapy. The trial randomized patients to receive either the combination of infliximab (given at 0, 2, and 6 weeks) and azathioprine (top-down therapy), or a taper with corticosteroids (step-up therapy). The top-down group received corticosteroids if they did not respond to infliximab and azathioprine. The step-up group received azathioprine if they relapsed after a second course of corticosteroids, and infliximab if they continued to have active disease after receiving azathioprine. Thus, there was significant overlap between groups in terms of which therapies could be received. In this non-blinded trial, the primary outcome was steroid-free remission. The patients who started on infliximab and azathioprine at baseline were more likely to be in steroid-free remission at 14 weeks compared with the step-up group according to our clinically meaningful and statistically significant thresholds (Table 11). However, at the final measurement at week 104, there was no clinically or statistically significant difference between the groups (Table 12). At week 104, less than 20 percent of either group was still receiving corticosteroids or infliximab, but patients did continue to use azathioprine with 90 percent of the top-down group receiving azathioprine compared with 71 percent of the step-up group.

Mucosal Healing

In the above trial,[48] 49 out of 129 patients underwent colonoscopy at the end of the followup period. At 104 weeks, 73 percent of the top-down group had no ulcers compared with 30 percent of the step-up group ($P=0.003$). However, the percent of patients with ulcers at baseline was not reported.

Patient-Reported Outcomes

After 10 weeks of treatment, patients receiving top-down therapy had clinically and statistically greater increases in the mean IBDQ change from baseline than patients receiving step-up therapy (mean between-group difference in change from baseline IBDQ, 21.8 points; 95% CI, 8.4 to 34.9 points; $P=0.0014$).[48] This trial did not report any long-term results for IBDQ, although IBDQ was assessed throughout the 104-week trial.

Infliximab and Methotrexate Versus Infliximab Alone

Disease Activity Measures

One small unblinded trial[47] compared the effectiveness of a combination of infliximab and methotrexate with infliximab monotherapy at inducing remission at 2 and 12 weeks and maintaining remission at 48 weeks. Across time points, the trial showed a clinically but not statistically significant difference in remission rates (Tables 9, 10, and 11).

Reduction of Steroids

In the above trial,[47] mean prednisolone dose decreased from 17 mg to 0 mg in the combination infliximab and methotrexate group compared to a decrease from 21 mg to 15 mg in the infliximab alone group at week 48. This was clinically (using a definition of a delta in steroid reduction of 10 mg or more of prednisone) and statistically significant (P=0.02).

Patient-Reported Outcomes

At 48 weeks, the mean IBDQ score rose from 113 to 163 points in the infliximab and methotrexate group and from 107 to 135 points in the infliximab alone group, meeting our threshold for clinical significance.[47] The trial did not provide a *P*-value to assess statistical significance.

Thiopurines

Twelve RCTs evaluated the effectiveness of thiopurines (azathioprine or 6-mercaptopurine) as monotherapy or in combination with other therapies to induce remission.[51-62]

Study Design

Ten of the 12 RCTs were double blind (Appendix D, Evidence Table 2). One trial stated that the investigators were blinded, but the patients were aware of the medication.[58] Another did not mention blinding.[52] The trials were heterogeneous in all aspects of design including the locations, years of recruitment, duration, minimum age of enrollment, definition of active disease, doses and administration of the trial medications, and definition of remission outcomes.

Two trials were multinational,[51,59] three took place at multiple centers in Israel[57] or the United States,[56,60] and six at single centers in Germany,[54] Italy,[58] South Africa,[53] Spain,[52] the United Kingdom,[61] and the United States.[62] Enrollment started between 1971[56] and 2004[51] although trials published in 1971 and 1974 did not report the enrollment year.[61,62] All but one trial[51] was completed prior to the approval of TNF-alpha inhibitors. The average time under trial per participant was longer than the natalizumab and TNF-alpha inhibitor trials with a median of 26 weeks (range, 12 weeks to 106 weeks). The minimum eligibility age was 18 years in four trials,[51,54,58,59] 17 years in one trial,[57] 15 years in four trials,[52,53,56,60] and not reported in two trials.[61,62]

Common disease activity inclusion criteria included a minimum CDAI of 150 to 220 and no greater than 450,[51-54,56,58,59] Harvey-Bradshaw Index (HBI) of 7 or greater,[57] and steroid dependency.[51,58,59] One trial required gastroenterologist-assessed active disease that had not previously responded to sulfasalazine or corticosteroids.[60] Two trials published during the 1970s required active disease based on weight loss, fistula, diarrhea, inflammation on sigmoidoscopy, failure to respond to other medications and need for surgery.[61,62] Common disease activity related exclusions included abscess,[54,57-59] symptomatic strictures,[51,53,57-59] and previous surgery

within 3 months.[51] Remission was defined as a CDAI less than 150 in seven trials,[51-54,56,58,59] with three trials using an even more stringent definition of remission including a CDAI less than 150 combined with the absence of corticosteroids.[51,58,59] Another trial required an HBI less than 3 and no use of corticosteroids.[57] One trial did not use the CDAI but the gastroenterologist assessed symptoms, steroid dose, and fistula healing to assign patients to "improvement" or not.[60] Two trials published during the 1970s reported patient assessments of symptoms,[61 62] with one also reporting reduction of steroids.[62]

In contrast with the TNF-alpha inhibitor trials, medication inclusion criteria were rare. Most trials allowed patients with previous use of the medications under trial.[51,53,54,56-59] One trial specifically excluded patients with prior use of thiopurines or methotrexate.[52] Six trials required that patients had not used medications within the previous 3 to 6 months.[51,53,54,57-59] Two trials specifically mentioned that patients with previous use of a biologic agent in a trial or practice settling were eligible as long as they had not used the medication 3 to 6 months prior.[51 59] In contrast with the TNF-alpha inhibitor trials that allowed patients to use other medications as long as the patient was receiving a stable dose, most of the thiopurine trials specifically mentioned that they did not allow patients to use medications other than those under trial.[51-53,56,58,59]

Population Characteristics

The 12 trials randomized a total of 786 patients with Crohn's disease (Appendix D, Evidence Table 3). One trial[52] included patients with Crohn's disease and ulcerative colitis, but we only included information from those with Crohn's disease.

The population characteristics had wide variability across the trials. The proportion of male participants in a treatment group ranged from 21[53] to 75[61] percent, among the trials that reported patient sex. One trial reported on race[56] with white patients comprising between 90 and 94 percent of participants across the four trial groups. Smoking status was reported in five trials[51-53,57,59] and ranged between 24[57] and 86 percent.[52] Average age at enrollment ranged between 27[54] to 38[57] years (mean) and 32[53] to 40[51] years (median). Duration of disease ranged between 3.3[56] to 8.4 years[57] (mean) and 0.6[51] to 7.1[59] years (median).

Disease location and disease activity were also heterogeneous across trials. Disease location was variable across trials: ileal location ranged between 5[54] and 83[51] percent, ileocolonic location between 25[57] and 67[54] percent, colonic location between 7[62] and 73[51] percent, and perianal lesions ranged between 14[52] and 25[52] percent. Baseline CDAI was reported for all seven trials using this measure, with mean CDAI ranging from 191[52] and 290[54] and median CDAI ranging from 244[59] and 301[53] points. In the trial that used HBI,[57] mean HBI scores ranged from 7.8 to 9 across the three trial groups.

Key Points

Table 13 summarizes the strength of evidence for the trials evaluating thiopurines in terms of induction of remission. We found at least moderate strength of evidence or a clinically meaningful difference for the following areas:

- 6-mercaptopurine (1.5 mg/kg/day) was more effective than placebo in inducing a remission at week 104 (absolute RD, 33 percent; placebo rate, 14 percent). (SOE: Low)
- 6-mercaptopurine (1.5 mg/kg/day) was more effective than placebo in healing fistulas between 54-104 weeks in patients with actively draining fistulas (absolute RD in fistula closure, 25 percent; placebo rate, 6 percent). (SOE: Low)

- Azathioprine (2.5 mg/kg/day) was less effective than prednisone in inducing a remission at week 17 (absolute RD, -24 percent; prednisone rate, 77 percent). (SOE: Low)
- Azathioprine (2.5 mg/kg/day) was less effective than prednisone in healing fistulas at week 17 (absolute RD, -17 percent; prednisone rate, 30 percent). (SOE: Low)
- Azathioprine (2.5 mg/kg/day) was less effective than sulfasalazine (1 g /15 kg) in inducing a remission at week 2 (absolute RD, -14 percent; sulfasalazine rate, 20 percent). (SOE: Low).
- 6-mercaptopurine (1.5 mg/kg/day) was more effective than aminosalicylates (3 g/day) in inducing a remission at week 30 (absolute RD, 80 percent; aminosalicylate rate, 14 percent). (SOE: Low)
- A combination of azathioprine (2.5 mg/kg/day) and corticosteroids was more effective than corticosteroids alone in inducing a remission at weeks 12 and 28 (absolute RD across time points, 10 percent; corticosteroid rate, 28 to 63 percent). (SOE: Low)
- A combination of azathioprine (2 mg/kg/day) and corticosteroids was less effective than a combination of methotrexate (25 mg intravenous/week) and corticosteroids in healing fistulas at 26 weeks in patients with actively draining fistulas (absolute RD in fistula closure, -42 percent; methotrexate and corticosteroids rate, 67 percent). (SOE: Low)

Table 13. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating thiopurines to induce remission among patients with active Crohn's disease at randomization

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of bias	Consistency	Directness	Precision	
Thiopurine vs. placebo–wks 3-4, 17-38	Disease activity measures	2 (158)[56 57]	High	Inconsistent	Indirect	Imprecise	Favors neither RD across time points, -5% to 13%; placebo rate, 5% to 48% SOE: Low
Thiopurine vs. placebo–wk 104	Disease activity measures	1 (33)[60]	High	Unknown (single trial)	Indirect	Imprecise	Favors 6-MP RD, 33%; placebo rate, 14% SOE: Low
Thiopurines vs. placebo–wk 16	Reduction of steroids	1 (26)[62]	Medium	Unknown (single trial)	Direct	Imprecise	Favors neither Reduction in steroid dose from baseline, 7 mg vs. 12 mg SOE: Low
Thiopurine vs. placebo–wk 17	Fistula response	1 (17)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD in perianal fistula closure, 2%; placebo rate, 11% SOE: Low
Thiopurine vs. placebo– wk 104	Fistula response	1 (46)[60]	High	Unknown (single trial)	Direct	Imprecise	Favors 6-MP RD in perianal fistula closure, 25%; placebo rate, 6% SOE: Low
Thiopurines vs. placebo–wk 8 and 16	Patient-reported outcomes	3 (116)[57 61 62]	Medium	Inconsistent	Direct	Imprecise	Favors neither Multiple measures; see text SOE: Low
Thiopurines vs. methotrexate (oral)–wks 4, 12, 30-38	Disease activity measures	2 (89)[52 57]	Medium	Inconsistent	Indirect	Imprecise	Favors neither RD across time points, -1% to 21%; placebo rate, 9% to 80% SOE: Low
Azathioprine vs. prednisone–wks 2, 13, 17	Disease activity measures	1 (144)[56]	High	Unknown (single trial)	Direct	Imprecise	Favors prednisone RD across time points, -24 to -12%; prednisone rate, 27-77% SOE: Low

Table 13. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating thiopurines to induce remission among patients with active Crohn's disease at randomization (continued)

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Azathioprine vs. prednisone–wk 17	Fistula response	1 (18)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors prednisone RD, -17%; prednisone rate, 30% SOE: Low
Azathioprine vs. sulfasalazine–wk 2	Disease activity measures	1 (133)[56]	High	Unknown (single trial)	Direct	Precise	Favors sulfasalazine RD, -14%; sulfasalazine rate, 20% SOE: Low
Azathioprine vs. sulfasalazine–wks 13, 17	Disease activity measures	1 (133)[56]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD across time points, 0% to 6%; sulfasalazine rate, 32% to 53% SOE: Low
Azathioprine vs. sulfasalazine–wk 17	Fistula response	1 (17)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD, -9%; sulfasalazine rate, 22% SOE: Low
6-MP vs. ASA–wks 12, 30	Disease activity measures	1 (23)[52]	High	Unknown (single trial)	Direct	Precise	Favors 6-MP RD across time points, 67% to 80%; ASA rate, 14% SOE: Low
Azathioprine (IV and oral) vs. thiopurine (oral)–wk 8, 16	Disease activity measures	1 (96)[59]	Medium	Unknown (single trial)	Indirect IV AZA is not presently used as a treatment	Imprecise	Favors neither RD across time points, 1% to 4%; oral azathioprine alone rate, 24% to 27% SOE: Low
Azathioprine + steroid vs. steroid–wks 12, 28	Disease activity measures	3 (186)[51 53 54]	Medium	Inconsistent	Direct	Imprecise	Favors azathioprine + steroid RD across time points, 10%; steroid rate, 28% to 63% SOE: Low
Azathioprine + prednisone vs. methotrexate (IV followed by oral) + prednisone–wk 13, 26	Disease activity measures	1 (54)[58]	Medium	Unknown (single trial)	Direct	Imprecise	Favors neither RD across time points, -11% to 7%; methotrexate + prednisone rate, 44% to 56% SOE: Low

Table 13. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating thiopurines to induce remission among patients with active Crohn's disease at randomization (continued)

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Azathioprine + prednisone vs. methotrexate (IV followed by oral) + prednisone–wk 26	Fistula response	1 (10)[58]	High	Unknown (single trial)	Direct	Imprecise	Favors methotrexate + prednisone RD in fistula closure, -42%; methotrexate + prednisone rate, 67% SOE: Low

6-MP = 6-mercaptopurine; ASA = aminosalicylates; IV = intravenous; mg = milligrams; RD = risk difference; SOE = strength of evidence; steroid = corticosteroids; vs. = versus; wk = weeks

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

Monotherapy Versus Placebo

Thiopurines Versus Placebo

Disease Activity Measures

Three trials, comprising 227 participants, compared thiopurines with placebo in inducing remission in those with active disease (Table 14; Appendix D, Table 4).[56,57,60] Two trials had neither clinically nor statistically significant difference in remission rates between thiopurines and placebo groups at 17 and 38 weeks, the first time disease activity was reported.[57,60] The trial that used physician assessment of disease activity did find a difference between groups.[60] This trial employed a crossover design and we included the information reported for those patients that did not cross over (N=33). 6-mercaptopurine was clinically and statistically favored over placebo at 104 weeks according to the physician assessment. Because the CDAI had not been developed as part of the initial design steps of another trial,[56] this measure was not used for inclusion or for outcome assessment. Because patients had to have no symptoms, fistula closure, or not use corticosteroids, the physician assessment could be considered a more difficult outcome to achieve than the CDAI less than 150 threshold which allows symptoms and does not assess corticosteroid use or fistula activity.

Table 14. Randomized controlled trials comparing the effectiveness of thiopurines with placebo or another treatment to induce remission among patients with active Crohn's disease at randomization

Author, Year	Followup (Weeks)	Main Intervention (Dose), n	Comparison (Dose), n	Remission Definition	Remission Rate (%)
Summers, 1979[56]	3	Azathioprine (2.5 mg/kg/day), 59	Placebo, 77	CDAI<150	6 vs. 10%
	13	Azathioprine (2.5 mg/kg/day), 59	Placebo, 77	CDAI<150	38 vs. 25%
	17	Azathioprine (2.5 mg/kg/day), 59	Placebo, 77	CDAI<150	53 vs. 48%
Present, 1980[60]	104	6-mercaptopurine (1.5mg/kg/day), 19	Placebo, 14	"Excellent improvement"[†]	47 vs. 14%[‡]
Oren, 1997[57]	4	6-mercaptopurine (50 mg/day), 32	Placebo, 26	HBI 3 and steroid-free	8 vs. 5%
	12	6-mercaptopurine (50 mg/day), 32	Placebo, 26	HBI 3 and steroid-free	30 vs. 27%
	38	6-mercaptopurine (50 mg/day), 32	Placebo, 26	HBI 3 and steroid-free	41 vs. 46%
Oren, 1997[57]	4	6-mercaptopurine (50 mg/day), 32	Methotrexate (12.5 mg/wk oral), 26	HBI 3 and steroid-free	8 vs. 9%
	12	6-mercaptopurine (50 mg/day), 32	Methotrexate (12.5 mg/wk oral), 26	HBI 3 and steroid-free	30 vs. 30%
	38	6-mercaptopurine (50 mg/day), 32	Methotrexate (12.5 mg/wk oral), 26	HBI 3 and steroid-free	41 vs. 38%
Mate-Jimenez, 2000[52]	12	6-mercaptopurine (1.5 mg/kg/day), 16	Methotrexate (15 mg/wk oral), 15	CDAI<150, steroid-free, normal serum orosomucoid concentrations	81 vs. 60%
	30	6-mercaptopurine (1.5 mg/kg/day), 16	Methotrexate (15 mg/wk oral), 15	CDAI<150, steroid-free, normal serum orosomucoid concentrations	94 vs. 80%
Summers, 1979[56]	2	Azathioprine (2.5 mg/kg/day), 59	Prednisone (0.25-0.75 mg/kg/day), 85	CDAI<150	6 vs. 27%
	13	Azathioprine (2.5 mg/kg/day), 59	Prednisone (0.25-0.75 mg/kg/day), 85	CDAI<150	38 vs. 50%
	17	Azathioprine (2.5 mg/kg/day), 59	Prednisone (0.25-0.75 mg/kg/day), 85	CDAI<150	53 vs. 77%
Summers, 1979[56]	2	Azathioprine (2.5 mg/kg/day), 59	Sulfasalazine (1 g/15 kg/day), 74	CDAI<150	6 vs. 20%
	13	Azathioprine (2.5 mg/kg/day), 59	Sulfasalazine (1 g/15 kg/day), 74	CDAI<150	38 vs. 32%
	17	Azathioprine (2.5 mg/kg/day), 59	Sulfasalazine (1 g/15 kg/day), 74	CDAI<150	53 vs. 53%
Mate-Jimenez, 2000[52]	12	6-mercaptopurine (1.5 mg/kg/day), 16	Aminosalicylates (3 g/day), 7	CDAI<150, steroid-free, normal serum orosomucoid concentrations	81 vs. 14%
	30	6-mercaptopurine (1.5 mg/kg/day), 16	Aminosalicylates (3 g/day), 7	CDAI<150, steroid-free, normal serum orosomucoid concentrations	94 vs. 14%[‡]
Sandborn, 1999[59]	8	Azathioprine (IV 40 mg/kg loading dose then oral 2 mg/kg/day), 51	Azathioprine (oral 2 mg/kg/day), 45	CDAI<150 and steroid-free	25 vs. 24%
	16	Azathioprine (IV 40 mg/kg loading dose then oral 2 mg/kg/day), 51	Azathioprine (oral 2 mg/kg/day), 45	CDAI<150 and steroid-free	31 vs. 27%
Ewe, 1993[54]	16	Azathioprine (2.5 mg/kg/day) + prednisolone (60 mg/day then taper), 21	Prednisolone (60 mg/day then taper), 21	CDAI<150 and 60-pt drop in CDAI	76 vs. 38%[‡]
Candy, 1995[53]	12	Azathioprine (2.5 mg/kg/day) + prednisolone (1 mg/kg/day then taper), 33	Prednisolone (1 mg/kg/day then taper), 30	CDAI<150 and steroid-free	73 vs. 63%

Table 14. Randomized controlled trials comparing the effectiveness of thiopurines with placebo or another treatment to induce remission among patients with active Crohn's disease at randomization (continued)

Author, Year	Followup (Weeks)	Main Intervention (Dose), n	Comparison (dose), n	Remission Definition	Remission Rate (%)
Reinisch, 2008[51]	28	Azathioprine (2.5 mg/kg/day) + prednisone (1 mg/kg/day or ≥ 40 mg/day then taper after response), 50	Prednisone (1 mg/kg/day or ≥ 40 mg/day then taper after response), 28	Treatment success[§]	38 vs. 28%
Ardizzone, 2003[58]	13	Azathioprine (2 mg/kg/day) + prednisone (40 mg/day), 27	Methotrexate (25 mg/wk)[‖] + prednisone (40 mg/day), 27	CDAI≤150 and steroid-free	33 vs. 44%
	26	Azathioprine (2 mg/kg/day) + prednisone (40 mg/day), 27	Methotrexate (25 mg/wk)[‖] + prednisone (40 mg/day), 27	CDAI≤150 and steroid-free	63 vs. 56%

CDAI = Crohn's Disease Activity Index; HBI = Harvey-Bradshaw Index; IV = intravenous, kg = kilogram; mg = milligram; pt = point; wk = week

†"Excellent improvement" – disappearance of symptoms, complete closure of fistula, total withdrawal from steroids

‡Trial reported $P < 0.05$

§Treatment success was defined as absence of treatment failure, which encompassed patients: who prematurely discontinued the trial drug due to unsatisfactory therapeutic effect; who failed to achieve steroid-free remission (i.e., CDAI ≥150) by the end of month 3; who used steroids after the end of month 3; who used any prohibited efficacy-related treatment; and with a relapse (i.e., any CDAI ≥150 points and a minimum increase in CDAI ≥70 compared with the score at beginning of remission) recorded after end of month 3.

‖Methotrexate was given intravenously for 12 weeks then orally.

Reduction of Steroids

One trial with 26 participants showed reduction in the average daily dose of corticosteroid use in azathioprine (from 13.3 mg to 6.3 mg) and placebo (from 19.8 mg to 7.8 mg) during 4 months of followup prior to crossover (Appendix D, Evidence Table 4).[62] Although the trial did not calculate statistical significance, the percent reduction in steroids between groups is not clinically significant (defined as delta reduction between groups as 10 mg of prednisone or more), especially in light of the much higher initial dose in the placebo group.

Fistula Response

Among a subset of 17 patients with draining perianal fistulas at the time of randomization,[56] fistula response at 17 weeks was no different between azathioprine at 2.5 mg/kg daily with placebo (13 vs. 11 percent).[55] However, 6-mercaptopurine resulted in greater fistula closer by 104 weeks, although statistical significance was not assessed.[60] Nine out of 29 (31 percent) fistulas in the 6-mercaptopurine group compared with one of 17 (6 percent) in the placebo group healed completely. However, some of the placebo patients eventually took 6-mercaptopurine and some 6-mercaptopurine patients discontinued use as part of the crossover design.

Patient-Reported Outcomes

Three trials with 116 participants compared azathioprine with placebo and included patient-reported outcomes.[57 61 62] Azathioprine did not improve patient reported outcomes in any trial. One trial,[57] using the Treatment Goal Score for Wellbeing where everyone starts out with a score of 0 at week 0 and is graded as having better (+3 maximum score) or worse (-3 minimum score) based on general well-being, Crohn's disease-related symptoms, steroids, and extraintestinal manifestations, reported a statistically significant difference after 16 weeks on the well-being and abdominal pain components but did not find a statistically significant difference on the overall score at any time point through 36 weeks.[57] A crossover trial showed no improvement in patient-reported quality of life ("feeling better") with azathioprine compared with placebo; in both groups, six patients reported symptomatic improvement after crossover at 16 weeks, while five reported no change.[62] In one trial[61] after 8 weeks, no patients reported subjective improvement in their symptoms with azathioprine or placebo. More patients reported that their symptoms were worse with azathioprine versus placebo and fewer patients reported that their symptoms were unchanged with azathioprine versus placebo. The lack of response at 8 weeks with azathioprine is not unexpected because azathioprine may take up to 16 weeks to become clinically effective based on its pharmacokinetics.[50] Pharmacokinetics cannot explain the lack of difference between azathioprine and placebo at 16 weeks.

Monotherapy Versus Monotherapy

Thiopurine Versus Methotrexate

Disease Activity Measures

Two trials including 89 participants compared thiopurine with methotrexate therapy (Table 14).[52,57] One trial of 58 participants[57] compared 6-mercaptopurine and placebo with oral methotrexate and placebo in steroid-dependent patients with active Crohn's disease defined by an HBI of 7 or greater. At 4, 12, and 38 weeks, there was no statistically significant difference in remission rates between the two groups. In a trial with unclear allocation concealment[52] of 31

steroid-dependent patients, the group randomized to 6-mercaptopurine 1.5 mg/kg/day had higher remission rates than those randomized to oral methotrexate 15 mg/week at 30 weeks (94 versus 80 percent), although the trial did not report on statistical significance (Table 14).

Thiopurines Versus Corticosteroids

Disease Activity Measures

A trial of 144 participants compared azathioprine with prednisone (Table 14).[56] At 2, 12, and 17 weeks, patients on azathioprine had a clinically meaningful lower rate of remission than patients on prednisone (week 17: 53 versus 77 percent), although the trial did not report statistical significance beyond showing that the standard errors did not overlap at any time point.

Fistula Response

Among a subset of 18 patients with draining perianal fistulas at the time of randomization,[56] fistula response at 17 weeks was lower in patients receiving azathioprine at 2.5 mg/kg daily versus patients receiving prednisone (13 vs. 30 percent).[55]

Thiopurine Versus Aminosalicylates

Disease Activity Measures

Two trials including 156 participants compared thiopurine with aminosalicylate therapy (Table 14).[52 56] One larger trial, comprising 133 participants, compared azathioprine with sulfasalazine therapy in inducing remission in those with active disease (CDAI greater than 150).[56] There was no clinically or statistically significant difference in remission rates between the groups at 13 or 17 weeks, although at week 2 sulfasalazine had a higher remission rate (16 percent versus 2 percent) and the standard errors did not overlap. In the other trial of 23 steroid-dependent participants,[52] the group receiving 6-mercaptopurine 1.5 mg/kg/day had clinically higher remission rates than the group receiving aminosalicylate 3 g/day at 12 and 30 weeks (statistically significant at 30 weeks).

Fistula Response

Among a subset of 17 patients with draining perianal fistulas at the time of randomization,[56] there was no difference in fistula response at 17 weeks between those receiving azathioprine at 2.5 mg/kg daily versus those receiving sulfasalazine (13 vs. 22 percent).[55]

Combination Therapy Versus Monotherapy

Intravenous and Oral Thiopurines Versus Oral Thiopurines Alone

Disease Activity Measures

One trial of 96 steroid-dependent participants with active Crohn's disease assessed whether a loading dose of intravenous azathioprine combined with an oral regimen of daily azathioprine would yield higher remission rates compared with an oral regimen alone (Table 14).[59] The trial standardized prednisone therapy in all participants to 20 mg per day during a 2-week period prior to randomization. There were no clinically or statistically significant differences in steroid-free remission rates between the two groups at 8 or 16 weeks.

Thiopurines and Corticosteroids Versus Corticosteroids Alone

Disease Activity Measures

Three trials[51,53,54] comprising 186 participants compared azathioprine and prednisolone taper with prednisolone taper and placebo to induce remission (Table 14). One trial,[54] which tapered prednisolone but continued it at a maintenance dose of 10 mg daily throughout the 16-week trial, found that the addition of azathioprine was favored to prednisolone alone according to the clinically meaningful and statistically significant thresholds. The other trials[51,53] which evaluated steroid-free remission, found that more patients on azathioprine had lower CDAI scores and were free of steroids at 12 and 28 weeks that met the clinically meaningful threshold, although the results were not statistically significant.

Combination Therapy Versus Combination Therapy

Thiopurines and Corticosteroids Versus Methotrexate and Corticosteroids

Disease Activity Measures

One trial blinded investigators but not patients and compared a combination of azathioprine and prednisone with a combination of methotrexate (intravenous route for 12 weeks followed by oral route) and prednisone in 54 patients (Table 14).[58] At 12 weeks, more methotrexate patients were in steroid-free remission, but at 26 weeks more azathioprine patients were in steroid-free remission, according to the clinically meaningful threshold. There were no statistically significant differences in remission rates between the two groups at 12 or 26 weeks.

Fistula Response

In the above trial,[58] 10 patients had active perianal fistulizing disease.[58] At week 26, one out of four patients in the azathioprine group and four out of six patients in the methotrexate group had fistula closure, but this finding was not statistically significant.

Methotrexate

Two trials evaluated the effectiveness of methotrexate as monotherapy to induce remission.[52,57] Both of these trials also included comparisons with azathioprine and are described above. An additional trial[63] compared methotrexate in combination with prednisone with placebo with prednisone. Two trials[52,57] used oral methotrexate between 12.5 mg and 15 mg weekly, while one trial[63] used intramuscular methotrexate at 25 mg a week.

Study Design

One of the three RCTs did not mention blinding (Appendix D, Evidence Table 2).[52] Two trials used the CDAI for inclusion and to define the outcome, while one used the HBI.[57] One trial took place in North America,[63] one took place in Europe,[52] and the last took place in Israel.[57] Two of the trials were multicenter in design.[57 63] All trials reported the starting year of enrollment, ranging between 1992 and 1994. The median trial duration was 39 weeks (ranging between 16 and 106 weeks). All trials included only steroid-dependent patients, except one[57] which required prior steroid use for at least 4 of the prior 12 months. In one trial,[63] patients who had a baseline prednisone dose under 20 mg daily raised their prednisone up to 20 mg daily for 2

weeks following randomization. One trial included adults ages 17 or older,[57] one included those 15 and older,[52] and one did not specify an age range.[63]

Population Characteristics

Three trials randomized a total of 215 Crohn's disease patients (Appendix D, Evidence Table 3). The proportion of male participants in each trial group ranged from 46 to 60 percent. No trials reported on race. Smoking status was reported in all trials, ranging between 24 and 86 percent across all trial groups. All but one trial reported mean age at enrollment,[52] ranging between 33 and 39 years. All trials reported mean duration of disease, ranging between 4 and 8 years. All trials reported disease location: ileal location ranged between 17 and 50 percent, ileocolonic location between 25 and 86 percent, colonic location between 14 and 40 percent, and perianal location between 14 and 20 percent. Two trials reported baseline CDAI[52,63] with mean CDAI ranging from 181 and 215 points. In the trial that used HBI,[57] mean baseline HBI scores was 7.8 and 9 in the relevant trial groups.

Key Points

Table 15 summarizes the strength of evidence for the trials evaluating methotrexate in terms of induction of remission. We found at least moderate strength of evidence or a clinically meaningful difference for the following comparisons:

- Oral methotrexate (15 mg a week) was more effective than aminosalicylates in inducing a remission at weeks 12, 30 (absolute RD across time points, 46 to 66 percent; aminosalicylates rate, 14 percent). (SOE: Moderate)
- Intramuscular methotrexate (25 mg per week) with prednisone was more effective than prednisone plus placebo in inducing a steroid-free remission at week 16 (absolute RD, 20 percent; prednisone plus placebo rate, 19 percent). (SOE: Moderate)
- Intramuscular methotrexate (25 mg per week) with prednisone did not differ from prednisone plus placebo in improving patient-reported outcomes at 16 weeks (absolute between-group difference in change in mean IBDQ from baseline, 15 points; prednisone plus placebo change in IBDQ, -8 points). (SOE: Moderate)

Table 15. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating methotrexate to induce remission among patients with active Crohn's disease at randomization

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Methotrexate (oral) vs. placebo–wks 4, 12, 38	Disease activity measures	1 (52)[57]	Medium	Unknown (single trial)	Direct	Imprecise	Favors neither RD across time points, -8% to 3%; placebo rate, 5% to 46% SOE: Low
Methotrexate (oral) vs. ASA–wks 12, 30	Disease activity measures	1 (22)[52]	Medium	Unknown (single trial)	Direct	Precise	Favors methotrexate RD, 46% to 66%; ASA rate, 14% SOE: Moderate
Methotrexate (IM) + prednisone vs. placebo + prednisone–wk 16	Disease activity measures	1 (141)[63]	Medium	Unknown (single trial)	Direct	Precise	Favors methotrexate + prednisone RD, 20%; prednisone only rate, 19% SOE: Moderate
Methotrexate (IM) + prednisone vs. placebo + prednisone–wk 16	Patient-reported outcomes	1 (141)[63]	Medium	Unknown (single trial)	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 15; prednisone only change in IBDQ, -8 SOE: Moderate

ASA = aminosalicylates; IBDQ = Inflammatory Bowel Disease Questionnaire; IM = intramuscular; RD = risk difference; SOE = strength of evidence; vs. = versus; wk = week
Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.
Scores for the Inflammatory Bowel Disease Questionnaire range from 32 to 224, with higher scores indicating better quality of life.[36] Treatment Score for Wellbeing starts at 0 and improvement and worsening are graded from +3 to -3.[60]

Monotherapy Versus Placebo

Methotrexate Versus Placebo

Disease Activity Measures

One trial included 52 steroid-dependent patients who had used at least 4 months of corticosteroids in the year prior to randomization.[57] There was no clinically meaningful or statistically significant difference in remission rates between 12.5 mg of oral methotrexate weekly compared with placebo (Table 16; see also Appendix D, Evidence Table 4).

Monotherapy Versus Monotherapy

Methotrexate Versus Aminosalicylates

Disease Activity Measures

One trial[52] of only 22 total patients compared methotrexate with aminosalicylates in steroid-dependent patients. A substantially higher proportion of Crohn's disease patients receiving oral methotrexate 15 mg per week achieved steroid-free remission (defined as CDAI < 150 and normal serum orosomucoid concentrations) than patients receiving 3 g per day of aminosalicylates therapy (80 vs.14 percent; $P < 0.01$). However, given the small sample size, and the fact that this was a subgroup analysis, the results should be interpreted with caution.

Combination Therapy Versus Monotherapy

Methotrexate and Corticosteroids Versus Corticosteroids Alone

Disease Activity Measures

We analyzed one RCT involving 141 patients.[63] Table 16 summarizes the effects of methotrexate therapy in terms of inducing remission.

A trial of 141 patients found 25 mg intramuscular methotrexate weekly and prednisone taper was superior to placebo plus prednisone taper in inducing steroid-free remission at 16 weeks (Table 16; see also Appendix D, Evidence Table 4).[63]

Patient-Reported Outcomes

At 16 weeks, there was no clinically meaningful difference in the IBDQ between the methotrexate and placebo groups.[63]

Table 16. Randomized controlled trials comparing the efficacy of methotrexate with placebo or another treatment to induce remission among patients with active Crohn's disease at randomization

Author, Year	Followup (Weeks)	Main Intervention (Dose), n	Comparison (Dose), n	Remission Definition	Remission Rate, %
Oren, 1997[57]	4	Methotrexate (12.5 mg oral/week), 26	Placebo, 26	HBI of 3 and steroid-free at any time during trial	8% vs. 5%
	12	Methotrexate (12.5 mg oral/week), 26	Placebo, 26	HBI of 3 and steroid-free at any time during trial	20% vs. 22%
	38	Methotrexate (12.5 mg oral/week), 26	Placebo, 26	HBI of 3 and steroid-free at any time during trial	38% vs. 46%
Mate-Jimenez, 2000†[52]	30	Methotrexate (15 mg oral/week), 15	Aminosalicylates (3 g/day), 7	CDAI<150 and steroid-free and normal serum orosomucoid concentrations	80% vs. 14%*
Feagan, 1995[63]	16	Methotrexate (25 mg IM/week) + prednisone, 94	Placebo + prednisone, 47	CDAI<150 and steroid-free	39% vs. 19%*

CDAI = Crohn's Disease Activity Index; g = grams; HBI = Harvey-Bradshaw Index; IM = intramuscular; mg = milligrams; NS = not significant; vs. = versus
*Trial reported $P < 0.05$
†Trial also randomized ulcerative colitis patients, but only Crohn's disease results included.

Corticosteroids

Thirteen RCTs compared corticosteroids therapy (alone or in combination with other medications) with placebo or other therapies to induce remission. One trial[64] included participants with both active (CDAI > 150) and inactive (CDAI < 150) disease at randomization and we included results for those with active disease only in this section. Three trials[56,65,66] evaluated corticosteroids (budesonide, prednisone) versus placebo. Three trials[67-69] evaluated budesonide versus prednisone or prednisolone. Six trials[56,70-74] evaluated corticosteroids (budesonide, prednisone, 6-methylprednisolone) versus aminosalicylates. One trial[75] evaluated a combination of prednisone and sulfasalazine versus prednisone alone. One trial also randomized patients to thiopurine and the results of thiopurine compared with corticosteroids are reported in the thiopurine section of the report.[56]

Study Design

The 13 RCTs were double blind (Appendix D, Evidence Table 2).[56 64-75] The trials were heterogeneous in all aspects of design including the locations, years of recruitment, and doses and administration of the trial medications.

The trials took place at multiple centers in the United States,[56,65,75] Canada,[66,73] Europe,[64,69,71,72] and Israel.[67] Three trials were multinational.[68,70,74] Enrollment started between 1971 and 2004. All but one trial was completed prior to the approval of TNF-alpha inhibitors.[74] Trial duration ranged from 6[64] to 17 weeks.[56] The minimum eligibility age was 18 years in ten trials, 15 years in one trial,[56] and two did not report the minimum eligibility age.[72,75]

Common disease activity inclusion criteria included a minimum CDAI of 150 or 200 with no upper limit or the use of a range of minimum (150 to 200) and maximum criteria (350 to 450). Common disease activity related exclusions included abscess,[64,68-70,74] fistula, obstructive symptoms or strictures,[67-71,74] and previous extensive surgery (more than 50 to 100 cm of

resection).[66,68-71,73,74] Six of the seven trials of budesonide included patients with disease in the ileum or ascending colon only where budesonide is released.[65-70] Remission was defined as a CDAI less than 150 in all trials.

Most trials prohibited patients from taking therapies that were not assigned as part of the trial. No trial specifically excluded patients with prior use of any medication, although exclusion of patients taking immunomodulators within 3 months of randomization,[65,67-74] aminosalicylates within 1 day to 30 days prior to randomization,[66-70,72-74] and corticosteroids within 1 week to 3 months of randomization[65-72,74] were common. The trial conducted after the approval of biologics[74] excluded patients who had used a TNF-alpha inhibitor within 6 months of randomization.

Population Characteristics

The trial that included patients with active and inactive disease did not report the population characteristics separately and is excluded from the description of population characteristics.[64] The other 12 trials randomized a total of 2,089 patients (Appendix D, Evidence Table 3). The proportion of male participants in each trial group ranged from 23 to 66 percent. Three trials reported on race[56,74,75] with Caucasian patients comprising between 86 and 99 percent of all participants across the five trial groups. Four trials[66,67,71,74] reported smoking status, ranging between 25 and 58 percent. All trials reported age at enrollment, ranging between 26 to 41 years (mean) and 30 to 38 years (median). All trials except two[75,76] reported duration of disease, ranging between 2.4 to 11.9 years (mean) and 4.6 to 9.2 years (median). All but four trials[65,68,69,74] reported disease location: ileal location ranged between 23 and 100 percent, ileocolonic location between 12 and 66 percent, and colonic location between 0 and 94 percent. All trials reported baseline CDAI, with mean CDAI ranging from 236 and 305 points and median CDAI ranging between 220 and 293 points. Prior medication use was as follows: aminosalicylates use ranged from 31 to 81 percent of participants in five trials,[56,67,70,71,75] antibiotic use ranged from 28 to 35 percent across two groups of one trial,[67] and corticosteroids use ranged from 25 to 52 percent across five trials.[56,66,67,73,75]

Key Points

Table 17 summarizes the strength of evidence for the trials evaluating corticosteroids in terms of remission induction. We found at least moderate strength of evidence or a clinically meaningful difference for the following comparisons:

- Budesonide (at least 9 mg daily) was more effective than placebo in inducing a remission at week 2 (absolute RD, 17 to 27 percent; placebo rate, 11 to 13 percent). (SOE: Moderate)
- Budesonide was more effective than placebo in inducing a remission at week 8 (absolute RD, 13 to 31 percent; placebo rate, 20 to 33 percent). (SOE: Moderate)
- 6-methylprednisolone was more effective than placebo in inducing a remission at week 3 (absolute RD, 14 percent; placebo rate, 79 percent). (SOE: Low)
- Corticosteroids (including prednisone, 6-methylprednisolone) were more effective than placebo in inducing a remission at weeks 16-17, and 104 (absolute RD across time points, 25 to 47 percent; placebo rate, 8 to 42 percent). (SOE: Low)
- Prednisone was more effective than placebo in healing fistulas at 17 weeks in patients with actively draining fistulas (absolute RD in fistula closure, 19 percent; placebo rate, 11 percent). (SOE: Low)

- Budesonide (9 mg a day) and corticosteroids (prednisone, prednisolone at 40 mg/day) did not differ in inducing a remission at weeks 2 and 8 (pooled RR at week 8, 0.9; 95% CI, 0.8 to 1.0; corticosteroid rate, 55 to 65 percent). (SOE: Moderate)
- Budesonide (9 mg daily) and prednisone (taper starting with 40 mg daily) did not differ in improving patient-reported outcomes at 8 weeks (absolute between-group difference in change in mean IBDQ from baseline, -8 points; prednisone change in IBDQ, 34 points). (SOE: Moderate)
- Corticosteroids (budesonide, prednisone, 6-methylprednisolone) were more effective than aminosalicylates in inducing a remission at weeks 2 to 3, 12 to 17, 54, and 104 (absolute RD across time points, -18 to 30 percent; aminosalicylates rate, 6 to 87 percent). (SOE: Low)
- Prednisone (taper starting at 40 mg daily) was more effective than aminosalicylates (Salofalk® 1 g, 3 times daily) in improving patient-reported outcomes at 2 weeks (absolute between-group difference in improvement in Quality of Life Index from baseline, 16 percent; Salofalk® improvement in Quality of Life Index, 7 percent). (SOE: High)
- Prednisone (taper starting at 40 mg daily) and aminosalicylates (Salofalk® 1 g, 3 times daily) did not differ in improving patient-reported outcomes at 12 weeks (absolute between-group difference in improvement in Quality of Life Index from baseline, 4 percent; Salofalk® improvement in Quality of Life Index, 33 percent). (SOE: Moderate)
- A combination of 6-methylprednisolone (48 mg/day) and sulfasalazine (3 g/day) was more effective than placebo in inducing a remission at weeks 3, 16, and 104 (absolute RD across time points, 19 to 47 percent; placebo rate, 8 to 79 percent). (SOE: Low)
- A combination of corticosteroids (prednisone, 6-methylprednisolone) and sulfasalazine was more effective than sulfasalazine alone in inducing a remission at weeks 3, 16, and 104 (absolute RD across time points, 11 to 26 percent; sulfasalazine rate, 22 to 87 percent). (SOE: Low)

Table 17. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating corticosteroids to induce remission among patients with active Crohn's disease at randomization

Comparison	Outcome	Number of trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Budesonide (≥ 9 mg) vs. placebo–wk 2	Disease activity measures	2 (391)[65 66]	Medium	Consistent	Direct	Precise	Favors budesonide RD, 17% to 27%; placebo rate, 11% to 13% SOE: Moderate
Budesonide (< 9 mg) vs. placebo–wk 2	Disease activity measures	1 (128)[66]	Medium	Unknown (single trial)	Direct	Imprecise	Favors neither RD, -1%; placebo rate, 11% SOE: Low
Budesonide vs. placebo–wk 8	Disease activity measures	2 (458)[65 66]	Medium	Consistent	Direct	Precise	Favors budesonide RD across time points, 13% to 31%; placebo rate, 20% to 33% SOE: Moderate
Budesonide vs. placebo–wk 8	Patient-reported outcomes	2 (458)[65 66]	High	Consistent	Direct	Imprecise	Favors neither Absolute between-group difference in change in IBDQ from baseline, 7 to 30; placebo change in IBDQ, 10 to 29 SOE: Low
Prednisone vs. placebo – wk 2	Disease activity measures	1 (162)[56]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD, 5%; placebo rate, 15% SOE: Low
6-methyl-prednisolone vs. placebo–wk 3	Disease activity measures	1 (105)[64]	High	Unknown (single study)	Direct	Precise	Favors 6-methylprednisolone RD, 14%; placebo rate, 79% SOE: Low
Steroid (6-methyl-prednisolone, prednisone) vs. placebo–wks 16-17, 104	Disease activity measures	2 (267)[56 64]	High	Consistent	Direct	Precise	Favors steroids RD across time points, 25% to 47%; placebo rate, 8% to 42% SOE: Low
Prednisone vs. placebo–wk 17	Fistula response	1 (19)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors prednisone RD in fistula closure, 19%; placebo rate, 11% SOE: Low

Table 17. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating corticosteroids to induce remission among patients with active Crohn's disease at randomization (continued)

Comparison	Outcome	Number of trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Budesonide vs. other steroid (prednisolone, prednisone)–wks 2, 8	Disease activity measures	3 (557)[67-69]	Medium	Consistent	Direct	Precise	Favors neither Pooled RR at wk 8, 0.9; CI, 0.8 to 1.0; steroid rate, 55% to 65% SOE: Moderate
Budesonide vs. prednisone–wk 8	Patient-reported outcomes	1 (201)[67]	Low	Unknown (single trial)	Direct	Imprecise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, -8; prednisone change in IBDQ, 34 SOE: Moderate
Steroid vs. ASA–wks 2-3, 12-17, 54-104	Disease activity measures	7 (919)[56 64 70-74]	Medium	Inconsistent	Direct	Imprecise	Favors steroids RD across time points, -18% to 30%; ASA rate, 6% to 87% SOE: Low
Prednisone vs. sulfasalazine	Fistula healing	2 (19)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD in fistula closure, 9%; sulfasalazine rate, 22% SOE: Low
Prednisone vs. ASA – wk 2	Patient-reported outcomes	1 (50)[73]	Low	Unknown (single trial)	Direct	Precise	Favors prednisone Absolute between-group difference in Quality of Life Index from baseline, 16%; ASA improvement in Quality of Life Index, 7% SOE: High
Prednisone vs. ASA – wk 12	Patient-reported outcomes	1 (50)[73]	Low	Unknown (single trial)	Direct	Imprecise	Favors neither Absolute between-group difference in Quality of Life Index from baseline, 4%; ASA improvement in Quality of Life Index, 33% SOE: Moderate

Table 17. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating corticosteroids to induce remission among patients with active Crohn's disease at randomization (continued)

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Prednisolone + sulfasalazine vs. placebo–wks 3,16, 104	Disease activity measures	1 (114)[64]	High	Unknown (single trial)	Direct	Precise	Favors prednisolone + sulfasalazine RD across time points, 19% to 47%; placebo rate, 8% to 79% SOE: Low
Steroid + sulfasalazine vs. steroid–wks 3, 8-16, 104	Disease activity measures	2 (192)[64 75]	Medium	Consistent	Direct	Imprecise	Favors neither RD across time points, 2% to 19%; steroid rate, 33% to 93% SOE: Low
Steroid + sulfasalazine vs. sulfasalazine–wks 3, 16, 104	Disease activity measures	1 (110)[64]	High	Consistent	Direct	Precise	Favors steroids + sulfasalazine RD across time points, 11% to 26%; sulfasalazine rate, 22% to 87% SOE: Low

ASA = aminosalicylates; CI = 95% confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; mg = milligrams; RD = absolute risk difference; RR = relative risk; SOE = strength of evidence; steroid = corticosteroids; vs. = versus; wk = week

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

Scores for the Inflammatory Bowel Disease Questionnaire and the Quality of Life Index range from 32 to 224, with higher scores indicating better quality of life.[36]

Monotherapy Versus Placebo

Corticosteroids Versus Placebo

Table 18 summarizes the effects of corticosteroids to induce remission compared with placebo (see also Appendix D, Evidence Table 4).

Disease Activity Measures

Four trials, comprising 725 participants, compared corticosteroids with placebo to induce remission.[56,64-66]

Budesonide 9 mg had higher remission rates at 2 and 8 weeks compared with placebo in two trials,[65,66] but the finding was statistically significant in only one of the trials at 2[65] and 8 weeks.[66] Budesonide 15 mg was clinically favored at 2 and 8 weeks and was statistically significant at 8 weeks.[66] Prednisone was clinically and statistically favored over placebo at 17 weeks, but not 2 weeks.[56] Methylprednisolone (48 mg/day with taper) was clinically favored over placebo at 3 and 104 weeks, but was statistically significant only at 104 weeks.[64] A meta-analysis of the four trials was not performed because the medications act in different portions of the intestines and the patient populations accordingly differed in location of disease.

Fistula Response

One trial reported in two publications compared prednisone with placebo.[55,56] Nineteen patients had draining perianal disease at the time of randomization. Fistula response was higher in the prednisone group (30 vs.11 percent; study reported $P > 0.05$).

Patient-Reported Outcomes

Two trials with 458 participants compared budesonide with placebo.[65,66] In the larger trial of 258 participants,[66] at 8 weeks mean IBDQ rose from a baseline value of 131 to 138 points in the 3 mg/day group, 125 to 165 points in the 9 mg/day group, 130 to 155 points in the 15 mg/day group, and 130 to 140 points in the placebo group. Budesonide was only clinically and statistically significant compared with placebo at the 9 mg dosage.[66] In a trial of 200 patients, there was no difference between groups.[65] The change in IBDQ score from baseline (values not provided) was 36 points in the 9 mg/day group, 34 points in the 4.5 mg oral twice daily group, and 29 points in the placebo group at 8 weeks.[65]

Table 18. Randomized controlled trials comparing the efficacy of corticosteroids with placebo or another treatment to induce remission among patients with active Crohn's disease at randomization

Author, Year	Followup (Weeks)	Main Intervention (Dose), n	Comparison (Dose), n	Remission Definition	Remission Rate (%)
Greenberg, 1994[66]	2	Budesonide (1.5 mg twice daily), 67	Placebo, 66	CDAI<150	10% vs. 11%
	2	Budesonide (4.5 mg twice daily), 61	Placebo, 66	CDAI<150	32% vs. 11%
	2	Budesonide (7.5 mg twice daily), 64	Placebo, 66	CDAI<150	28% vs. 11%
	8	Budesonide (1.5 mg twice daily), 67	Placebo, 66	CDAI<150	33% vs. 20%
	8	Budesonide (4.5 mg twice daily), 61	Placebo, 66	CDAI<150	51% vs. 20%*
	8	Budesonide (7.5 mg twice daily), 64	Placebo, 66	CDAI<150	43% vs. 20%*
Tremaine, 2002[65]	2	Budesonide (9 mg/day), 80	Placebo, 41	CDAI<150	31% vs. 13%*
	2	Budesonide (4.5 mg twice daily), 79	Placebo, 41	CDAI<150	40% vs. 13%*
	8	Budesonide (9 mg/day), 80	Placebo, 41	CDAI<150	48% vs. 33%
	8	Budesonide (4.5 mg twice daily), 79	Placebo, 41	CDAI<150	53% vs. 33%
Summers, 1979[56]	2	Prednisone (0.5-0.75 mg/kg), 85	Placebo, 77	CDAI<150†	20% vs. 15%
	17	Prednisone (0.5-0.75 mg/kg), 85	Placebo, 77	CDAI<150†	59% vs. 42%*
Malchow, 1984[64]	3	6-methylprednisolone (48 mg/day with taper), 47	Placebo, 58	CDAI<150‡	93% vs. 79%*
	16	6-methylprednisolone (48 mg/day with taper), 47	Placebo, 58	CDAI<150‡	83% vs. 36%*
	104	6-methylprednisolone (48 mg/day with taper), 47	Placebo, 58	CDAI<150‡	33% vs. 8%*
Rutgeerts, 1994[69]	2	Budesonide (9 mg/day), 86	Prednisolone (40 mg/day), 86	CDAI≤150	45% vs. 56%
	10	Budesonide (9 mg/day), 86	Prednisolone (40 mg/day), 86	CDAI≤150	53% vs. 66%
Bar-Meir, 1998[67]	8	Budesonide (9 mg/day), 100	Prednisone (40 mg/day), 101	CDAI<150	51% vs. 53%
Campieri, 1997[68]	2	Budesonide (4.5 mg twice daily), 58	Prednisolone (40 mg/day), 61	CDAI≤150	27% vs. 37%
	2	Budesonide (9 mg/day), 61	Prednisolone (40 mg/day), 61	CDAI≤150	48% vs. 37%
	8	Budesonide (4.5 mg twice daily), 58	Prednisolone (40 mg/day), 61	CDAI≤150	48% vs. 60%
	8	Budesonide (9 mg/day), 61	Prednisolone (40 mg/day), 61	CDAI≤150	60% vs. 60%
Thomsen, 1998[70]	8	Budesonide (9 mg/day), 93	Mesalamine (4 g/day), 89	CDAI<150	69% vs. 45%*
	16	Budesonide (9 mg/day), 93	Mesalamine (4 g/day), 89	CDAI<150	62% vs. 36%*
Tromm 2011[74]	8	Budesonide (9mg/day), 154	Mesalamine (4.5 g/day), 153	CDAI<150	69% vs. 62%
Summers, 1979[56]	3	Prednisone (0.5-0.75 mg/kg/day), 85	Sulfasalazine (1.5 mg/15 kg/day), 74	CDAI<150†	25% vs. 6%
	17	Prednisone (0.5-0.75 mg/kg/day), 85	Sulfasalazine (1.5 mg/15 kg/day), 74	CDAI<150†	59% vs. 29%
Malchow, 1984[64]	3	6-methylprednisolone (48 mg/day with taper), 47	Sulfasalazine (3g/day), 54	CDAI<150‡	93% vs. 87%
	16	6-methylprednisolone (48 mg/day with taper), 47	Sulfasalazine (3g/day), 54	CDAI<150‡	83% vs. 57%
	104	6-methylprednisolone (48 mg/day with taper), 47	Sulfasalazine (3g/day), 54	CDAI<150‡	33% vs. 22%

Table 18. Randomized controlled trials comparing the efficacy of corticosteroids with placebo or another treatment to induce remission among patients with active Crohn's disease at randomization (continued)

Author, year	Followup (Weeks)	Main Intervention (Dose), n	Comparison (Dose), n	Remission Definition	Remission Rate (%)
Gross, 1995[72]	8	6-methylprednisolone (48 mg/day), 16	Aminosalicylates (4.5 g/day), 15	CDAI<150, 60-pt decrease in CDAI	56% vs. 40%
Prantera, 1999[71]	3	6-methylprednisolone (40 mg/day), 31	Aminosalicylate tablets (4 g/day), 35	CDAI<150	61% vs. 46%
	3	6-methylprednisolone (40 mg/day), 31	Aminosalicylate granules (4 g/day), 28	CDAI<150	61% vs. 61%
	12	6-methylprednisolone (40 mg/day), 31	Aminosalicylate tablets (4 g/day), 35	CDAI<150	61% vs. 60%
	12	6-methylprednisolone (40 mg/day), 31	Aminosalicylate granules (4 g/day), 28	CDAI<150	61% vs. 79%
Martin, 1990[73]	12	Prednisone (40 mg/day), 26	Mesalamine (750 mg/day), 19	CDAI < 150	46% vs. 47%
Malchow, 1984[64]	3	6-methylprednisolone (48 mg/day with taper) + sulfasalazine (3g/day), 56	Placebo, 58	CDAI<150‡	98% vs. 79%*
	16	6-methylprednisolone (48 mg/day with taper) + sulfasalazine (3g/day), 56	Placebo, 58	CDAI<150‡	83% vs. 36%*
	104	6-methylprednisolone (48 mg/day with taper) + sulfasalazine (3g/day), 56	Placebo, 58	CDAI<150‡	35% vs. 8%*
Singleton, 1979[75]	8	Prednisone (0.25-0.75 mg/kg/day) + sulfasalazine (1 g/15 kg/day), 46	Prednisone (0.25-0.75 mg/kg/day), 43	CDAI<150	76% vs. 57%
Malchow, 1984[64]	3	6-methylprednisolone (48 mg/day with taper) + sulfasalazine (3g/day), 56	6-methylprednisolone (48 mg/day with taper), 47	CDAI<150‡	98% vs. 93%
	16	6-methylprednisolone (48 mg/day with taper) + sulfasalazine (3g/day), 56	6-methylprednisolone (48 mg/day with taper), 47	CDAI<150‡	83% vs. 75%
	104	6-methylprednisolone (48 mg/day with taper) + sulfasalazine (3g/day), 56	6-methylprednisolone (48 mg/day with taper), 47	CDAI<150‡	35% vs. 33%
Malchow, 1984[64]	3	6-methylprednisolone (48 mg/day with taper) + sulfasalazine (3g/day), 56	Sulfasalazine (3g/day), 54	CDAI<150‡	98% vs. 87%
	16	6-methylprednisolone (48 mg/day with taper) + sulfasalazine (3g/day), 56	Sulfasalazine (3g/day), 54	CDAI<150‡	83% vs. 57%
	104	6-methylprednisolone (48 mg/day with taper) + sulfasalazine (3g/day), 56	Sulfasalazine (3g/day), 54	CDAI<150‡	35% vs. 22%

CDAI = Crohn's Disease Activity Index; g = grams; kg = kilograms; mg = milligrams; pt = point; vs. = versus

*Study reported significance at the 0.05 alpha level. For Malchow 1984,[64] significance level does not specify time point in the 104 week trial – thus all time points are marked as significant for a given comparison where appropriate

†One component of a composite outcome

‡One component of a composite outcome including CDAI criteria (decrease or less than 100 points increase during first treatment, no increase during second treatment, and score less than 150 or 60 point decrease after third treatment), no need to repeat induction therapy, absence of clinical criteria (death due to Crohn's disease, fever for more than 2 weeks, need for Crohn's disease surgery, development of new fistulas or abscesses, or disease worsening by endoscopy or radiography) and not withdrawn from the trial

Monotherapy Versus Monotherapy

Budesonide Versus Other Corticosteroids

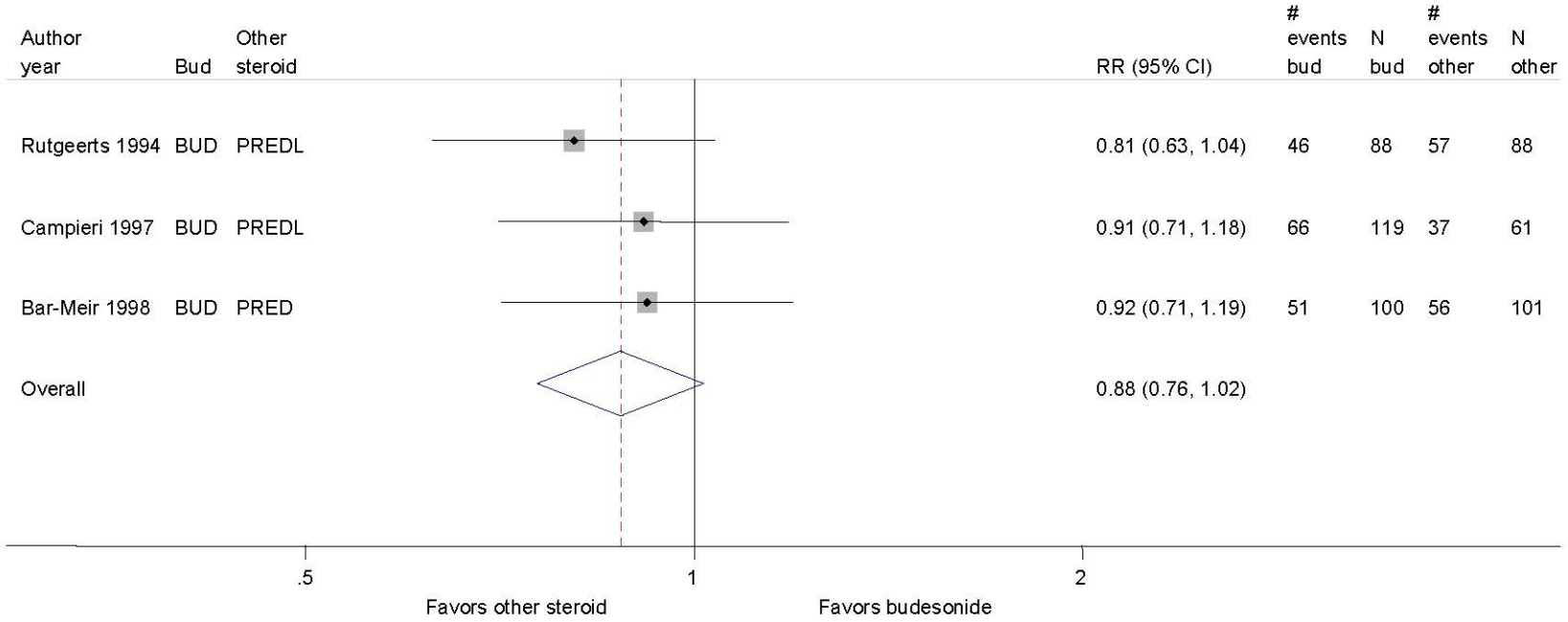
Disease Activity Measures

Three trials, including 553 participants, compared budesonide with prednisone or prednisolone in the ability to induce remission at 2, 8, and 10 weeks after randomization.[67-69] The daily doses were consistent across the trials. The daily dose of budesonide was 9 mg and 40 mg for prednisolone or prednisone. A meta-analysis was performed (Figure 7). We found no clinically meaningful or statistically significant difference in pooled remission rates at 8 weeks (RR of inducing remission, 0.88; 95% CI, 0.76 to 1.02). There was no significant heterogeneity (I-squared, 0 percent).

Patient-Reported Outcomes

One trial with 201 participants compared prednisone and placebo with budesonide and placebo.[67] At 8 weeks, mean IBDQ rose from 130 to 164 in the prednisone group and 136 to 162 in the budesonide group, which did not meet the 17-point difference threshold for clinical significance. Additionally, there were no difference in the Short Form-36 (SF-36) mental score (increase from 42.2 to 60.9 points vs. 46.5 to 56.9 points, respectively) or physical score (increase from 40.8 to 62.3 points vs. 44.8 to 58.3 points, respectively).

Figure 7. Pooled relative risk of inducing remission* of Crohn's disease at week 8 comparing budesonide with another corticosteroid



Pooled Relative Risk and 95% Confidence Intervals of Remission at Week 8

BUD = budesonide; CI = confidence interval; PRED = prednisone; PREDL = prednisolone; RR = relative risk; Steroid = corticosteroid

*In all trials, remission was defined as a Crohn's Disease Activity Index less than 150. Boxes indicate individual trial point estimates. The box size denotes the weight of the trial, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each trial. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q=0.65 with 2 degrees of freedom (p=0.72)

I-squared statistic = 0%

Corticosteroids Versus Aminosalicylates

Disease Activity Measures

Seven trials, including 874 participants, compared corticosteroids with aminosalicylates to induce remission.[56,64,70-74] Meta-analysis was not performed because of the disease location differences in the budesonide trials[70,74] compared with the other trials and differences in time periods of the study and definition of remission in the methylprednisolone and prednisone trials.[56,64,71-73]

The budesonide trials had inconsistent findings.[70,74] The 1998 trial found clinically meaningful and statistically significant results favoring budesonide 9 mg/day compared with mesalamine 4 mg/day at 8 and 16 weeks,[70] but the 2011 budesonide trial found no difference using the same dose of budesonide and 0.5 mg/day more of mesalamine at 8 weeks.[74]

The prednisone trials also had inconsistent results.[56,73] Prednisone 0.5 to 0.75 mg/kg/day was clinically favored over sulfasalazine 1.5 mg/15 kg/day at 3 and 17 weeks, although statistical significance was not reported in the trial.[56] Prednisone 40 mg/day for 2 weeks followed by a decrease in the dose for an additional 10 weeks was no different than mesalamine 750 mg/d at 12 weeks at inducing remission.[73]

The three 6-methylprednisolone trials also had inconsistent results.[64,71,72] The remission outcomes and formulations and doses of aminosalicylates were different between the trials prohibiting meta-analysis. 6-methylprednisolone 48 mg/day was clinically, but not statistically, favored over aminosalicylates 4.5 g/day at 8 weeks.[72] The other two 6-methylprednisolone trials had inconsistent results based on the time of measure and formulation of the aminosalicylate.[64 71]

Fistula Response

Among a subset of 19 patients with draining perianal fistulas at the time of randomization,[56] there was no difference in fistula response at 17 weeks between those receiving prednisone daily versus those receiving sulfasalazine (30 vs. 22 percent).[55]

Patient-Reported Outcomes

One trial with 50 participants compared prednisone with aminosalicylates using the McMaster University Quality of Life Index.[73] At 2 weeks, improvement, not defined in the manuscript, in the Quality of Life Index was 23 percent in the prednisone group and 7 percent in the aminosalicylates group, which met our 10 percent between group difference threshold ($P < 0.005$). At 12 weeks, the improvement was 37 and 33 percent, respectively, and was not clinically meaningful nor statistically significant ($P > 0.05$).

Combination Therapy Versus Placebo

Corticosteroids and Aminosalicylates Versus Placebo

Disease Activity Measures

In the trial[64] that randomized patients with active and inactive disease, the active disease patients that received combination therapy with methylprednisolone (48 mg/day with taper) and sulfasalazine (3 g/day) had clinically and statistically significantly higher rates of remission than the placebo group at 3, 16, and 104 weeks after randomization.

Combination Therapy Versus Monotherapy

Corticosteroids and Aminosalicylates Versus Corticosteroids Alone

Disease Activity Measures

Two trials[64,75] including 192 participants compared a combination of corticosteroids and aminosalicylates versus corticosteroids alone.

One trial found a clinically meaningful difference, but the other trial did not. A trial of 89 participants[75] compared a combination of prednisone and sulfasalazine with prednisone alone. The trial favored combination therapy over prednisone at week 8, but this finding was not statistically significant. The other trial,[64] did not find a clinically meaningful difference between combination therapy with methylprednisolone (48 mg/day with taper) and sulfasalazine (3 g/day) and 6-methylprednisolone (48 mg/day with taper) alone.

Corticosteroids and Aminosalicylates Versus Aminosalicylates Alone

Disease Activity Measures

One trial,[64] including 110 participants, compared a combination of corticosteroids and aminosalicylates with aminosalicylates alone. Combination therapy with 6-methylprednisolone (48 mg/day with taper) and sulfasalazine (3 g/day) resulted in higher rates of remission at 3, 16, and 104 weeks than sulfasalazine (3 g/day) alone. Statistical tests were not reported in the publication for this medication comparison.

Aminosalicylates

Five trials evaluated the effectiveness of aminosalicylates as monotherapy to induce remission.[56,64,77-79] Two trials evaluated sulfasalazine at doses between 1 g/15 kg and 6 g a day,[56 64] two trials evaluated mesalamine (Asacol) between 1 g to 4 g a day,[77,79] and one trial evaluated mesalamine (Pentasa) at 1.5 g a day.[78] Two of these trials included comparisons with corticosteroids[56,64] and one included comparisons with immunomodulators.[56] These trials are also reported in those sections of the report.

Study Design

The five RCTs were double blind (Appendix D, Evidence Table 2).[56,64,77-79] One trial[64] included participants with both active (CDAI greater than 150) and inactive (CDAI less than 150) disease at randomization; patients with active disease were analyzed as part of a subgroup analysis. The trials were conducted in the United States and Europe and had very few inclusions but used different definitions of remission.

The trials took places at multiple centers in the United States,[56,79] Canada,[56] and Europe.[64,78] One trial occurred at a single center in the United States.[77] One trial occurred in the United States and Canada.[56] The trials occurred during the 1970s through 1990s with the most recent publication in 1994.[77] Trial duration ranged from 6[64] to 17 weeks.[56 77] The minimum eligibility age was 18 years in 3 trials and 15 years in two trials.[56 78]

Four trials required a minimum CDAI of 150 and one trial required at least two bowel movements a day to indicate active disease.[78] Maximum CDAI inclusion criteria included 400,[79] 450[56,77] and no upper limit.[64] The trial that required at least two bowel movements per day excluded patients with more than five bowel movements per day or any patient with fever,

inability to work, or other symptoms indicative of severe disease.[78] Disease activity related exclusions were rare. One study excluded patients with abscess,[64] another excluded patients with an extensive resection.[77] Disease location requirements included ileal disease,[64] small bowel disease,[78] and colonic disease.[77]

Remission was defined as a CDAI less than 150 in one trial.[64] Another trial used CDAI less than 150 as part of a composite outcome included clinical events.[56] Two trials required CDAI less than 150 combined with a 50[79] or 70[77] point decrease in the CDAI. The trial that required bowel movements per day for inclusion defined remission based on a review of the clinical notes and endoscopic records.[78]

Most trials prohibited patients from taking therapies that were not assigned as part of the trial. No trial specifically excluded patients with prior use of any medication, although exclusion of patients taking immunomodulators, aminosalicylates, or corticosteroids one week to 90 days before randomization occurred in three trials.[77-79]

Population Characteristics

The trial[64] that included patients with active and inactive disease at randomization did not report the population characteristics separately by disease activity and is not included in the population characteristics summary. The four remaining trials randomized 710 participants (Appendix D, Evidence Table 3). The proportion of male participants in each trial group ranged from 27 to 67 percent. Only two trials[56,77] commented on the percentage of Caucasians, which ranged from 90 to 100 percent among all groups. Only one trial reported on smoking ("smoker"),[79] ranging between 29 and 50 percent across the four groups. Two trials reported mean age at enrollment with means of 30 and 37 years with the other two trials reporting median age at enrollment of 31 and 38 years. All trials reported duration of disease, ranging between 3.3 and 9.9 years (mean) and 3.5 and 7 years (median). All but one trial[77] reported on disease location: ileal-only location ranged between 23 and 100 percent, ileocolonic location between 44 and 85 percent, and colonic location between 9 and 25 percent. All trials reported baseline CDAI, ranging between 205 and 277 (mean) and 153 and 177 (median). We derived the value of 153 from the trial[78] that included participants based on bowel movements per day. None of the trials reported concurrent medication use. Prior medication use was reported in two trials[56,79]: aminosalicylate use was 17 and 38 percent and prior corticosteroids use was 16 and 38 percent.

Key Points

Table 19 summarizes the strength of evidence for the trials evaluating aminosalicylates in terms of remission induction. We found at least moderate strength of evidence or a clinically meaningful difference in the following comparisons:

- Aminosalicylates (mesalamine at least 3.2 g daily, or sulfasalazine) were more effective than placebo in inducing a remission at weeks 16-17 (absolute RD, 12 to 25 percent; placebo rate, 18 to 36 percent). (SOE: Low)
- Sulfasalazine (3 g/day) was more effective than placebo in inducing a remission at week 104 (absolute RD, 14 percent; placebo rate, 8 percent). (SOE: Low)
- Sulfasalazine (1 g/15 kg) was more effective than placebo in healing fistulas at 17 weeks in patients with actively draining fistulas (absolute RD in fistula closure, 11 percent; placebo rate, 11 percent). (SOE: Low)

Table 19. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating aminosalicylates to induce remission among patients with active Crohn's disease at randomization

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect
			Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
ASA vs. placebo-wks 2-3	Disease activity measures	5 (330)[56 64 78]	Medium	Inconsistent	Direct	Imprecise	Favors neither RD, -8 to 9%; placebo rate, 8 to 79% SOE: Low
ASA (mesalamine ≥ 3.2 g daily or sulfasalazine) vs. placebo-wks 16-17	Disease activity measures	5 (456)[56 64 77 79]	Medium	Consistent	Direct	Imprecise	Favors ASA RD, 12 to 25%; placebo rate, 18 to 36% SOE: Low
ASA (mesalamine < 3.2 g daily) vs. placebo-wk 16	Disease activity measures	5 (302)[78 79]	Medium	Consistent	Direct	Imprecise	Favors neither RD, 2 to 6%; placebo rate, 18 to 25% SOE: Low
Sulfasalazine vs. placebo – wk 104	Disease activity measures	1 (112)[64]	High	Unknown (single trial)	Direct	Precise	Favors sulfasalazine RD, 14%; placebo rate, 8% SOE: Low
Sulfasalazine vs. placebo-wk 17	Fistula response	1 (18)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors sulfasalazine RD in fistula closure, 11%; placebo rate, 11% SOE: Low

ASA = aminosalicylates; RD = risk difference; SOE = strength of evidence; vs. = versus; wk = week

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

Monotherapy Versus Placebo

Aminosalicylates Versus Placebo

Disease Activity Measures

Five RCTs involving 678 patients met the inclusion criteria.[56,64,77-79] Table 20 summarizes the effects of aminosalicylate therapy to induce remission (see also Appendix D, Evidence Table 4). A meta-analysis was not performed due to variability in aminosalicylate preparation, doses, outcome definitions, and outcome time points. Four of five trials clinically favored aminosalicylates over placebo at one or more time points but only two trials reported statistical significance at the last reported time point.[64,79]

Fistula Response

One trial reported in two publications compared daily sulfasalazine with placebo.[55,56] Eighteen patients had draining perianal disease at the time of randomization. Fistula response was higher in the sulfasalazine group (22 vs. 11 percent) but was not statistically significant ($P > 0.05$).

Table 20. Randomized controlled trials comparing the efficacy of aminosalicylates with placebo to induce remission among patients with active Crohn's disease at randomization

Author, Year	Followup (Weeks)	Main Intervention (Dose), n	Total Dose (g/day)	Comparison, n	Remission Definition	Remission Rate (%)
Summers, 1979[56]	3	Sulfasalazine (1 g/15 kg/day), 74	1g/15 kg	Placebo, 77	CDAI<150†	20% vs. 11%
	17	Sulfasalazine (1 g/15 kg/day), 74	1 g/15 kg	Placebo, 77	CDAI<150†	42% vs. 30%
Malchow, 1984[64]	3	Sulfasalazine (3 g/day), 54	3	Placebo, 58	CDAI<150‡	87% vs. 79%*
	16	Sulfasalazine (3 g/day), 54	3	Placebo, 58	CDAI<150‡	57% vs. 36%*
	104	Sulfasalazine (3 g/day), 54	3	Placebo, 58	CDAI<150‡	22% vs. 8%*
Rasmussen, 1987[78]	2	Mesalamine (1500 mg every 24 hr), 30	1.5	Placebo, 37	CDAI decrease by >33%	0% vs. 8%
	16	Mesalamine (1500 mg every 24 hr), 30	1.5	Placebo, 37	CDAI decrease by >33%	27% vs. 25%
Singleton, 1993[79]	16	Mesalamine (1 g every 24 hr), 80	1	Placebo, 80	CDAI≤150 and 50-pt decrease	23% vs. 18%
	16	Mesalamine (2 g every 24 hr), 75	2	Placebo, 80	CDAI≤150 and 50-pt decrease	24% vs. 18%
	16	Mesalamine (4 g every 24 hr), 75	4	Placebo, 80	CDAI≤150 and 50-pt decrease	43% vs. 18%*
Tremaine, 1994[77]	16	Mesalamine (800 mg every 6 hr), 20	3.2	Placebo, 18	CDAI<150 and 70-pt decrease	45% vs. 22%

CDAI = Crohn's Disease Activity Index; g = gram; HBI = Harvey-Bradshaw Index; hr = hour; kg = kilogram; mg = milligram; pt = point; vs. = versus

*Study report significant difference at 0.05 alpha level. For Malchow 1984,[64] significance level does not specify time point in the 104 week trial – thus all time points are marked as significant for a given comparison where appropriate

†One component of a composite outcome.

‡One component of a composite outcome including CDAI criteria (decrease or less than 100 points increase during first treatment, no increase during second treatment, and score less than 150 or 60-point decrease after third treatment), no need to repeat induction therapy, absence of clinical criteria (death due to Crohn's disease, fever for more than 2 weeks, need for Crohn's disease surgery, development of new fistulas or abscesses, or disease worsening by endoscopy or radiography) and not withdrawn from the trial

Comparative Effectiveness of Therapies To Induce Remission in Adult Subgroups

We abstracted all subgroup analyses that reported on all levels of the effect-modifying variable (Appendix G). Only trials that performed a statistical test for interaction were included in this section.

Key Points

- We saw no consistent relationship for the interaction of a medication and disease characteristic on remission rates in adults with Crohn's disease.

Baseline CRP

Three trials reported results by baseline CRP in categories of high versus low CRP.[37 38 45] Only one trial,[38] which evaluated remission at 4 weeks for adalimumab versus placebo, reported a *P*-value for an interaction term. Remission rates for high-versus-low CRP (cutoff at 10 mg/L) did not differ between groups ($P=0.67$).

Baseline Corticosteroid Use

Three trials reported a subgroup analysis by baseline corticosteroid use.[38 44 45] Only one trial,[38] that evaluated remission at 4 weeks for adalimumab versus placebo, reported a *P*-value for an interaction term. Remission rates were higher for patients who were on corticosteroids at the time of randomization ($P=0.01$).

Baseline Immunomodulator Use

Four trials reported a subgroup analysis by baseline immunomodulator use.[33,37-39] Two of the trials[33,38] reported a *P*-value for an interaction term. One trial,[38] evaluating 4 week remission for adalimumab versus placebo, found no effect of baseline immunomodulator use ($P=0.88$). Another trial, evaluating natalizumab versus placebo at 10 weeks, found higher response and remission rates for patients on baseline immunomodulators at randomization ($P < 0.05$).

Prior TNF-Alpha Inhibitor Exposure

Three trials reported a subgroup analysis by prior TNF-alpha inhibitor use.[33,39,80] Only one trial,[33] which evaluated natalizumab versus placebo at 10 weeks, reported a *P*-value for an interaction term. Response rates were higher for patients with prior TNF-alpha inhibitor exposure ($P < 0.05$). The trial saw no effect for remission ($P > 0.05$).

The following subgroup analyses were reported in the trials, but did not meet the criteria for inclusion: baseline mucosal lesions, baseline aminosalicylates, baseline antibiotic use, prior immunomodulator exposure, prior aminosalicylates exposure, prior corticosteroids exposure, disease duration, disease location, and prior Crohn's disease-related surgery.

Quality Assessment

Out of the 53 trials included in this report that addressed KQ1, 32 percent were rated as good quality, 45 percent as fair quality, and 23 percent as poor quality (Appendix D, Evidence Table 5). All were RCTs with parallel group design by inclusion criteria for the systematic review. Among these 53 RCTs, 59 percent reported adequately generated allocation sequence. Sixty-two

percent adequately concealed allocation. Seventy-two percent reported being double blinded while 28 percent were not double blinded or did not report on blinding. Seventy percent of trials reported withdrawals and dropouts while 30 percent had incomplete outcome data. Fifty-one percent of these RCTs had some form of threat to the validity of results that they reported such as not clearly differentiating between patients with active and inactive disease or not performing a statistical test for interaction in subgroup analyses. Seventy percent received pharmaceutical support with 38 percent having pharmaceutical company employed co-authors. Twenty-three percent did not report on conflicts.

Key Question 2: Effectiveness of Therapies To Maintain Remission in Adults

Table 21 summarizes the evidence grades and specific conclusions for each comparison. Details of the evidence grades are included in the Results and in Appendix D, Table 6.

Table 21. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to maintain remission*

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 48-54	Disease Activity Measure After 54 Weeks	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Natalizumab vs. placebo 48 weeks	Favors natalizumab; Moderate	Insufficient	Insufficient	Insufficient	Insufficient	*Week 48* Favors natalizumab; Moderate	Insufficient	*Week 48* Favors natalizumab; Moderate
Adalimumab vs. placebo 52 weeks	Favors adalimumab; Low	Insufficient	Insufficient	*Week 52* Favors adalimumab for all-cause hospitalizations Favors neither for CD-related hospitalizations; Moderate	*Week 52* Favors neither; Moderate	*Week 52* Favors adalimumab; Low	Insufficient	*Week 52* Favors neither; Low
CP vs. placebo 18 weeks	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 18* Favors neither; Low
Infliximab vs. placebo 52 weeks	Favors neither among all randomized Favors infliximab among responders; Low	Insufficient	*Week 52* Favors infliximab; Low	*Week 52* Favors infliximab; Moderate	*Week 52* Favors neither among patients with fistulizing disease; Moderate	*Week 52* Favors infliximab; Low	*Week 40* Favors infliximab; Low	*Week 52* Favors infliximab; Low
Infliximab + azathioprine vs. infliximab 104 weeks	Insufficient	*Week 104* Favors neither; Low	*Week 104* Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	*Week 104* Favors neither; Low
Infliximab + azathioprine vs. infliximab + hydrocortisone 104 weeks	Favors neither; Low	*Week 104* Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table 21. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to maintain remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 48-54	Disease Activity Measure After 54 Weeks	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Azathioprine vs. placebo 104 weeks	Favors azathioprine (≥1.7 mg/kg/day) Favors neither (<1 mg/kg/day); Low	*Week 104* Favors azathioprine (≥1.7 mg/kg/day) Favors neither (<1 mg/kg/day); Low	Insufficient	Insufficient	Insufficient	*Week 26* Favors azathioprine; Low	Insufficient	Insufficient
Azathioprine vs. budesonide 52 weeks	Favors azathioprine; Low	Insufficient	*Week 52* Favors azathioprine; Moderate	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Azathioprine vs. prednisone 104 weeks	Favors azathioprine; Low	*Week 104* Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Azathioprine vs. sulfasalazine 104 weeks	Favors neither; Low	*Week 104* Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Methotrexate (IM) vs. placebo 40 weeks	*Week 40* Favors methotrexate; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide vs. placebo 52 weeks	Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 52* Favors neither; Low
Prednisone vs. placebo 104 weeks	Favors neither; Low	*Week 104* Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table 21. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to maintain remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure Weeks 48-54	Disease Activity Measure After 54 Weeks	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
6-methyl-prednisolone vs. placebo 104 weeks	Favors 6-methyl-prednisolone; Low	*Week 104* Favors 6-methyl-prednisolone; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide vs. mesalamine 52 weeks	Favors budesonide; Moderate	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 52* Favors budesonide; Moderate
Steroids (other) vs. sulfasalazine 104 weeks	Favors neither; Low	*Week 104* Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
6-methyl-prednisolone + sulfasalazine vs. placebo 104 weeks	Favors neither; Low	*Week 104* Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. steroids 104 weeks	Favors neither; Low	*Week 104* Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. sulfasalazine 104 weeks	Favors neither; Low	*Week 104* Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Mesalamine (controlled-release) vs. placebo 52 weeks	Favors mesalamine; Low	*Week 104 Favors neither; Moderate*	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Week 48 Favors neither; Low

Table 21. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to maintain remission* (continued)

Comparison Maximum trial duration	Disease activity measure Weeks 48-54	Disease activity measure After 54 weeks	Mucosal healing	Hospitalizations	Surgeries	Reduction of steroids	Fistula response	Inflammatory Bowel Disease Questionnaire†
Mesalamine (pH-release) vs. placebo 208 weeks	Favors mesalamine; Low	*Week 104* Favors placebo; Low *Week 208* Favors mesalamine; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Olsalazine vs. placebo 52 weeks	Favors neither; Moderate	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Sulfasalazine vs. placebo 104 weeks	Favors neither; Low	*Week 104* Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

ASA = aminosalicylates; CP = certolizumab pegol; NA = not applicable; evidence grading was not conducted for this comparison and outcome; Steroids = corticosteroids; TNF = tumor necrosis factor-alpha inhibitor; vs. = versus

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

*All other comparisons and outcomes were graded as insufficient because there were no eligible trials.

†Patient reported outcomes were measured by the Inflammatory Bowel Disease Questionnaire except where indicated by a footnote. Scores for the Inflammatory Bowel Disease Questionnaire range from 32 to 224, with higher scores indicating better quality of life.[36]

Natalizumab

Trial Design and Population Characteristics

One placebo-controlled RCT reported in two publications evaluated the efficacy of natalizumab to maintain remission subsequent to an induction trial reported in KQ1 (Appendix D, Evidence Tables 7 and 8).[33,81] The maintenance trial randomized 339 patients who responded to natalizumab or placebo as defined by a 70-point decrease from baseline CDAI at weeks 10 and 12, had an absolute CDAI less than 220 at week 12 and who did not require an intervention.[33] The induction responders were randomized to the same dose used in the induction trial. The induction non-responders were randomized, but their results were not reported. Participants received an intravenous infusion every 4 weeks of natalizumab 300 mg (n=168) or placebo (n=171) for 44 weeks and were followed for 48 weeks. Concomitant medications allowed during the trial period included aminosalicylates, corticosteroids, immunomodulators, and antibiotics.

The population characteristics are described in KQ1.[81] There were no major differences between the induction and maintenance populations. However, the placebo and natalizumab groups differed in the maintenance trial. Placebo patients were more likely to be female, more likely to smoke, and had a 13-point higher mean CDAI at the beginning of the maintenance trial.[33]

Key Points

Table 22 summarizes the strength of evidence for the trial evaluating natalizumab in terms of maintenance of remission. We found at least moderate strength of evidence or a clinically meaningful difference for the following areas:

- Natalizumab (300 mg every 4 weeks) was more efficacious than placebo to maintain remission at week 48 among patients who achieved at least a response during a natalizumab induction trial (48-week absolute RD, 33 percent; placebo rate, 22 percent). (SOE: Moderate)
- Natalizumab patients were less likely to require steroids than placebo among patients in a sustained remission at 48 weeks (absolute RD, 27 percent; placebo rate, 15 percent). (SOE: Moderate)
- Natalizumab was favored over placebo as measured by a patient-reported outcome at week 48, although both natalizumab and placebo patients had lower scores at the end of the trial (absolute between-group difference in change in mean IBDQ from randomization, 19 points; placebo mean change in IBDQ, -23 points). (SOE: Moderate)

Table 22. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating natalizumab to maintain remission

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Natalizumab vs. placebo–wk 48	Disease activity measures	1 (339)[33]	Medium	Unknown (single study)	Direct	Precise	Favors natalizumab RD, 33%; placebo rate, 22% SOE: Moderate
Natalizumab vs. placebo–wk 48	Reduction of steroids	1 (143)[33]	Medium	Unknown (single study)	Direct	Precise	Favors natalizumab RD, 27%; placebo rate, 15% SOE: Moderate
Natalizumab vs. placebo–wk 48	Patient-reported outcomes	1 (217)[81]	Medium	Unknown (single study)	Direct	Precise	Favors natalizumab Absolute between-group difference in change in mean IBDQ from randomization to induction trial, 19 pts; placebo change in mean IBDQ, -23 pts SOE: Moderate

IBDQ = Inflammatory Bowel Disease Questionnaire; pts = points; pts = points; RD = absolute risk difference; SOE = strength of evidence; wk = week

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

Scores for the Inflammatory Bowel Disease Questionnaire range from 32 to 224, with higher scores indicating better quality of life.[36]

Monotherapy Versus Placebo

Natalizumab Versus Placebo

Disease Activity Measures

At week 48, 33 percent more natalizumab patients were in remission than placebo, which was clinically meaningful and statistically significant (Table 23).[33] The persistence of remission from the time of randomization was also reported. Of the 250 patients who were in remission at the time of randomization, 39 percent in the natalizumab group and 15 percent in the placebo group (24 percent difference) remained in remission for all measures through 48 weeks (trial reported $P < 0.001$). We presented details of the results in Appendix D, Evidence Table 9.

Table 23. Randomized controlled trials comparing the efficacy of natalizumab with placebo to maintain remission at week 48 in patients with Crohn's disease who have at least achieved a response to a prior induction trial

Author, Year	Followup (Weeks)	Main Intervention (Dose), n	Comparison, n	Remission Rate (CDAI<150, No Need for Rescue Therapy, and No Missing Data), %
Sandborn, 2005[33]	48	Natalizumab (300 mg IV every 4 wks), 168	Placebo, 171	55% vs. 22%*

IV = intravenous; wks = weeks
*Trial reported $P < 0.05$

Reduction of Steroids

Of the 143 patients in sustained remission at 48 weeks, 42 percent of the natalizumab group no longer required treatment with corticosteroids compared with 15 percent in the placebo group. This finding is clinically meaningful and statistically significant ($P < 0.001$).[33]

Patient-Reported Outcomes

Patient-reported outcomes were reported in a separate publication from the disease activity measures.[81] Forty-eight weeks after the initiation of maintenance therapy, the mean change in IBDQ decreased in both groups, but the decrease was not as substantial for natalizumab and the difference met the clinically meaningful difference threshold. At 48 weeks, the mean total IBDQ score dropped from 184 to 180 in the natalizumab group and from 179 to 156 in the placebo group, the difference between groups was statistically significant when measured from the value at the beginning of the induction trial ($P < 0.001$), but was not reported from the beginning of the maintenance trial. There were no meaningful differences between any component of the SF-36 between randomization for the maintenance trial and week 48.

TNF-Alpha Inhibitors

Eight trials evaluated a TNF-alpha inhibitor as monotherapy or in combination with another drug to maintain remission. Six of the trials compared TNF-alpha inhibitor monotherapy with placebo: two evaluated adalimumab,[82,83] one evaluated certolizumab pegol,[84] and three evaluated infliximab.[85-87] The two combination therapy trials focused on the role of azathioprine with infliximab. One trial compared a combination of infliximab and azathioprine versus infliximab with hydrocortisone pretreatment.[88] An azathioprine withdrawal trial[89] examined a combination

of infliximab and azathioprine versus infliximab alone in patients that previously controlled their disease for at least 6 months using a combination of infliximab and azathioprine.

Trial Design

Eight RCTs reported in 16 publications met the inclusion criteria (Appendix D, Evidence Table 7).[82-97] Trials reported in multiple publications included an adalimumab trial with four publications,[82,90,95,96] an infliximab trial with four publications,[86,91,93,94] and another infliximab trial with three publications.[87,92,97]

Six of the eight RCTs were blinded.[82-87] The two combination therapy trials were not blinded. In the hydrocortisone pre-treatment trial, the patients were aware which medications they were taking but the investigators were not.[88] In the azathioprine withdrawal trial, all participants and study personnel were aware of the treatment assignment.[89] All trials except the azathioprine withdrawal trial[89] had run-in periods when all patients received the study drug prior to randomization. The duration of the run-in period ranged between 2 and 12 weeks. Subsequent to the run-in period, the trials randomized all patients or those that had a clinical response (CDAI drop of 70 to 100 points) or remission (CDAI<150). In five trials, an inclusion criteria at the start of the trial (before the run-in) was a CDAI of 220 to 450.[82-86] All trials reported a CDAI outcome except one study that used fistula closure at 14 weeks as a measure of response.[87]

All trials allowed patients to take medications to treat their Crohn's disease as long as they were using them at stable doses during the trial. Most studies allowed for stable doses of prednisone (20-30mg or less), thiopurines or methotrexate, aminosalicylates, and antibiotics at entry. Two studies evaluating adalimumab and certolizumab pegol allowed for prior exposure to an TNF-alpha inhibitor more than 12 weeks from randomization[82 84] as long as the patients responded to the drug and did not have an adverse reaction. Two trials[83 88] did not permit prior TNF-alpha inhibitor use. In the azathioprine withdrawal trial, all participants had used infliximab and azathioprine for at least 6 months prior to randomization.[89] Because infliximab was the first approved TNF-alpha inhibitor agent for Crohn's disease, patients in the three infliximab trials[85-87] would not have received TNF-alpha inhibitors prior to the induction or run-in period.

Not all patients had entered remission by using the study drug. In two trials,[83 85] the run-in period occurred as part of induction trials that are described in KQ1.[37 43] These two trials differ from the others because patients who experienced clinical remission[85] or response[83] using placebo were eligible for randomization. In three trials, all patients who received the induction doses during the run-in period were randomized, even if they did not experience clinical remission or response after the induction dose.[82,86,87] The results for the responders are reported because these results are most representative of maintenance of remission consistent with our definition for this KQ. The results for all patients who were randomized, representing the intention to treat population, are also summarized when available.

In four studies randomized patients were not required to complete the study using the assigned treatment.[82,83,86,87] Patients who relapsed were permitted to withdraw from the trial and initiate active drug or increase the dose of the drug. Patients who withdrew were considered not in remission for the disease activity endpoints. For hospitalization and surgery, one study considered patients as hospitalized or as having had surgery among those who withdrew and initiated active drug or increased dose,[90] while another allowed patients to switch to active drug or increase dose and were not considered treatment failures in the hospitalization and surgery analyses.[94] For other outcomes including fistula response, reduction of steroids, and patient-reported outcomes, it was unclear if patients who withdrew were considered treatment failures.

To account for the patients who were no longer followed under ideal RCT conditions (unaware of treatment assignment and disease activity unrelated to treatment), the risk of bias was considered Medium or High for these trials. Early withdrawal and downgrading of the risk of bias for outcomes other than disease activity occurred for adalimumab at 8 weeks[82,95] and infliximab at 12 weeks.[86,87,94]

Five out of eight trials took place in North America,[82,83,85-87] while seven out of eight took place in Europe.[82,83,85-89] All of the trials but one[88] was multicenter in design. The starting year of enrollment ranged between 1995 and 2004. Following randomization, the maximum trial duration was 52 weeks (range, 18 to 104 weeks). All trials were limited to adult patients with Crohn's disease, although one trial[89] included patients 16 years and older.

Population Characteristics

The trials randomized 1,798 patients (Appendix D, Evidence Table 8). Males comprised 44 percent of participants. Response to open-label induction was 64 percent for the largest adalimumab maintenance trial,[82] 64 percent for the only certolizumab pegol trial,[84] and 59 percent for the largest infliximab maintenance trial.[86] Response to open-label drug in the infliximab fistula trial was 69 percent.[87] The remission rate of those who enrolled from the primary adalimumab induction trial[37] into a subsequent maintenance trial[83] was 20 percent. Only one trial reported race,[90] which was more than 90 percent Caucasians. Of trials that reported current smokers, rates ranged from 32 to 45 percent. Median duration of disease ranged from 5 to 12 years. Mean age at enrollment ranged between 34 to 38 years old. Disease location distribution was as follows: ileal, 16 to 30 percent; ileocolonic, 46 to 62 percent; and colonic 17 to 39 percent. Mean CDAI after the run-in period ranged from 152 to 170, reflecting that some patients attained a remission while others attained only a response. Drug use rates were as follows: concomitant aminosalicylates, 38 to 74 percent; corticosteroids, 21 to 56 percent; thiopurine, 11 to 42 percent, and methotrexate, 0 to 12 percent.

Key Points

Table 24 summarizes the strength of evidence for the trials evaluating a TNF-alpha inhibitor in terms of maintenance of remission. We found at least moderate strength of evidence or a clinically meaningful difference in the following comparisons:

- Adalimumab was more efficacious than placebo in maintaining a remission at week 52 among patients who had at least a response to open-label adalimumab (range in week 52 absolute RD, 11 to 39 percent; placebo rate range, 12 percent to 44 percent). (SOE: Low)
- Adalimumab was superior to placebo in decreasing Crohn's disease-related hospitalization rates during a 52-week period in patients who have achieved at least a response to open-label drug (HR, 0.4; 95% CI, 0.2 to 0.7). (SOE: Moderate)
- Adalimumab and placebo did not differ in decreasing surgical rates during a 52-week period in patients who had achieved at least a response to open-label drug (surgery rates, 0.3 percent for adalimumab group and 4.1 percent for placebo group). (SOE: Moderate)
- Adalimumab was superior to placebo in maintaining a steroid-free state at 52 weeks in patients who had achieved at least a response to open-label drug and were able to come off steroids (absolute RD in steroid-free state, 10 to 31 percent; placebo rate, 6 to 57 percent). (SOE: Low)

- Certolizumab pegol (400 mg every 4 weeks) was more efficacious than placebo to maintain remission at week 18 among patients who had at least a response to open-label certolizumab pegol (absolute RD, 19 percent; placebo rate, 29 percent). (SOE: Low)
- Infliximab was more efficacious than placebo to maintain remission at week 52 among patients who had at least a response to open-label infliximab (absolute RD, 6 to 25 percent; placebo rate, 15 to 35 percent). (SOE: Low)
- Infliximab was superior to placebo in achieving mucosal healing at week 52 in patients who have achieved at least a response to open-label drug (absolute RD, 26 to 43 percent; placebo rate, 7 to 18 percent). (SOE: Low)
- Infliximab was superior to placebo in decreasing Crohn's disease-related hospitalization rates during a 52-week period (including both responders and non-responders to induction) (9 to 23 per 100 patients in the infliximab group, 19 to 38 per 100 patients in the placebo group). (SOE: Moderate).
- Infliximab was no different from placebo in decreasing Crohn's disease-related surgeries during a 52-week period (including both responders and non-responders to induction) (3% in the infliximab group, 8% in the placebo group). (SOE: Moderate)
- Infliximab was superior to placebo in decreasing surgical rates during a 40-week period in patients with active fistulizing disease who had achieved fistula response to open-label drug (number of surgeries and procedures per 100 patients, 65 surgeries/procedures for infliximab and 126 surgeries/procedures per 100 patients for placebo). (SOE: Moderate)
- Infliximab was superior to placebo in reducing corticosteroid use at week 52 in patients who had achieved at least a response to open-label drug (discontinuation of steroids while in remission, OR, 4.2; 95% CI, 1.5 to 11.5). (SOE: Low)
- Infliximab was superior to placebo in closing fistulas at week 40 in adults with Crohn's disease who had achieved an initial fistula response to open-label drug (absolute RD, 17 percent; placebo rate, 19 percent). (SOE: Low)
- Infliximab was superior to placebo in improving patient-reported outcomes at weeks 28 and 52 in patients who had achieved at least one response to open-label drug (absolute between-group difference in change in mean IBDQ from baseline [prior to open-label run-in], -5 to 23 points; placebo mean change in IBDQ, -31 to 9 points). (SOE: Low)

Table 24. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating a TNF-alpha inhibitor to maintain remission

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Adalimumab vs. placebo–wk 52	Disease activity measures	2 (554)[82 83 95]	High	Consistent	Direct	Precise	Favors adalimumab RD range, 11% to 39%; placebo rate range, 12% to 44% SOE: Low
Adalimumab vs. placebo–wk 52	Hospitalization	1 (778)[90]	Medium	Unknown (single study)	Direct	Precise	Favors adalimumab for all-cause hospitalizations Favors neither for Crohn's disease related hospitalizations RD range, -6% to -13%; placebo rate range, 16% to 25% SOE: Moderate
Adalimumab vs. placebo–wk 52	Surgery	1 (778)[90]	Medium	Unknown (single study)	Direct	Precise	Favors neither RD, -3.4%; placebo rate, 3.8% SOE: Moderate
Adalimumab vs. placebo–wk 52	Reduction of steroids	2 (219)[82 83]	High	Consistent	Direct	Precise	Favors adalimumab RD, 10% to 31%; placebo rate, 6% to 57% SOE: Low
Adalimumab vs. placebo–wk 52	Patient-reported outcomes	2 (554)[95 96]	High	Consistent	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from randomization, 14 to 22 pts; placebo mean change, -10 to -25 pts SOE: Low
CP vs. placebo–wk 18	Disease activity measures	1 (428)[84]	Medium	Unknown (single study)	Indirect	Precise	Favors CP RD, 19%; placebo rate, 29% SOE: Low
CP vs. placebo–wk 18	Patient-reported outcomes	1 (424)[84]	Medium	Unknown (single study)	Indirect	Precise	Favors neither Difference in final adjusted mean IBDQ, 8 pts; final placebo mean, 163 pts SOE: Low

Table 24. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating a TNF-alpha inhibitor to maintain remission (continued)

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Infliximab vs. placebo–wk 52	Disease activity measures	1 (573)[86 94]	High	Unknown (single study)	Direct	Imprecise	Favors neither among all randomized Favors infliximab among responders to induction RD range, 6% to 25%; placebo rate, 15% to 35% SOE: Low
Infliximab vs. placebo–wk 52	Mucosal healing	1(58)[91 94]	High	Unknown (single study)	Direct	Precise	Favors infliximab RD, 26% to 43%; placebo rate, 7% to 18% SOE: Low
Infliximab vs. placebo–wk 40, 52	Hospitalization	2 (855)[92 94]	Medium	Consistent	Direct	Precise	Favors infliximab Crohn's disease-related hospitalizations per 100 patients, 9 to 23 in infliximab group, 19 to 38 in placebo group SOE: Moderate
Infliximab vs. placebo–wk 52	Surgery	1 (573)[94]	Medium	Unknown (single study)	Direct	Precise	Favors neither Rate of Crohn's disease-related surgery, 3%; placebo rate, 8% SOE: Moderate
Infliximab vs. placebo (patients with fistulas) –wk 40	Surgery	1 (195)[92]	Medium	Unknown (single study)	Direct	Precise	Favors infliximab Rate of Crohn's disease-related surgery per 100 patients, 65; placebo rate per 100 patients, 126 SOE: Moderate
Infliximab vs. placebo–wk 52	Reduction of steroids	1 (325)[86]	High	Unknown (single study)	Direct	Precise	Favors infliximab RD, 20%; placebo rate, 9% SOE: Low
Infliximab vs. placebo–wk 40	Fistula response	1 (282)[87]	Medium	Unknown (single study)	Indirect	Precise	Favors infliximab RD, 17%; placebo rate, 19% SOE: Low

Table 24. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating a TNF-alpha inhibitor to maintain remission (continued)

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Infliximab vs. placebo–wks 36-52	Patient-reported outcomes	3 (603)[85 87 93]	High	Inconsistent	Direct	Imprecise	Favors infliximab Absolute between-group difference in change in median IBDQ -5 to 23 pts; placebo mean change, -31 to 9 pts SOE: Low
Infliximab + azathioprine vs. infliximab–wk 104	Disease activity measures	1 (80)[89]	High	Unknown (single study)	Direct	Imprecise	Favors neither Absolute difference [with regard to need for infliximab stoppage or change in dosage interval], 5%; infliximab alone rate, 55% SOE: Low
Infliximab + azathioprine vs. infliximab–wk 104	Mucosal healing	1 (49)[89]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD for absence of ulcers, 3%; infliximab alone rate, 61% SOE: Low
Infliximab + azathioprine vs. infliximab–wk 104	Patient-reported outcomes	1 (80)[89]	High	Unknown (single study)	Direct	Imprecise	Favors neither Difference in overall median IBDQ, -2 pts; infliximab only median, 176 pts SOE: Low
Infliximab + azathioprine vs. infliximab + hydrocortisone IV premedication –wk 52, 104	Disease activity measures	1 (46)[88]	High	Unknown - (single study)	Direct	Imprecise	Favors neither RD across time points, -5%; infliximab and hydrocortisone rate range, 77% to 84% SOE: Low

CI = 95% confidence interval; CP = certolizumab pegol; HR = hazard ratio; IBDQ = Inflammatory Bowel Disease Questionnaire; NA = not applicable; OR = odds ratio; pts = points; RD = absolute risk difference; SOE = strength of evidence; TNF = tumor necrosis factor; wk = week

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

Scores for the Inflammatory Bowel Disease Questionnaire range from 32 to 224, with higher scores indicating better quality of life.[36]

Monotherapy Versus Placebo

TNF-Alpha Inhibitors Versus Placebo

Disease Activity Measures

Six trials published in nine publications reported on disease activity.[82-86,94,95,97] Table 25 summarizes the effects of TNF-alpha inhibitor therapy versus placebo to maintain remission at week 52. Among all patients who were randomized and among those who responded to induction dosing, adalimumab was consistently favored over placebo according to the clinically meaningful difference and statistical significance. Infliximab was favored over placebo only among responders to induction dosing.

Three trials (totaling 889 patients) compared infliximab or adalimumab with placebo at 52 weeks.[82,83,86,94,95] The efficacy differed between the analyses that included responders to induction and all randomized patients. Two of these trials reported results for all randomized patients and responders to induction dosing. In the analysis of all randomized patients for the adalimumab trial at 52 weeks, remission rates were 51, 49, and 38 percent for the 40 mg every other week, 40 mg weekly, and placebo groups, respectively ($P < 0.05$ for both groups vs. placebo).[95] The responders to induction dosing also had clinically and statistically significant results at 52 weeks.[82] In contrast, the infliximab trial did not have clinically or statistically significant results when all randomized patients were analyzed at 52 weeks (41 vs. 35 percent),[94] but did have clinically and statistically significant results in the responders to induction analysis.[86] In the third trial[83] that randomized patients who achieved remission in an induction trial,[37] remission rates were clinically and statistically significantly higher in the adalimumab compared with the placebo group. A meta-analysis was not performed because two trials randomized all patients after induction dosing and one trial randomized those in remission after an induction trial.

In two trials, the last reported time point was earlier than 48 weeks: 18 weeks for certolizumab pegol[84] and 28 weeks for infliximab.[85] Both trials found clinically meaningful differences compared with placebo, although only the certolizumab pegol results were statistically significant. An infliximab trial that included women with rectovaginal fistulas was not included because it reported changes in median CDAI scores rather than remission and the last reported time point was 40 weeks.[97]

Mucosal Healing

One infliximab trial[94] included 58 patients with ulceration at baseline who received an additional colonoscopy at 52 weeks.[91] In the analysis of all randomized patients (44 vs. 18 percent; $P=0.04$)[94] and the analysis of responders to induction (50 vs. 7 percent; $P=0.007$),[91] the infliximab groups were more likely to have clinically meaningful and statistically significant complete mucosal healing (absence of ulcers) at 52 weeks compared with placebo.

Hospitalization

Three trials reported on hospitalizations.[90,92,94] Adalimumab and infliximab were consistently favored over placebo at 52 weeks according to the clinically meaningful threshold and were statistically significant.

One trial[90] with 778 randomized participants compared adalimumab with placebo at 52 weeks with regard to Crohn's disease-related and all-cause hospitalizations. The results were

clinically meaningful for all-cause but not Crohn's disease-related hospitalizations. Those who received the drug either every other week or weekly had a 14 and 12 percent risk of 12-month all-cause hospitalization respectively, compared with 25 percent for placebo ($P < 0.01$ for both comparisons with placebo based on a log-rank test). The 12-month risk of Crohn's disease-related hospitalizations was 10 and 7 percent, respectively, compared with 16 percent for placebo ($P < 0.02$ for both comparisons with placebo based on a log-rank test). The clinically meaningful results for all-cause but not Crohn's disease-related hospitalizations was also found in analysis restricted to responders to induction therapy.

Two infliximab trials reported on hospitalizations.[92,94] One infliximab trial[94] randomized 573 participants and evaluated the rate of hospitalization. At 52 weeks, the rates of Crohn's disease-related hospitalization per 100 patients were 23, 24, and 38 in the 5 mg/kg infliximab, 10 mg/kg infliximab, and placebo groups, respectively ($P < 0.05$ for both comparisons). The finding was clinically meaningful and statistically significant for both doses of infliximab.

The infliximab trial that included only patients with draining fistulas[92] compared infliximab with placebo among the 282 randomized patients and the 195 patients to had a response to the induction dose. Among the 282 randomized patients, hospitalizations occurred in 9 percent of the infliximab and 19 percent of the placebo group by week 40. This difference was clinically meaningful and statistically significant for all randomized patients and among those who responded to the induction dose ($P < 0.05$).

Surgery

The same three trials that reported on hospitalizations also reported on surgeries.[90,92,94] Compared with placebo, there was no difference in the occurrence of surgery according to the clinically meaningful threshold when considering the rate equivalent of the 10 percent difference threshold to be a difference in 10 per 100 patients between groups. All three trials reported statistically significant findings.

One trial compared adalimumab with placebo with regard to Crohn's disease-related surgeries in 778 randomized patients.[90] Surgeries for abscess drainage and seton placement were not counted as events.[90] At 52 weeks, fewer Crohn's disease-related surgeries occurred in the groups who received adalimumab every other week and weekly compared with placebo (0.4 and 0.8 vs. 3.8 per 100 patients; $P < 0.05$ for all comparisons vs. placebo), but the differences were not clinically meaningful. Statistically significant but not clinically meaningful differences were also observed among those that responded to induction therapy.

Another trial[94] evaluated the rate of hospitalization in 573 patients randomized to infliximab or placebo. At 52 weeks, the number of patients requiring Crohn's disease-related intra-abdominal surgeries in the 5 and 10 mg scheduled infliximab groups combined was 11 of 385 (3%), compared with 14 of 188 (8%) in the placebo group, which was not clinically meaningful but was statistically significant. Reported values are for both responders and non-responders to induction; values for responders only were not reported separately.

One trial with 195 total responders (among 282 total randomized patients with fistulas) compared infliximab with placebo.[92] Among patients who responded to open-label infliximab, infliximab maintenance had a significantly decreased rate of all surgeries and procedures (65 vs. 126 surgeries per 100 patients; $P < 0.05$) as well as major surgeries (2 vs. 11 surgeries per 100 patients; $P < 0.05$) at 40 weeks compared with those who received placebo. The findings were clinically meaningful for all surgeries but not major surgeries. Results for all randomized patients were similar.

Reduction of Steroids

Three trials reported on reduction in steroids, including two adalimumab[82 83] and one infliximab trials.[86] All three found clinically meaningful differences favoring the TNF-alpha inhibitor over placebo.

One trial[82] randomized patients to placebo, 40 mg of adalimumab every other week, and 40 mg of adalimumab weekly. Of the 198 responders who did not require steroids at randomization, the proportion of individuals who remained steroid-free at 52 weeks was 6, 29, and 23 percent, respectively. Adalimumab was clinically favored and statistically significant compared with placebo ($P < 0.001$ for both adalimumab groups compared with placebo). In a smaller trial,[83] 21 of 55 patients were on systemic steroids or budesonide at randomization and had results available at 52 weeks. At 52 weeks, rates of steroid discontinuation for the placebo, 40 mg every other week and 40 mg every week groups were 57, 67, and 88 percent, respectively. The difference was clinically meaningful, but statistical significance was not provided.

One trial with 335 participants compared infliximab (5 mg every 8 weeks or 10 mg every 8 weeks) with placebo.[86] At 52 weeks, three times as many patients in the infliximab groups combined had discontinued corticosteroids while in remission compared with placebo (29 vs. 9 percent; OR, 4.2; 95% CI, 1.5 to 11.5). This finding was clinically meaningful and statistically significant.

Fistula Response

One trial[87] with 282 participants compared infliximab with placebo for fistula healing. At 40 weeks, infliximab was favored over placebo according to the clinically meaningful and statistically significant thresholds. All of the patients had a fistula for at least 3 months' duration and received open-label induction with infliximab as part of the trial. The trial assessed response (50 percent reduction in the number of draining fistulas) 10 and 14 weeks after starting induction, and randomized 195 total responders to infliximab or placebo. Eight weeks after randomization, all patients who had lost response (both groups) could receive infliximab. At week 40 after randomization, the proportion of patients in the placebo group with complete fistula healing (complete absence of draining fistulas) was 19 percent, compared with 36 percent in the infliximab group ($P=0.009$). This finding was clinically meaningful and statistically significant.

Patient-Reported Outcomes

Six trials with 2,581 participants compared TNF-alpha inhibitors with placebo.[82-85,87,93,95] There was not a consistent finding that TNF-alpha inhibitors were favored over placebo according to the clinically meaningful difference. A meta-analysis was not performed because some studies reported the mean IBDQ values at baseline and followup while others reported the percent of patients who achieved a particular IBDQ threshold, two studies reported at less than 48 weeks[84,85] and one study included only fistulizing disease patients.[87]

Two trials with 554 participants compared adalimumab with placebo.[95,96] In both trials, there was no clinically meaningful difference between adalimumab and placebo at 52 weeks when all randomized patients were analyzed.[95] Among patients who responded to induction,[96] clinically meaningful results were observed for some patient-reported outcomes.

One trial compared certolizumab pegol with placebo.[84] At 18 weeks after randomization, patients on certolizumab pegol did not have clinically meaningful adjusted mean IBDQ scores than those on placebo (final IBDQ scores 171 versus 163, respectively). This trial did not report

baseline IBDQ scores by intervention group, so the change in IBDQ per group was not calculable.

Three trials compared infliximab with placebo.[85 87 93] In the largest trial, there was not a clinically meaningful difference in the IBDQ score at 52 weeks in the 5 mg/kg group, but there was a meaningful difference in the 10 mg/kg group, although neither was statistically significant.[93] At 52 weeks, the proportion of patients in the 5 and 10 mg/kg infliximab groups with an IBDQ greater than 170 was 38 and 46 percent, compared with 35 percent in the placebo group ($P > 0.05$). One trial[87] looked exclusively at fistulizing Crohn's disease and did not find a clinically meaningful difference between 5 mg/kg infliximab and placebo at 40 weeks. Another infliximab trial[85] had its final time point at 36 weeks and observed a decrease in both groups although the decrease was less in the infliximab group and met the clinically meaningful difference threshold (8-point median decrease from baseline in the 10 mg/kg infliximab group compared with a 31-point decrease in the placebo group), although statistical significance was not reported. A meta-analysis was not performed for the infliximab trials because only one trial reported at 52 weeks.[93]

Table 25. Randomized controlled trials comparing the efficacy of TNF-alpha inhibitor therapy with placebo or another treatment to maintain remission in patients with Crohn's disease who had a response to the study medication prior to randomization

Author, Year	Time Point	Main Intervention (Dose), n	Comparison, n	Remission Rate (CDAI<150 and Remained on Randomized Treatment or Did Not Require Rescue Therapy), %
Colombel, 2007[82]	52 wks	Adalimumab (40 mg sc every 2 wks), 172	Placebo, 170	36% vs. 12%*
	52 wks	Adalimumab (40 mg sc every wk), 157	Placebo, 170	41% vs. 12%*
Sandborn, 2007[83]	52 wks	Adalimumab (40 mg sc every 2 wks), 19	Placebo, 18	79% vs. 44%*
	52 wks	Adalimumab (40 mg sc every wk), 18	Placebo, 18	83% vs. 44%*
Schreiber, 2007[84]	18 wks	Certolizumab pegol (400 mg sc every 4 wks), 216	Placebo, 212	48% vs. 29%*
Hanauer, 2002[86]	52 wks	Infliximab (5 mg/kg IV every 8 wks), 113	Placebo, 110	30% vs. 15%*
	52 wks	Infliximab (10 mg/kg IV every 8 wks), 112	Placebo, 110	40% vs. 15%*
Rutgeerts, 1999[85]	28 wks	Infliximab (10 mg/kg IV every 8 wks), 37	Placebo, 36	64% vs. 35%
Van Assche, 2008[89]	104 wks	Infliximab (5 mg/kg IV every 8 wks) + azathioprine (pre-trial dose), 40	Infliximab (5 mg/kg IV every 8 wks), 40	40% vs. 45%
Mantzaris, 2009[88]	52 wks	Infliximab (5 mg/kg IV every 8 wks) + azathioprine (2-2.5 mg/kg/day), 21	Infliximab (5 mg/kg IV every 8 wks) + hydrocortisone (250 mg), 22	79% vs. 84%
	104 wks	Infliximab (5 mg/kg IV every 8 wks) + azathioprine (2-2.5 mg/kg/day), 21	Infliximab (5 mg/kg IV every 8 wks) + hydrocortisone (250 mg), 22	72% vs. 77%

CDAI = Crohn's Disease Activity Index; IV = intravenous infusion; mg = milligrams; mg/kg = milligrams per kilogram; NR = not reported; sc = subcutaneous injections; vs. = versus; wk = week
*Trial reported $P < 0.05$

Combination Therapy Versus Monotherapy

Infliximab and Azathioprine Versus Infliximab Alone

Disease Activity Measures

One trial[89] with 80 participants examined Crohn's patients who were in an extended remission (>6 months) on combination infliximab and azathioprine. The trial then randomized patients to continue or discontinue azathioprine and studied them for 104 weeks. Both the patients and study personnel where aware of the treatment assignment for the duration of the trial. Twenty-four out of 40 (60 percent) patients in the azathioprine continuation group and 22 out of 40 (55 percent) patients in the discontinuation group required a change in the infliximab dosing interval or stoppage of infliximab, the outcome most closely related to disease activity. The difference between groups was not clinically meaningful.

Mucosal Healing

The above trial[89] performed baseline and end of trial colonoscopy in 49 out of 80 randomized patients (all but one patient had colonic lesions at baseline). Sixteen out of 25 (64 percent) participants on a combination of infliximab and immunomodulators showed an absence of

ulcers, compared with 14 out of 23 (61 percent) participants on infliximab alone. There was no clinically meaningful difference in mucosal healing between groups.

Patient-Reported Outcomes

This trial[89] reported that the median IBDQ from week 8 through week 104 did not differ between the two groups. Baseline IBDQ was not provided and the IBDQ at each measure was not reported so the change in IBDQ could not be calculated.

Combination Therapy Versus Combination Therapy

Infliximab and Azathioprine Versus Infliximab With Hydrocortisone Intravenous Premedication

Disease Activity Measures

In one trial of 46 participants[88] rates of remission at 12 and 24 months were not clinically meaningfully different between the groups. At 12 months, 79 percent in the infliximab and azathioprine group and 84 percent in the infliximab with hydrocortisone premedication group were in remission. At 24 months, rates of remission were 72 and 77 percent, respectively. This trial had two major limitations. The trial blinded the investigators, but not the subjects. Additionally, the groups were not well balanced with respect to prior Crohn's medication use. All of the patients in the infliximab and azathioprine group were azathioprine naïve, whereas only six out of 23 patients in the infliximab and corticosteroids group were azathioprine naïve.

Thiopurines

We identified six trials. Five trials[56,98-101] compared azathioprine with placebo, two trials[56,102] compared azathioprine with corticosteroids, and one trial[56] compared azathioprine with sulfasalazine. No trials used 6-mercaptopurine. One trial is also included in the corticosteroids and aminosalicylates sections.[56]

Trial Design

Per our inclusion criteria, all six trials were RCTs (Appendix D, Evidence Table 7). In all trials, patients were in remission at the time of randomization. All trials were multicenter with five trials[98-102] conducted in Europe, and one in the U.S.[56] The years of enrollment ranged from 1971 to 2009. In one trial the azathioprine dose was 1 mg/kg/day,[56] in two trials the dose was 2.0 mg/kg/day,[99,103] and in one trial the dose was 2.0 to 2.5 mg/kg/day.[102] Prior to randomization, patients were in remission for one month,[102] 6 months,[100] 24 months,[101] or 42 months.[98] Two trials[56,99] did not report duration of remission prior to randomization. In three trials,[98,100,101] patients had to have been in remission on azathioprine. Trial duration ranged between 6 and 18 months. Relapse was defined by CDAI scores in four trials[56,98,101,102] while two trials used an unnamed disease activity score.[99,100]

One trial required steroid dependence for entry, but with a prednisone dose less than 30 mg.[102] One trial[101] excluded patients receiving corticosteroids or aminosalicylates at the time of randomization. One trial[98] excluded patients taking more than 10 mg of prednisone in addition to any immunosuppressant, aminosalicylates, or antibiotic. The remainder allowed prednisone or aminosalicylates at trial entry. Three trials excluded patients with previous surgery,[98,101,102] while

the other trials allowed remission to be achieved with medication or surgery. One trial excluded patients with left-sided colonic disease.[102]

Population Characteristics

Half of the patients were males (Appendix D, Evidence Table 8). The mean ages ranged from 28 to 40 years and the median ages ranged from 31 to 47 years. Race was reported in one trial (92 percent Caucasian).[56] All trials reported mean duration of disease at randomization ranging from 2 to 11 years. Mean CDAI ranged from 39 to 132 across all reporting trial groups. Two trials reported smoking histories ranging from 42 to 92 percent.[98,102] In trials that reported disease distribution, ileal involvement ranged from 3 to 60 percent, ileocolonic 11 to 67 percent, and colonic 7 to 63 percent. Concomitant steroid use ranged from 5 to 100 percent across trial groups, while concomitant aminosalicylates use was excluded in two trials,[98,102] allowed in two trials,[100,101] and use was not mentioned or unclear in two trials.[99,100]

Key Points

Table 26 summarizes the strength of evidence for the trials evaluating a thiopurine in terms of maintenance of remission. We found at least moderate strength of evidence or a clinically meaningful difference for the following comparisons:

- Azathioprine (1.7 to 2.1 mg/kg/day) was more efficacious than placebo to maintain remission at weeks 52, 78, and 104 (range in absolute RD, 13 to 39 percent; placebo rate, 47 to 79 percent). (SOE: Low)
- Azathioprine was superior to placebo in reducing steroid use at week 26 in adults with Crohn's disease participating in a maintenance trial (absolute reduction in prednisone use from baseline, 9.4 mg; placebo reduction, 6.1 mg). (SOE: Low)
- Azathioprine was more efficacious than budesonide to maintain remission at week 52 (absolute RD, 15 percent; budesonide rate, 64 percent). (SOE: Low)
- Azathioprine was more efficacious than prednisone to maintain remission at week 52 (absolute RD, 12 percent; prednisone rate, 57 percent). (SOE: Low)
- Azathioprine was superior to budesonide in achieving mucosal healing at week 52 in adults with Crohn's disease participating in a maintenance trial (absolute RD for absence of ulcers, 55 percent; budesonide rate, 5 percent). (SOE: Moderate)

Table 26. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating a thiopurine to maintain remission

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Azathioprine (1 mg/kg/d) vs. placebo - wks 52, 104	Disease activity measures	1 (155)[56]	Medium	Unknown (single study)	Direct	Imprecise	Favors neither RD, -11 to 5%; placebo rate, 40 to 64% SOE: Low
Azathioprine (1.7 to 2.1 mg/kg/d) vs. placebo - wks 52, 78, 104	Disease activity measures	3 (163)[98 100 101]	Medium	Inconsistent	Direct	Imprecise	Favors azathioprine RD, 13 to 39%; placebo rate, 47 to 79% SOE: Low
Azathioprine vs. placebo - wk 26	Reduction of steroids	1 (20)[104]	Medium	Unknown (single study)	Indirect	Precise	Favors azathioprine Absolute reduction in prednisone use from baseline, 9.4 mg; placebo reduction, 6.1 mg SOE: Low
Azathioprine vs. budesonide - wk 52	Disease activity measures	1 (77)[102]	Medium	Unknown (single study)	Direct	Imprecise	Favors azathioprine RD, 15%; budesonide rate, 64% SOE: Low
Azathioprine vs. prednisone - wk 52	Disease activity measures	1 (115)[56]	High	Unknown (single study)	Direct	Imprecise	Favors azathioprine RD, 12%; prednisone rate, 57% SOE: Low
Azathioprine vs. prednisone - wk 104	Disease activity measures	1 (115)[56]	High	Unknown (single study)	Direct	Imprecise	Favors neither Wk 104: RD, -3%; corticosteroid rate, 32% SOE: Low
Azathioprine vs. budesonide - wk 52	Mucosal healing	1 (77)[102]	Medium	Unknown (single study)	Direct	Precise	Favors azathioprine RD for absence of ulcers, 55%; budesonide rate, 5% SOE: Moderate
Azathioprine vs. sulfasalazine - wks 52, 104	Disease activity measures	1 (115)[56]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD range, -2% to 7%; sulfasalazine rate range, 31% to 62% SOE: Low

mg = milligrams; RD = absolute risk difference; vs. = versus; wk = weeks

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

Monotherapy Versus Placebo

Azathioprine Versus Placebo

Disease Activity Measures

Five trials[56,98-101] with 328 patients compared azathioprine with placebo (Table 27 and Appendix D, Evidence Table 9). Among the trials using 2 mg/kg/day of azathioprine, azathioprine was favored over placebo. The two trials that used less than 2 mg/kg/day did not find a clinically meaningful difference between azathioprine and placebo.[56,98]

Three trials[98,100,101] involving 163 patients assessed the efficacy of withdrawing azathioprine in patients who were in remission for at least 6 months using azathioprine (range 6 to 42 months). Two of these trials included 80 participants and found azathioprine to be clinically and statistically superior to placebo at 52 weeks.[100,101] One trial[98] found that azathioprine was clinically, but not statistically favored compared with placebo at 78 weeks. The trial that did not find statistical significance included lower doses of azathioprine (1.7 mg/kg/day) and patients had been in remission for a longer duration of time prior to randomization (minimum of 42 months) than the statistically significant trials. Meta-analysis was not performed because only two studies[100,101] analyzed doses of 1.7 mg/kg/day or above at 52 weeks.

One trial[56] involving 155 patients included patients who had inactive disease within the year before randomization that had been induced medically, as part of an induction trial reported in the same publication, or surgically. No meaningful differences between azathioprine and placebo were found at 1 or 2 years. The trial used a low dose of azathioprine at 1 mg/kg/day. Post-operative patients may behave differently from those who are medically induced into remission, but no subgroup analysis was reported to examine if disease activity differed by method of remission induction.

One trial[99] included steroid-dependent patients at randomization and involved steroid tapering as part of the design, but did not report results at 48 weeks or later. Disease activity results were clinically meaningful at 24 weeks but the trial did not report statistical significance. The trial included ten patients in total.

Reduction in Steroids

One trial with 20 participants compared azathioprine with placebo.[104] Average baseline daily prednisone dose was 19 mg in the azathioprine group and 17 mg in placebo. The trial compared the numerical reduction (in grams) in dose of steroid between the groups at 26 weeks. Patients on azathioprine had a 15.5 mg mean reduction in steroids compared with 6.1 mg for patients given placebo ($P < 0.05$). Although there was a substantial decrease in prednisone dose in both groups, and especially azathioprine, it is not possible to assess the clinical meaning given our definitions.

Monotherapy Versus Monotherapy

Azathioprine Versus Corticosteroids

Disease Activity Measures

We included two trials[56,102] with 192 patients (Table 27). In both trials, the remission rate at 1 year was higher in the azathioprine group according to the clinically meaningful threshold but was not statistically significant.[56,102] At 2 years there was no clinically meaningful difference.[56]

Mucosal Healing

One trial with 77 participants compared azathioprine with budesonide at 52 weeks.[102] The rate of complete mucosal healing (absence of ulcers) was 60 percent in the azathioprine group and 5 percent in the budesonide group, which was clinically meaningful and statistically significant ($P < 0.0001$). Comparisons using the CDEIS also favored azathioprine.

Azathioprine Versus Sulfasalazine

Disease Activity Measures

One trial[56] with 115 patients was included (Table 27). There was no meaningful difference between the azathioprine and sulfasalazine groups at 1 or 2 years.

Table 27. Randomized controlled trials comparing the efficacy of thiopurines with placebo or another treatment to maintain remission in patients with inactive Crohn's disease

Author, Year	Time Point	Main Intervention (Dose), n	Comparison, n	Relapse Definition	Remission Rate, %
Willoughby, 1971[99]	24 wks	Azathioprine (2 mg/kg/d), 5	Placebo, 5	Significant deterioration in clinical state requiring change in treatment	80% vs. 40%
O'Donoghue 1978[100]	1 yr	Azathioprine (2 mg/kg/d), 24	Placebo, 27	Significant deterioration in clinical state requiring change in treatment	95% vs. 59%
Summers, 1979[56]	1 yr	Azathioprine (1 mg/kg/d), 54	Placebo, 101	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	69% vs. 64%
Summers, 1979[56]	2 yr	Azathioprine (1 mg/kg/d), 54	Placebo, 101	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	29% vs. 40%
Villien, 2004[101]	1 yr	Azathioprine (median dose 2.1 mg/kg), 14	Placebo, 15	CDAI rise of >75 and CDAI >150, or increased disease activity requiring new medication or surgical therapy	86% vs. 47%*
Lemann, 2005[98]	18 mos	Azathioprine (median dose 1.7 mg/kg), 40	Placebo, 43	CDAI > 250, CDAI of 150-250 on 3 consecutive weeks with at least 75 points above baseline, or need for Crohn's abdominal surgery	92% vs. 79%
Mantzanis, 2009[102]	1 yr	Azathioprine (2.0-2.5 mg/kg/d),38	Budesonide (6-9 mg/d), 39	CDAI increase of > 100 points from baseline and > 150	79% vs. 64%
Summers, 1979[56]	1 yr	Azathioprine (1 mg/kg/d), 54	Prednisone (1-4 mg/kg), 61	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	69% vs. 57%
Summers, 1979[56]	2 yr	Azathioprine (1 mg/kg/d), 54	Prednisone (1-4 mg/kg), 61	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	29% vs. 32%
Summers, 1979[56]	1 yr	Azathioprine (1 mg/kg d), 54	Sulfasalazine (1-2 g/15 kg), 58	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	69% vs. 62%
Summers, 1979[56]	2 yr	Azathioprine (1 mg/kg d), 54	Sulfasalazine (1-2 g/15 kg), 58	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	29% vs. 31%

CDAI = Crohn's Disease Activity Index; d = day; g = gram; kg = kilogram; mg = milligrams; mos = months; NA = not applicable; vs. = versus; wks = weeks; yr = year
*Study reported $P < 0.05$

Methotrexate

One trial[105] randomized 76 patients to intramuscular methotrexate or placebo (Appendix D, Evidence Table 9). All patients had previously taken part in an induction trial reported in KQ1.[63]

Trial Design

The trial blinded both participants and study personnel and randomized adults with Crohn's disease who were in a steroid-free remission (CDAI < 150) at entry (Appendix D, Evidence Table 7). Patients achieved remission through methotrexate at 25 mg intramuscular weekly for a period of 16 to 24 weeks. The trial randomized participants to receive weekly intramuscular injections of either 15 mg of methotrexate or placebo for a period of 40 weeks. The primary outcome measure was relapse, defined as an increase in the CDAI of at least 100 points or the initiation of steroids or thiopurines. Immunomodulators, corticosteroids, infliximab, aminosalicylates, antibiotics, tube feeding, and parental nutrition were not allowed.

Population Characteristics

A total of 76 patients participated (Appendix D, Evidence Table 8). Males ranged from 40 to 61 percent across both groups. Mean age ranged from 32 to 38 years. Forty-two to 50 percent were smokers. Mean duration of disease ranged from 4 to 8 years. Mean CDAI ranged from 84 to 94. Ranges of disease location were as follows: ileal disease 31 to 45 percent, ileocolonic disease 28 to 44 percent, and colonic disease 25 to 28 percent. Prior thiopurine use was less than 5 percent in both groups.

Key Points

Table 28 summarizes the strength of evidence for the trial evaluating methotrexate in terms of remission maintenance. We found at least moderate strength of evidence or a clinically meaningful difference for the following comparison:

- Intramuscular methotrexate (15 mg weekly) was more efficacious than placebo to maintain remission at week 40 (absolute RD, 26 percent; placebo rate, 39 percent). (SOE: Low)

Table 28. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating methotrexate to maintain remission

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Methotrexate (intramuscular) vs. placebo – wk 40	Disease activity measures	1 (76)[105]	Medium	Unknown (single study)	Indirect	Precise	Favors methotrexate RD, 26%; placebo rate, 39% SOE: Low

RD = absolute risk difference; SOE = strength of evidence; vs. = versus; wk = weeks

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

Monotherapy Versus Placebo

Methotrexate Versus Placebo

Disease Activity Measures

One RCT[105] evaluated the difference between methotrexate and placebo to maintain remission in patients with Crohn's disease (Table 29). Sustained remission was not reported in the trial. Relapses were less common in the methotrexate than placebo group. The difference in relapse met the clinically meaningful and statistically significant thresholds at 40 weeks.

Table 29. Remission rates reported in randomized controlled trials comparing the efficacy of methotrexate with placebo in patients with inactive Crohn's disease

Author, Year	Followup (Weeks)	Main Intervention (Dose), n	Comparison, n	Relapse Definition	Remission Rate, %
Feagan, 2000[105]	40	Methotrexate (15 mg/wk IM), 36	Placebo, 40	(≥100 increase in CDAI or use of a thiopurine or steroid	65% vs. 39%*

CDAI = Crohn's Disease Activity Index; IM = intramuscular; mg/wk = milligrams per week; vs. = versus
*Trial reported difference in relapse rates significant at 0.05 alpha level

Corticosteroids

Eleven trials evaluated the efficacy of corticosteroids to maintain remission in patients with inactive Crohn's disease (Appendix D, Evidence Table 7). Nine trials compared corticosteroids with placebo.[56,64,106-112] Two trials[56,64] compared corticosteroids with aminosalicylates in addition to placebo, one trial compared budesonide directly with mesalamine,[113] and one trial[75] compared a combination of corticosteroids and aminosalicylates with aminosalicylates alone. Seven trials used budesonide 3 to 6 mg per day, two trials used prednisone 0.25 mg/kg per day alone and in combination with sulfasalazine,[56,75] and two trials used 6-methylprednisolone 0.25 mg/kg per day to 8 mg per day alone[112] or in combination with sulfasalazine.[64]

Five trials also appear in KQ1. One trial[64] reported relapse rates in the population with inactive disease at randomization with the active disease patients reported in KQ1. Four trials included patients who had previously participated in an induction trial.[65,66,68,69] One trial is also included in the thiopurines and aminosalicylates sections.[56]

Trial Design

Nine of the 11 trials were described as double-blind. One study blinded investigators, but not patients,[113] and blinding was not reported in one study.[56] Of the 11 trials, four trials were conducted in the U.S. and North America, seven in Europe, one in Australia, one in Asia, and one in Africa (Appendix D, Evidence Table 7). One was a single center trial[113] and the remaining ten took place at multiple sites. Seven trials reported enrollment dates; these trials took place between 1971 and 1996. Six trials had run-in periods from 4 to 12 weeks in duration; in these trials the participants were already in remission due to a separate prior trial comparing corticosteroids with placebo;[75,106,108-111] in one trial[75] the run-in period was part of the same trial comparing corticosteroids or corticosteroids and aminosalicylates. Five trials did not have a run-in period,[56,64,107,112,113] with one trial[113] requiring all patients to taper their corticosteroids dose before beginning the trial. Median trial duration was 52 weeks (range from 13 to 104 weeks).

Nine trials included patients with CDAI less than or equal to 150 while one trial[107] defined inactive disease as having a CDAI less than or equal to 200 and another[64] included patients with both active (CDAI ≥ 150) and inactive (CDAI < 150) disease initially, and then analyzed them separately (the active disease results are reported in KQ1). Two trials[106,109] required a minimum duration of remission beyond the induction period, from 8 to 10 weeks. Two trials required patients to be steroid-dependent.[107,113] All trials reported a minimum age of inclusion of 18 years, with three exceptions,[56,75,112] which did not report a minimum age. No trials required any other prior medication use aside from what is mentioned above. One trial[113] excluded patients who had been maintained on mesalamine or azathioprine at the time of enrollment. Another trial[106] excluded patients who had received mesalamine at any time, or immunomodulator or corticosteroids at the time of the initial run-in trial.[65] All trials used CDAI as the outcome measure. No trials used alternative activity indices.

Population Characteristics

The description of the population characteristics exclude one trial[64] because it included both active and inactive disease in the baseline population. These ten trials randomized a total of 1,028 patients across all trial groups (Appendix D, Evidence Table 8). The proportion of male participants in each trial group ranged from 22 to 67 percent. Only two trials[56,107] reported on race, with Caucasian participants making up 91 to 98 percent across all trial groups. Only one trial[113] reported smoking (with no definition given), which ranged between 82 and 86 percent across both trial groups. Six trials reported mean age at enrollment, which ranged between 32 and 41 years. Seven trials reported mean duration of disease, which ranged between 3 to 9 years. Seven trials reported disease location: ileal location ranged between 33 and 89 percent, ileocolonic location between 11 and 49 percent, and colonic location between 0 and 33 percent. No trials reported perianal location. All but two trials reported mean baseline CDAI,[75,112] ranging from 65 to 139. Only one trial reported concurrent medication use:[107] aminosalicylates in 48 to 49 percent of participants and thiopurine in 9 to 15 percent of participants across both trial groups. One trial reported prior thiopurine use[113] in 41 to 43 percent of all participants across both trial groups. Of the six trials where patients were in an induction trial involving corticosteroids, corticosteroid frequency ranged from 80 to 100 percent across groups of five trials. In one trial[75] corticosteroids use prior to entry ranged from 47 to 52 percent across groups.

Key Points

Table 30 summarizes the strength of evidence for the trials evaluating corticosteroids to maintain remission. We found at least moderate strength of evidence or a clinically meaningful difference for the following comparisons:

- 6-methylprednisolone was more efficacious than placebo to maintain remission at weeks 54 and 104 (absolute RD across time points, 11 to 12 percent; placebo rate, 32 to 48 percent). (SOE: Low)
- Budesonide (6 mg daily) was more efficacious than mesalamine (3 g daily) to maintain remission at week 52 (absolute RD, 27 percent; mesalamine rate, 18 percent). (SOE: Moderate)
- Budesonide was favored over mesalamine as measured by the IBDQ quality of life outcome at 12 months, although both budesonide and mesalamine patients had lower quality of life at the end of the trial than at the beginning (absolute between-group

difference in change in mean IBDQ, 30 to 36 points; mesalamine mean change, -51 to -76 points). (SOE: Moderate)

Table 30. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating a corticosteroid to maintain remission

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Budesonide vs. placebo--wk 52	Disease activity measures	5 (557)[106 108-111]	Medium-	Inconsistent	Direct	Imprecise	Favors neither 3mg pooled RR, 1.0; CI, 0.8 to 1.2; placebo rate, 33% to 40% 6mg pooled RR, 1.2; CI, 0.9 to 1.5; placebo rate, 33% to 42% SOE: Low
Budesonide vs. placebo--wks 13 and 52	Patient-reported outcomes	2 (122)[107 111]	Medium	Consistent	Direct	Imprecise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 2 to 11 pts; placebo mean change, -4 to -31 pts SOE: Low
Prednisone vs. placebo--wks 54 and 104	Disease activity measures	1 (162)[56]	High	Unknown (single study)	Direct	Imprecise	Neither favored RD across time points, 0% to 9%; placebo rate, 59% to 72% SOE: Low
6-methylprednisolone vs. placebo--wks 54 and 104	Disease activity measures	1 (118)[64]	High	Unknown (single study)	Direct	Imprecise	Favors 6-methylprednisolone RD across time points, 11% to 12%; placebo rate, 32% to 48% SOE: Low
Budesonide vs. mesalamine--wk 52	Disease activity measures	1 (57)[113]	Medium	Unknown (single study)	Direct	Precise	Favors budesonide RD, 27%; mesalamine rate, 18% SOE: Moderate
Budesonide vs. mesalamine--wk 52	Patient-reported outcomes	1 (57)[113]	Medium	Unknown (single study)	Direct	Precise	Favors budesonide Absolute between-group difference in change in mean IBDQ, 30 to 36 pts; mesalamine mean change, -51 to -76 pts SOE: Moderate

Table 30. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating a corticosteroid to maintain remission (continued)

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining To Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Prednisone or 6-methylprednisolone vs. sulfasalazine --wks 54, 104	Disease activity measures	2 (248)[56 64]	High	Consistent	Direct	Imprecise	Favors neither RD across time points, 5% to 9%; ASA rate, 37% to 67% SOE: Low
6-methylprednisolone + sulfasalazine vs. placebo--wks 54, 104	Disease activity measures	1 (108)[64]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD across time points, 2% to 5%; placebo rate, 32% to 48% SOE: Low
Steroids + sulfasalazine vs. steroids--wks 26-54, 104	Disease activity measures	2 (181)[64 75]	Medium	Inconsistent	Direct	Imprecise	Favors neither RD across time points, -9% to -6%; steroid rate, 22% to 60% SOE: Low
6-methylprednisolone + sulfasalazine vs. sulfasalazine--wks 54, 104	Disease activity measures	1(119)[64]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD, -3% to -2%; sulfasalazine rate, 37% to 55% SOE: Low

ASA = aminosalicylates; CI = 95% confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; NA = not applicable; pt = points; RD = absolute risk difference; RR = relative risk; SOE = strength of evidence; steroid = corticosteroids; vs. = versus; wk = weeks

Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable.

Scores for the Inflammatory Bowel Disease Questionnaire range from 32 to 224, with higher scores indicating better quality of life.[36]

Monotherapy Versus Placebo

Corticosteroids Versus Placebo

Disease Activity Measures

Nine trials, including 854 participants, compared corticosteroids with placebo (Table 31; Appendix D, Evidence Table 9).[56,64,106-112] Six trials used budesonide 3 to 6 mg per day, two[64,112] used 6-methylprednisolone, and one[56] used prednisone. In two trials[107,112] the final time point was at 26 weeks or less.

Two meta-analyses were conducted on five trials[106 108-111] comparing budesonide 3 and 6 mg per day with placebo at 52 weeks (Figure 8). Four of the trials included participants from induction trials summarized in KQ1.[106 108 110 111] There was no difference between budesonide and placebo to maintain remission at 52 weeks for the 3 mg dose (RR of remission, 1.0; 95% CI, 0.8 to 1.2) nor the 6 mg dose (RR of remission, 1.2; 95% CI, 0.9 to 1.5). There was no significant heterogeneity among the trials for either dose (I-squared, 0). The excluded budesonide trial found that 33 percent more patients who switched to 6 mg budesonide were in remission compared with placebo at 13 weeks, which was clinically and statistically significant.[107]

There was no meaningful difference in relapse rates in the prednisone trial at 54 or 104 weeks.[56]

More 6-methylprednisolone patients were in remission compared with placebo at 54 and 104 weeks, although statistical significance was not reported.[64] A 6-methylprednisolone trial that reported its last measure at 26 weeks also favored 6-methylprednisolone to placebo according to the clinically meaningful threshold, but did not report statistical significance.[112]

Patient-Reported Outcomes

Two trials with 122 participants compared budesonide with placebo and did not find clinically meaningful differences.[107,111] In a trial[111] of patients who had participated in an 8-week induction trial, the IBDQ decreased in all groups and there were not clinically meaningful nor statistically significant differences. At 12 months, IBDQ decreased from 185 to 156 in the budesonide 3 mg group, 184 to 161 in the budesonide 6 mg group, and 181 to 150 in the placebo group.[114] Another trial[107] examined steroid-dependent patients and measured the IBDQ at week 13. The mean IBDQ score rose from 162 to 169 in the budesonide group and dropped from 158 to 154 in the placebo group, which was not clinically meaningful but was statistically significant.[107]

Monotherapy Versus Monotherapy

Corticosteroids Versus Aminosalicylates

Disease Activity Measures

Three trials,[56,64,113] involving 305 participants, included comparisons of corticosteroid therapy with aminosalicylates to maintain remission from 52 to 104 weeks (Table 31). An investigator- but not patient-blinded trial of 6 mg budesonide found a clinically and statistically significant difference compared with 3 g mesalamine at 52 weeks,[113] but the 6-methylprednisolone[64] and prednisone[56] trials did not find clinically meaningful differences

compared with sulfasalazine. No meta-analysis was performed because of the different formulations of corticosteroids and aminosalicylates used.

Patient-Reported Outcomes

In the budesonide trial, all patients reported worse quality of life at the end of the trial.[113] At 1 year, mean IBDQ score decreased from 188 to 148 in the budesonide group and 186 to 110 in the mesalamine group. Budesonide was clinically and statistically (P=0.0001) favored to mesalamine, although the budesonide patients also reported feeling significantly worse.

Combination Therapy Versus Placebo

Combination of Corticosteroids and Aminosalicylates Versus Placebo

Disease Activity Measures

In one trial[64] of 108 participants (Table 31), there was no clinically meaningful difference in remission at 54 and 104 weeks between those on 6-methylprednisolone 8 mg per day and sulfasalazine 3 g per day combination therapy and those on placebo.

Combination Therapy Versus Monotherapy

Combination of Corticosteroids and Aminosalicylates Versus Corticosteroids Alone

Disease Activity Measures

Two trials,[64,75] including 181 participants, compared a combination of corticosteroids and sulfasalazine with corticosteroids alone to maintain remission of Crohn's disease (Table 31). Neither trial found a clinically meaningful difference.

Combination of Corticosteroids and Aminosalicylates Versus Aminosalicylates Alone

Disease Activity Measures

In one trial[64] of 119 participants (Table 31), there was no clinically meaningful difference in relapse rates at 54 or 104 weeks in those randomized to the combination of 6-methylprednisolone 8 mg/day and sulfasalazine 3 g/day compared with those randomized to sulfasalazine 3 g/day alone.

Table 31. Remission rates reported in randomized controlled trials comparing the efficacy of corticosteroids with placebo or another treatment in patients with inactive Crohn's disease

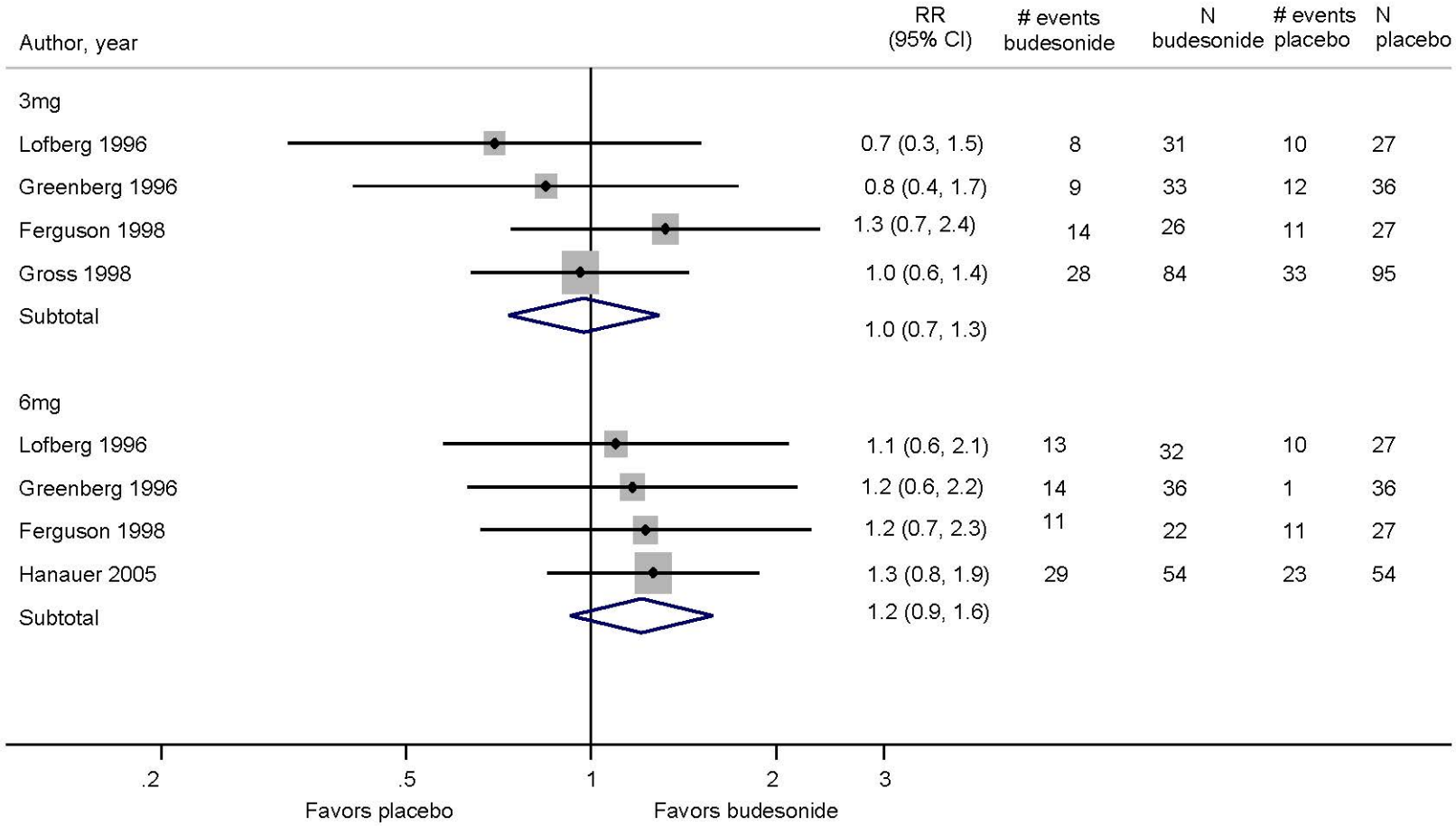
Author, Year	Followup (Weeks)	Main Intervention (Daily Dose), n	Comparison (Daily Dose), n	Relapse Definition	Remission Rate (%)
Lofberg, 1996[110]	52	Budesonide (3 mg), 31	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or acute deterioration in status	26 vs. 37%
Lofberg, 1996[110]	52	Budesonide (6 mg), 32	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or acute deterioration in status	41 vs. 37%
Greenberg, 1996[111]	52	Budesonide (3 mg), 33	Placebo, 36	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline	30 vs. 33%
Greenberg, 1996[111]	52	Budesonide (6 mg), 36	Placebo, 36	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline	39 vs. 33%
Ferguson, 1998[108]	52	Budesonide (3 mg), 26	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or any deterioration requiring a different medication or surgery	54 vs. 40%
Ferguson, 1998[108]	52	Budesonide (6 mg), 22	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or any deterioration requiring a different medication or surgery	52 vs. 40%
Gross, 1998[109]	52	Budesonide (3 mg), 84	Placebo, 95	CDAI > 150 on 2 consecutive weeks	33 vs. 35%
Cortot, 2001[107]	13	Budesonide (6 mg), 59	Placebo, 58	CDAI > 200 and ≥ 60-pt increase in CDAI from baseline	68 vs. 35%*
Hanauer, 2005[106]	52	Budesonide (6 mg), 54	Placebo, 54	CDAI ≥ 150 and ≥ 60-pt increase in CDAI from baseline or clinical deterioration	53 vs. 42%
Summers, 1979[56]	54	Prednisone (0.25 mg/kg), 61	Placebo, 101	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	72 vs. 72%
Summers, 1979[56]	104	Prednisone (0.25 mg/kg), 61	Placebo, 101	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	68 vs. 59%
Malchow, 1984[64]	54	6-Methylprednisolone (8 mg), 66	Placebo, 52	CDAI > 150 or clinical deterioration	60 vs. 48%
Malchow, 1984[64]	104	6-Methylprednisolone (8 mg), 66	Placebo, 52	CDAI > 150 or clinical deterioration	43 vs. 32%
Brignola, 1988[112]	26	6-Methylprednisolone (0.25 mg/kg), 9	Placebo, 9	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 weeks	89 vs. 22%
Mantzaris, 2003[113]	52	Budesonide (6 mg), 29	Mesalamine (3 g), 28	CDAI > 150 and ≥ 100-pt increase in CDAI	45 vs. 18%*
Summers, 1979[56]	54	Prednisone (0.25 mg/kg), 61	Sulfasalazine (0.5 mg/kg), 58	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	72 vs. 67%
Summers, 1979[56]	104	Prednisone (0.25 mg/kg), 61	Sulfasalazine (0.5 mg/kg), 58	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	68 vs. 59%

Table 31. Remission rates reported in randomized controlled trials comparing the efficacy of corticosteroids with placebo or another treatment in patients with inactive Crohn's disease (continued)

Author, Year	Followup (Weeks)	Main Intervention (Daily Dose), n	Comparison (Daily Dose), n	Relapse Definition	Remission Rate (%)
Malchow, 1984[64]	54	6-Methylprednisolone (8 mg), 66	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	60 vs. 55%
Malchow, 1984[64]	104	6-Methylprednisolone (8 mg), 66	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	43 vs. 37%
Malchow, 1984[64]	54	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Placebo, 52	CDAI > 150 or clinical deterioration	53 vs. 48%
Malchow, 1984[64]	104	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Placebo, 52	CDAI > 150 or clinical deterioration	34 vs. 32%
Singleton, 1979[75]	26	Prednisone (0.25 mg/kg) + sulfasalazine (1 mg/15 kg), 29	Prednisone (0.25 mg/kg), 30	CDAI > 150 and CDAI 100-point increase	16 vs. 22%
Malchow, 1984[64]	54	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	6-Methylprednisolone (8 mg), 66	CDAI > 150 or clinical deterioration	53 vs. 60%
Malchow, 1984[64]	104	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	6-Methylprednisolone (8 mg), 66	CDAI > 150 or clinical deterioration	34 vs. 43%
Malchow, 1984[64]	54	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	53 vs. 55%
Malchow, 1984[64]	104	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	34 vs. 37%

CDAI = Crohn's Disease Activity Index; mg = milligrams; kg = kilograms; pt = points; vs. = versus
*Trial reported significant at the 0.05 alpha level.

Figure 8. Pooled relative risk of a remission* of Crohn's disease at week 52 comparing budesonide with placebo



Pooled Relative Risk and 95% Confidence Intervals of Remission at Week 52 by Budesonide Dose

CI = confidence interval; mg = milligrams; RR = relative risk

Note: Boxes indicate individual trial point estimates. The box size denotes the weight of the trial, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each trial. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.3 mg Test for heterogeneity: Q=1.83 with 3 degrees of freedom (p=0.61).6 mg Test for heterogeneity: Q=0.30 with 3 degrees of freedom (p=0.96).3 mg and 6 mg I-squared statistic = 0%.*In all trials, relapse was defined as a Crohn's Disease Activity Index more than 150 with at least a 60-point increase from baseline. Ferguson 1998, Lofberg 1996, and Hanauer 2005 also defined relapse to include clinical deterioration. All patients who did not relapse were considered in remission for the analysis.

Aminosalicylates

Fourteen trials compared aminosalicylates versus placebo to maintain remission (Appendix D, Evidence Table 7).[56,64,115-126] One trial[64] included both those with active (CDAI greater than 150) and inactive disease (CDAI less than 150) at randomization, with the active disease group reported in KQ1. One trial is also included in the thiopurines and corticosteroids sections.[56]

Trial Design

Of the 14 trials, ten trials were conducted in Europe, four in North America and the U.S., two in Asia, and one in Africa (Appendix D, Evidence Table 7). All were multicenter trials except two,[124,125] and one[126] which said that patients were recruited from outpatient clinics but did not specify the study sites. Eleven trials used mesalamine; seven used pH-release mesalamine and four used controlled-release. The pH-release mesalamine begins release in the terminal ileum but is mainly released in the colon. The controlled-release mesalamine begins release in the proximal small bowel. Two trials used sulfasalazine and one used olsalazine. Mesalamine doses ranged from 1 to 4 grams daily. The starting year of enrollment was between 1971 and 2000. Three trials[115,118,119] had run-in periods involving induction of remission with 6-methylprednisolone or prednisone for 4 to 8 weeks. Median trial duration was 52 weeks (range, 6 to 208 weeks).

Twelve trials included only patients with a CDAI less than 150, one with a CDAI less than 120,[126] and one with a HBI less than 4.[121] Five trials required a minimum duration of remission prior to the trial, ranging from 4 weeks to 24 months.[116,121,122,124,126] No trials required patients to be steroid-dependent or resistant. Seven trials reported a minimum age of inclusion of 18 years, with two[119,122] including those 15 years old and over, and the remaining trials not reporting a minimum age. Regarding medication use in the 1 to 3 months prior to the trials, four trials[116,122,124,126] excluded patients who had used corticosteroids within this time frame, four[116,118,120,122,]excluded those on any other immunosuppressives, and one trial[117] excluded those with recent thiopurine or cyclosporine use.

Population Characteristics

All of the following statistics exclude one trial[64] due to its inclusion of both those with active and inactive disease in the baseline population (Appendix D, Evidence Table 8). Thirteen trials are summarized here. Another trial[117] did not distinguish between those patients in medical remission and those in surgical remission when reporting population characteristics, so we included statistics on both groups in the totals below.

The included trials randomized a total of 1,825 patients across all trial groups. The proportion of male participants in each trial group ranged from 39 to 70 percent. Only one trial[56] reported on race, with Caucasian participants making up 94 to 98 percent across both trial groups. Three trials[117,118,121] reported smoking ("smoker" or "present smoker"), which ranged between 18 and 38 percent. Six trials reported mean age at enrollment, which ranged between 29 and 40 years. All seven trials reported mean duration of disease, which ranged between 3 and 7 years. The trials reported disease location as follows: ileal location ranged between 11 and 100 percent, ileocolonic location between 18 and 91 percent, and colonic location between 9 and 97 percent. One trial reported perianal location,[122] which ranged from 11 to 14 percent. All but four trials reported baseline CDAI.[115,121,122,126] Mean CDAI ranged from 48 to 89 points. One trial[121] reported mean HBI values, ranging from 2.2 to 2.3 across the two groups. No trials reported concurrent medication use. Prior corticosteroid use ranged from 13 to 94 percent across three

trials.[119,124,125] In one trial,[121] 82 to 87 percent of patients were on an aminosalicylate at trial entry.

Key Points

Table 32 summarizes the strength of evidence for the trials evaluating aminosalicylates in terms of remission maintenance. Listed are the comparisons with at least moderate strength of evidence or a clinically meaningful difference.

- Mesalamine (controlled-release) at 3 to 4 g daily was more efficacious than placebo to maintain remission at weeks 48 to 52 (absolute RD across time points, 7 to 11 percent; placebo rate, 22 to 58 percent). (SOE: Low)
- Mesalamine (controlled-release) at 2 g daily was no more efficacious than placebo to maintain remission at week 104 (absolute RD, 6 percent, placebo rate, 58 percent). (SOE: Moderate).
- Mesalamine (pH-release) at 2.4 g daily was more efficacious than placebo to maintain remission at week 208 (absolute RD, 18 percent; placebo rate, 29 percent). (SOE: Low)
- Olsalazine at 2 g daily was no more efficacious than placebo to maintain remission at week 52 (absolute RD, 2 percent, placebo rate, 74 percent). (SOE: Moderate).

Table 32. Numbers of trials and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for trials evaluating an aminosalicylate to maintain remission

Comparison	Outcome	Number of Trials (Participants)	Domains Pertaining to Strength of Evidence				Magnitude of Effect Strength of Evidence
			Risk of Bias	Consistency	Directness	Precision	
Mesalamine (controlled-release) vs. placebo—wks 48, 52	Disease activity measures	2 (309)[117 119]	High	Consistent	Direct	Imprecise	Favors mesalamine (controlled-release) RD, 7 to 11%; placebo rate, 22 to 58% SOE: Low
Mesalamine (controlled-release) vs. placebo—wk 104	Disease activity measures	1 (161)[122]	Low	Unknown (single study)	Direct	Imprecise	Favors neither RD, 6%; placebo rate, 58% SOE: Moderate
Mesalamine (controlled-release), vs. placebo--wk 48	Patient-reported outcomes	1 (246)[117]	Medium	Unknown (single study)	Direct	Imprecise	Favors neither Absolute between-group difference in change in mean IBDQ, 1 pt; placebo mean change, -14 pts SOE: Low
Mesalamine (pH-release) vs. placebo—wk 52	Disease activity measures	7 (756)[115 118 120 121 123 125 126]	Medium	Inconsistent	Direct	Precise	Favors mesalamine (pH-release) RR, 1.1; 95% CI, 1.0 to 1.3 SOE: Low
Mesalamine (pH-release) vs. placebo—wk 104	Disease activity measures	1 (117)[118]	High	Unknown (single study)	Direct	Imprecise	Favors placebo RD, -17%; placebo rate, 42% SOE: Low
Mesalamine (pH-release) vs. placebo—wk 208	Disease activity measures	1 (59)[121]	Medium	Unknown (single study)	Direct	Imprecise	Favors mesalamine (pH-release) RD, 18%; placebo rate, 29% SOE: Low
Olsalazine vs. placebo—wk 52	Disease activity measures	1 (328)[116]	Low	Unknown (single study)	Direct	Imprecise	Favors neither RD, 2%; placebo rate, 74% SOE: Moderate
Sulfasalazine vs. placebo—wks 54, 104	Disease activity measures	2 (274)[56 64]	High	Inconsistent	Direct	Imprecise	Favors neither RD, -5 to 7%; placebo rate, 32 to 72% SOE: Low

ASA = aminosalicylates; IBDQ = Inflammatory Bowel Disease Questionnaire; pt = points; RD = absolute risk difference; SOE = strength of evidence; vs. = versus; wk = weeks
Note: The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Moderate = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable
Scores for the Inflammatory Bowel Disease Questionnaire range from 32 to 224, with higher scores indicating better quality of life.[36]

Monotherapy Versus Placebo

Aminosalicylates Versus Placebo

Disease Activity Measures

Fourteen trials, including 1,789 participants, compared aminosalicylate compounds with placebo to maintain remission (Table 33; Appendix D, Evidence Table 9).[56,64,115-126] One trial[64] included both patients with active and inactive Crohn's disease at randomization with the active disease results reported in KQ1. There was a great deal of heterogeneity in the absolute relapse rates across the included trials with a range of 0 to 71 percent for the groups receiving aminosalicylates and 14 to 78 percent for placebo.

Thirteen of 14 trials reported at 48 weeks or later (Figure 9). One controlled-release mesalamine trial reported the last measure at 16 weeks and found no clinically meaningful difference between mesalamine and placebo.[124] Of the remaining 13 trials, there was variation in efficacy by the formulation of the aminosalicylate and, particularly, the brand of mesalamine.

pH-release mesalamine was favored over placebo in seven trials[115,118,120,121,123,125,126] at 52 weeks (RR, 1.1; 95% CI, 1.0 to 1.3) (Figure 9). At 104 weeks, placebo was favored over pH-release mesalamine, while at 208 weeks pH-release mesalamine was favored over placebo. Controlled-release mesalamine was favored over placebo in one[117] of two trials at 48 to 52 weeks,[117,119] but there was no difference from placebo at 104 weeks.[122] There was no clinically meaningful difference between sulfasalazine and placebo at 54 or 104 weeks,[56,64] or olsalazine and placebo at 52 weeks.[116]

Patient-Reported Outcome

One 48-week trial with 246 patients compared controlled-release mesalamine (750 mg every 6 hours) with placebo.[117] At the last visit (early termination or trial completion), mean IBDQ dropped from 193 to 180 in the controlled-release mesalamine group, while it dropped from 193 to 179 in the placebo group. The difference is not clinically meaningful. Patients who were randomized after a surgically induced remission were included in the results and no subgroup analysis was performed to examine the effect of the medication on medically induced remission.

Table 33. Remission rates reported in randomized controlled trials comparing the efficacy of aminosalicylates with placebo in patients with inactive Crohn's disease

Author, Year	Followup (Weeks)	Main Intervention (daily dose), n	Comparison, n	Relapse Definition	Remission Rate (%)
Summers, 1979[56]	54	Sulfasalazine (0.5 g/15 kg), 58	Placebo, 101	CDAI > 150 and 100-pt rise in CDAI or clinical criteria	67 vs. 72%
Summers, 1979[56]	104	Sulfasalazine (0.5 g/15 kg), 58	Placebo, 101	CDAI > 150 and 100-pt rise in CDAI or clinical criteria	59 vs. 59%
Malchow, 1984[64]	54	Sulfasalazine (3 g), 63	Placebo, 52	CDAI > 150 or clinical deterioration	55 vs. 48%
Malchow, 1984[64]	104	Sulfasalazine (3 g), 63	Placebo, 52	CDAI > 150 or clinical deterioration	37 vs. 32%
Wellmann, 1988[126]	52	Mesalamine (pH-release), 31	Placebo, 35	CDAI > 150	68 vs. 60%
Prantera, 1992[123]	52	Mesalamine (pH-release) (2.4 g), 64	Placebo, 61	CDAI > 150 and 100-pt increase in CDAI	66 vs. 45%*
Brignola, 1992[124]	16	Mesalamine (controlled-release) (2 g), 21	Placebo, 22	CDAI > 150 for 2 weeks or 100-pt increase in CDAI	48 vs. 41%
Gendre, 1993[122]	104	Mesalamine (controlled-release) (2 g), 80	Placebo, 81	CDAI > 250 or CDAI between 150 and 250 with 50-pt increase for 2 weeks	64 vs. 58%
Arber, 1995[121]	52	Mesalamine (pH-release) (1 g), 28	Placebo, 31	HBI > 4	73 vs. 45%
Bresci, 1995[125]	52	Mesalamine (pH-release) (2.4 g), 32	Placebo, 31	CDAI ≥ 150 or 100-pt increase in CDAI and LI ≥ 100 – cumulative†	84 vs. 71%
Bresci, 1995[125]	208	Mesalamine (pH-release) (2.4 g), 32	Placebo, 31	CDAI ≥ 150 or 100-pt increase in CDAI and LI ≥ 100 – cumulative†	47 vs. 29%
Thomson, 1995[120]	52	Mesalamine (pH-release) (3 g), 102‡	Placebo, 105‡	CDAI > 150 and 60-pt increase in CDAI	73 vs. 68%‡
Thomson, 1995[120]	52	Mesalamine (pH-release) (3 g), 36§	Placebo, 43§	CDAI > 150 and 60-pt increase in CDAI	60 vs. 74%§
Modigliani, 1996[119]	52	Mesalamine (controlled-release) (4 g), 65	Placebo, 64	CDAI > 150 and 100-pt increase in CDAI or failure to discontinue steroids	29 vs. 22%
de Franchis, 1997[118]	52	Mesalamine (pH-release) (3 g), 58	Placebo, 59	CDAI > 150 and 60-pt increase in CDAI and increase in at least 2 of 3 acute phase reactants	34 vs. 41%
de Franchis, 1997[118]	104	Mesalamine (pH-release) (3 g), 58	Placebo, 59	CDAI > 150 and 60-pt increase in CDAI and increase in at least 2 of 3 acute phase reactants	25 vs. 42%
Sutherland, 1997[117]	48	Mesalamine (controlled-release) (3 g), 87	Placebo, 93	CDAI > 150 and 60-pt increase in CDAI, or physician-diagnosed disease flare, hospitalization for disease flare, or need for corticosteroids therapy	69 vs. 58%
Mahmud, 2001[116]	52	Olsalazine (2 g), 167	Placebo, 161	CDAI > 150 or 60-pt increase in CDAI	76 vs. 74%
Prantera, 2005[115]	52	Mesalamine (pH-release) (4 g), 23	Placebo, 17	CDAI > 150 or withdrawal for other reasons	13 vs. 18%

CDAI = Crohn's Disease Activity Index; g = grams; HBI = Harvey-Bradshaw Index; ITT = intention-to-treat; LI = Laboratory Index; pt = points; vs. = versus

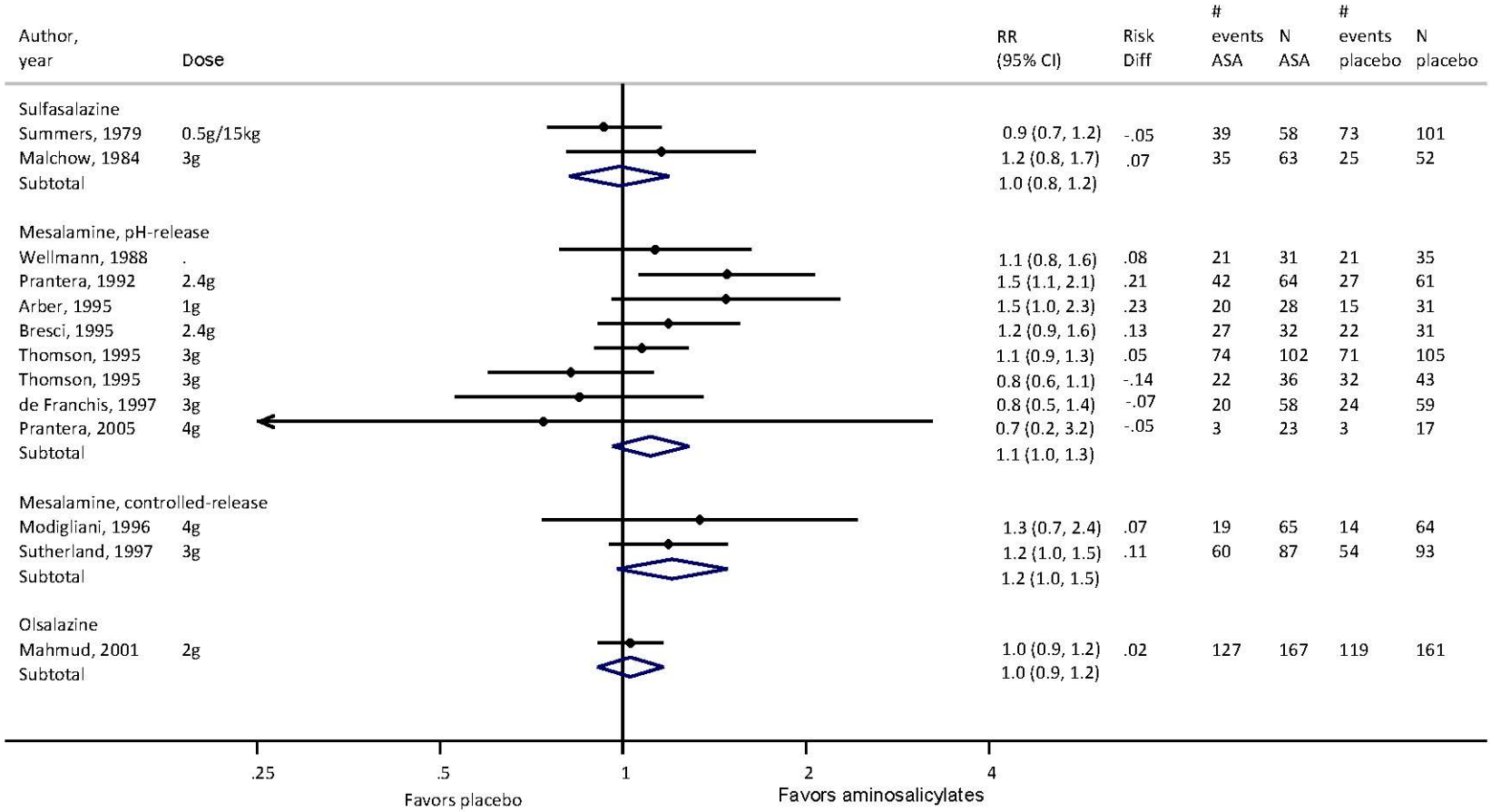
*Trial reported significant at the 0.05 alpha level

†LI - laboratory index (-26 + (1.3 X erythrocyte sedimentation rate) + (0.03 X white blood cell) + (5.5 X C-reactive protein) + (0.08 X alpha-1-antitrypsin)

‡Results were reported separately for patients with Crohn's colitis and Crohn's ileitis. These are the results for patients with Crohn's colitis.

§Results were reported separately for patients with Crohn's colitis and Crohn's ileitis. These are the results for patients with Crohn's ileitis.

Figure 9. Pooled relative risk of remission* of Crohn's disease at weeks 48 to 54 comparing an aminosalicylate with placebo



Pooled Relative Risk and 95% Confidence Intervals of Remission at Weeks 48-54

ASA = aminosalicylates; CI = confidence interval; diff = difference; g = grams; kg = kilograms; RR = relative risk

Note: Boxes indicate individual trial point estimates. The box size denotes the weight of the trial, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each trial. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimateSulfasalazine test for heterogeneity: Q=1.03 with 1 degree of freedom (p=0.31); I-squared = 3%Mesalamine, pH-release test for heterogeneity: Q=10.06 with 7 degrees of freedom (p=0.19); I-squared = 30%

Mesalamine, controlled-release test for heterogeneity: Q=0.13 with 1 degree of freedom (p=0.72); I-squared = 0%

Olsalazine test for heterogeneity: Q=0 with 0 degrees of freedom; I-squared is not applicable.

Comparative Effectiveness of Therapies To Maintain Remission in Adult Subgroups

Key Points

- We saw no consistent relationship for the interaction of a medication and disease characteristic on remission rates in adults with Crohn's disease.

We planned to report results for trials that performed a statistical test for interaction. The following subgroup analyses were performed, but did not contain any trials that reported a *P*-value for an interaction term: baseline CRP, baseline immunomodulator use, baseline antibiotic use, prior TNF-alpha inhibitor exposure, disease location, and prior Crohn's disease-related surgery (Appendix G).

Quality Assessment

Among the 47 included RCTs, 66 percent adequately generated their allocation sequence and 32 percent were unclear in how they generated their allocation sequence (Appendix D, Evidence Table 10). Seventy-two percent of these RCTs adequately concealed their allocation of participants into the different trial groups. Seventy percent of trials were double blind, while 30 percent were not double blinded or did not report on blinding. Fifty-three percent of these trials reported withdrawals and dropouts, but the other 47 percent did not report on withdrawals or dropouts. Forty-three percent of these RCTs had some additional form of threat to the validity of results that they reported such as not clearly differentiating between patients with active and inactive disease or not performing a statistical test for interaction in subgroup analyses. Fifty-seven percent and 33 percent of these RCTs received pharmaceutical support and company involvement in the design, conduct or reporting of the trial, respectively. The funding source was not reported in 23 percent of the trials. The overall quality ratings included 30 percent were rated as good quality, 43 percent as fair quality, and 27 percent as poor quality.

Five TNF-alpha inhibitor trials were double blind trials at randomization, but allowed patients to increase the dose of the drug or switch from placebo to active drug if they were not responding to the randomized dose.[83,87,88,94,95] When assessing the risk of bias, we downgraded these trials to at least medium risk of bias.

Key Question 3: Safety of Therapies in Adults

Forty-seven RCTs including 9,139 Crohn's disease patients and 61 observational studies including 136,583 inflammatory bowel disease (IBD) patients reported data on one or more adverse effects of treatment. As noted for Key Questions 1 and 2, the main drug classes of interest were biologics, thiopurines, methotrexate, corticosteroids, and aminosalicylates. Because some observational studies combined thiopurines and methotrexate as immunomodulators, the additional classification of immunomodulators appears in this section. If more than three trials of similar design (e.g., induction trial, maintenance trial, prospective, retrospective, or case-control study) reported on a medication-outcome relationship, we considered a meta-analysis.

Key Points

We summarized the key points below with the corresponding evidence grades. We provided additional details about the evidence grades in Table 34 and Appendix D, Evidence Table 11.

Mortality

- Mortality rates were less than 1 percent in most of the observed comparisons.
- The only comparison for which mortality differed between groups was treatment with corticosteroids compared with treatment without corticosteroids. The relative risks (RRs) in observational studies ranged from 1.0 to 2.5, favoring no corticosteroids, with followup ranging from 6 weeks to 7 years. (SOE: Low)
- In other comparisons, mortality did not differ between groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, aminosalicylates, or combinations of these drugs. The RRs in observational studies compared with no treatment or another treatment ranged from 0.8 to 1.0 for TNF-alpha inhibitors, 0.7 to 1.3 for immunomodulators, and 0.7 for aminosalicylates, with followup ranging from 4 weeks to 12 years. (SOE: Low)

Hepatosplenic T-Cell Lymphoma

- We identified 37 unique cases of hepatosplenic T-cell lymphoma associated with treatment of Crohn's disease from research reports, case series, and the Adverse Events Reporting System.
- Ninety-five percent of the cases used a thiopurine, and 76 percent of the cases used at least one biologic, but we could not establish a causal relationship because of limitations in the available information.

Lymphoma

- Lymphoma occurred in less than 1 percent of patients in most observed comparisons.
- The risk of lymphoma did not differ between groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, corticosteroids, aminosalicylates, or combinations of these drugs. The observational RRs, compared with no treatment or another treatment, ranged from 0.6 to 1.7 for TNF-alpha inhibitors, 0.3 to 5.3 for immunomodulators, 1.0 for corticosteroids, and 1.0 for aminosalicylates, with followup ranging from 4 weeks to 12 years. (SOE: Low)
- RCTs of immunomodulators, corticosteroids, or aminosalicylates did not report lymphoma as an outcome.

Cervical Cancer

- The studies reported very few cervical cancer cases.
- The risk of cervical cancer did not differ between groups that received TNF-alpha inhibitors, immunomodulators, corticosteroids, or aminosalicylates, or combinations of these drugs, with followup ranging from 26 weeks to 3 years. (SOE: Low)
- Most of the RCTs, and all of the studies of natalizumab, did not include cervical cancer as an outcome.

All Cancers

- The risk of non-melanoma skin cancer was higher with TNF-alpha inhibitors alone or with immunomodulators used recently (within 90 days) or persistently (within 90 days and greater than 365 days), than it was with no TNF-alpha inhibitors or no immunomodulators. The odds ratios (ORs) in observational studies ranged from 2.1 to 6.8. (SOE: Low)
- The risk of non-melanoma skin cancer was higher with thiopurines used recently (within 90 days) or persistently (within 90 days and greater than 365 days), than it was with no thiopurines. The ORs in

observational studies ranged from 3.8 to 4.3. (SOE: Low)
- The risk of adenocarcinoma of the small bowel was higher with 6-mercaptopurine than with no 6-mercaptopurine. The odds ratio (OR) in an observational study was 10.8, with an unreported length of followup. (SOE: Low)
- For all other comparisons, the risk of specific cancers or all cancers did not differ between treatment groups. The RRs, compared with no treatment or another treatment, from observational studies ranged from 0 to 10.8, with followup ranging from 4 weeks to 12 years. (SOE: Low)

Infections

- Trials frequently reported serious infections, and they occurred in less than 5 percent of patients in most trials.
- Trials occasionally reported opportunistic infections, and they occurred less than 5 out of every 100 person-years.
- Trials frequently reported infections (including serious and opportunistic), with a maximum incidence of 83 percent of patients in one trial. Most trials reported far fewer infections (5 to 20 percent of patients).
- The risk of infection did not differ between groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, or aminosalicylates. The RRs, hazard ratios (HRs), or ORs from RCTs and observational studies, compared with no treatment or another treatment, were 0.3 to 1.3 for natalizumab, 0.3 to 11.1 for TNF-alpha inhibitors, 0.3 to 5.4 for immunomodulators, 0.4 to 3.4 for corticosteroids, and 0.9 to 1.8 for aminosalicylates, with followup ranging from 4 weeks to 9 years. (SOE: Low)
- The risk of infection was lower with prednisone and sulfasalazine than with prednisone alone. The RR from one RCT was 0.3, with 8 weeks of followup. (SOE: Moderate)

Tuberculosis

- The studies reported only six cases of tuberculosis, most likely because many RCTs screened patients for tuberculosis or treated them before enrollment.
- The risk of developing tuberculosis did not differ between treatment groups in five RCTs comparing TNF-alpha inhibitors with placebo, one RCT comparing a combination of infliximab and immunomodulators with infliximab, and one RCT comparing a combination of infliximab and immunomodulators with immunomodulators. The followup ranged from 4 to 52 weeks. (SOE: Low)

Infusion- and Injection-Site Reactions

- Trials of biologics frequently reported infusion and injection-site reactions, with infusion reactions occurring in 0 to 40 percent of patients. Most trials reported that fewer than 20 percent of patients experienced reactions.
- The rate of infusion reactions did not differ between treatment groups in most comparisons. (SOE: Low) The RRs from RCTs and observational studies were as follows: for natalizumab versus placebo, RR ranged from 0.8 to 1.5; for certolizumab pegol versus placebo, RR ranged from 0.2 to 1.7; for combinations with infliximab versus infliximab alone, RR ranged from 0.3 to 1.5; and for infliximab combined with thiopurine versus infliximab combined with methotrexate, RR ranged from 0.8 to 1.4.
- The rate of infusion reactions was higher with infliximab and adalimumab than with placebo. The RRs from RCTs ranged from 1.1 to 3.2. (SOE: Low)
- The rate of infusion reactions was higher with infliximab than with azathioprine. The RR from one RCT was 3.0, with 1 year of followup. (SOE: High)
- We did not find any trials that administered corticosteroids or aminosalicylates intravenously.

Bone Fractures

- None of the studies of biologics, immunomodulators, or aminosalicylates reported on bone fractures.
- The risk of bone fracture did not differ between treatment groups that received budesonide or prednisolone. The RR from one RCT with 2 years of followup was 1.0. (SOE: Moderate)
- The risk of bone fracture did not differ between corticosteroid users and corticosteroid non-users. The RR from observational studies ranged from 0 to 2.5, with 2 years of followup. (SOE: Low)

Table 34. Key findings and strength of the available evidence comparing pharmacologic therapies for the management of Crohn's disease in terms of safety-related outcomes

Comparison	Mortality	Lymphoma	Cervical Cancer	All Cancers	Infections	Tuberculosis	Infusion- and Injection-Site Reactions	Bone Fractures
Natalizumab vs. placebo	NF; Low SOE	NF; Low SOE		NF; Low SOE	NF; Low SOE		NF; Low SOE	
Natalizumab + infliximab vs. infliximab		NF; Low SOE		NF; Low SOE	NF; Low SOE		NF; Low SOE	
TNF vs. no TNF			NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE		
Infliximab vs. placebo	NF; Low SOE	NF; Low SOE					Placebo favored; Low SOE	
Adalimumab vs. placebo	NF; Low SOE	NF; Low SOE					Placebo favored; Low SOE	
CP vs. placebo	NF; Low SOE	NF; Low SOE					NF; Low SOE	
Infliximab vs. azathioprine	NF; Low SOE			NF; Low SOE	NF; Low SOE		Azathioprine favored; Low SOE	
TNF + IMM vs. no therapy		NF; Low SOE		NF; Low SOE	NF; Low SOE			
Infliximab + IMM vs. infliximab	NF; Low SOE	NF; Low SOE		NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE	
Infliximab + IMM vs. IMM	NF; Low SOE			NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE	
Infliximab + IMM vs. steroids	NF; Low SOE	NF; Low SOE			NF; Low SOE			
Infliximab + Thiopurine vs. infliximab + methotrexate							NF; Low SOE	
TNF + IMM + steroids vs. no therapy		NF; Low SOE		NF; Low SOE	NF; Low SOE			
Infliximab + steroids vs. no therapy		NF; Low SOE		NF; Low SOE	NF; Low SOE			
Infliximab + steroids vs. infliximab				NF; Low SOE			NF; Low SOE	

Table 34. Key findings and strength of the available evidence comparing pharmacologic therapies for the management of Crohn's disease in terms of safety-related outcomes (continued)

Comparison	Mortality	Lymphoma	Cervical Cancer	All Cancers	Infections	Tuberculosis	Infusion- and injection-Site Reactions	Bone Fractures
IMM vs. placebo	NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE		Placebo favored; High SOE	
Azathioprine vs. steroids	NF; Low SOE			NF; Low SOE	NF; Low SOE			
Azathioprine vs. sulfasalazine	NF; Low SOE			NF; Low SOE	NF; Low SOE			
Thiopurine + prednisone vs. placebo		NF; Low SOE		NF; Low SOE	NF; Low SOE			
Azathioprine + prednisone vs. azathioprine	NF; Low SOE							
IMM + steroids vs. steroids					NF; Low SOE			
Thiopurine + ASA vs. thiopurine		NF; Low SOE		NF; Low SOE	NF; Low SOE			
Steroids vs. placebo	Placebo favored; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE			NF; Low SOE
Budesonide vs. prednisone								NF; Moderate SOE
Prednisone vs. ASA	NF; Low SOE			NF; Low SOE	NF; Low SOE			
Steroids + ASA vs. other	NF; Low SOE				NF; Low SOE			
ASA vs. placebo	NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE			

ASA = aminosalicylates; CP = certolizumab pegol; IMM = immunomodulator; NF = neither favored; SOE = strength of evidence; steroids = corticosteroids; TNF = tumor necrosis factor-alpha inhibitor

Note: We defined the strength of the evidence as follows: High = High confidence that the evidence reflects the true effect. Mod = Moderate confidence that the evidence reflects the true effect. Low = Low confidence that the evidence reflects the true effect. Insufficient = Evidence is unavailable. Blank cells indicate insufficient evidence.

Study Design and Population Characteristics

Forty-seven RCTs and 61 observational studies reported on one or more safety-related outcomes. Tables 12 and 13 in Appendix D list the study designs and population characteristics of those studies.

Forty-five of 87 RCTs (52 percent) that reported efficacy also reported a safety outcome of interest by treatment group. The 45 RCTs reporting safety included 9,139 Crohn's disease patients. The majority of RCTs assessed safety at study visits but did not indicate how they ascertained safety (e.g., study-specific form or open-ended question) nor did they indicate if there were specific safety concerns of interest. We assumed all RCTs that actively assessed efficacy outcomes also actively assessed safety. Similarly, we assumed all RCTs that used blinded assessment for efficacy outcomes also used blinded assessment of safety.

The observational studies included 12 prospective studies (n=29,075), 37 retrospective studies (n=66,177), 11 case-control studies (n=40,040), one cross-sectional study (n=207),[127] and two observational studies of unclear study design (n=694).[128 129] All of the case-control and 75 percent of the prospective studies clearly stated a specific safety outcome of interest. Eight case-control studies reported cancer outcomes, two reported on infections, and one reported on bone fractures. All of the retrospective studies aimed to assess safety, but only about half of the studies specified the exact safety outcomes of interest. No observational study mentioned active ascertainment or blinded assessment of safety outcomes. Three of the prospective studies relied upon the patients' personal gastroenterologists to complete study-specific forms related to safety.[130-132]

Multiple publications used data from several cohorts. These included 23 studies based on a general practice database, a single health center with care delivered at multiple sites, or a single IBD clinic.[128,133-154] Most cohorts with multiple publications reported different outcomes in each publication. However, when relevant, we noted the duplication of outcomes in different studies from the same center.

Some of the centers also served as sites for clinical trials. Unless the authors of the observational study reported that the patients' outcomes were also reported in clinical trials, we did not note duplication of reporting in clinical trials and observational studies.

Study Design of Observational Studies

Thirty-two observational studies occurred at multiple centers. Twenty-eight observational studies occurred at single centers. Of the single-center studies, 13 occurred in the United States (U.S.), one in Canada, 12 in Europe, one in Australia, and one in Africa. Of the multi-center studies, eight occurred in the U.S., one occurred in the U.S. and Europe, and the remainder occurred in Canada, Australia, or a single country in Europe. No single or multi-center study included a site in Asia. Among 45 studies that reported year of enrollment, the starting year ranged from 1946 to 2009 (seven studies did not report year of enrollment). Median followup ranged from 16 weeks to 9 years (mean 34 weeks to 3.7 years). Eighteen studies did not report average followup. The majority of case-control studies used information from electronic records collected for routine care from multiple centers.

Population Characteristics of Observational Studies

Thirty-two studies reported results for IBD patients without reporting results for Crohn's disease patients separately. Twenty-nine studies reported results separately for Crohn's disease

patients or included these patients exclusively. The age distribution was very inclusive with some studies including patients of all ages (zero to 90 years).

The majority of observational studies reporting safety included all activity levels and severities of Crohn's disease. One study explicitly included patients by disease behavior and activity. One study included patients without abscess or stricture with either fistulizing disease or luminal refractory Crohn's disease with a Crohn's Disease Activity Index (CDAI) of 220 to 400.[128] A study on maintenance of remission required patients have 6 months of remission with azathioprine therapy to be eligible.[146] Another prospective azathioprine study required patients to have well-controlled IBD to be eligible.[155]

Most of the observational studies had no restrictions for previous medication use. Twenty studies included only patients who had used infliximab, five studies required adalimumab use, one study required certolizumab pegol use, and two studies required that patients had used a TNF-alpha inhibitor. These studies compared safety of the TNF-alpha inhibitors alone or in combination with other medications. Three retrospective studies required azathioprine use as they aimed to compare effectiveness of azathioprine with or without another medication.[146,156,157]

Mortality

Twenty-seven RCTs including 6,867 Crohn's disease patients reported mortality by comparison group. No RCTs of methotrexate reported on mortality. Seven prospective, 13 retrospective, and one observational study of unclear study design (including 41,877 Crohn's disease patients in total) reported mortality as an outcome by comparison group[128] (Appendix D, Evidence Table 14).

Biologics

Tables 35 and 36 summarize the RCTs and Figure 10 summarizes the observational studies evaluating biologics in terms of mortality. We provided additional details about these studies below.

Table 35. Summary of reported mortality results in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease

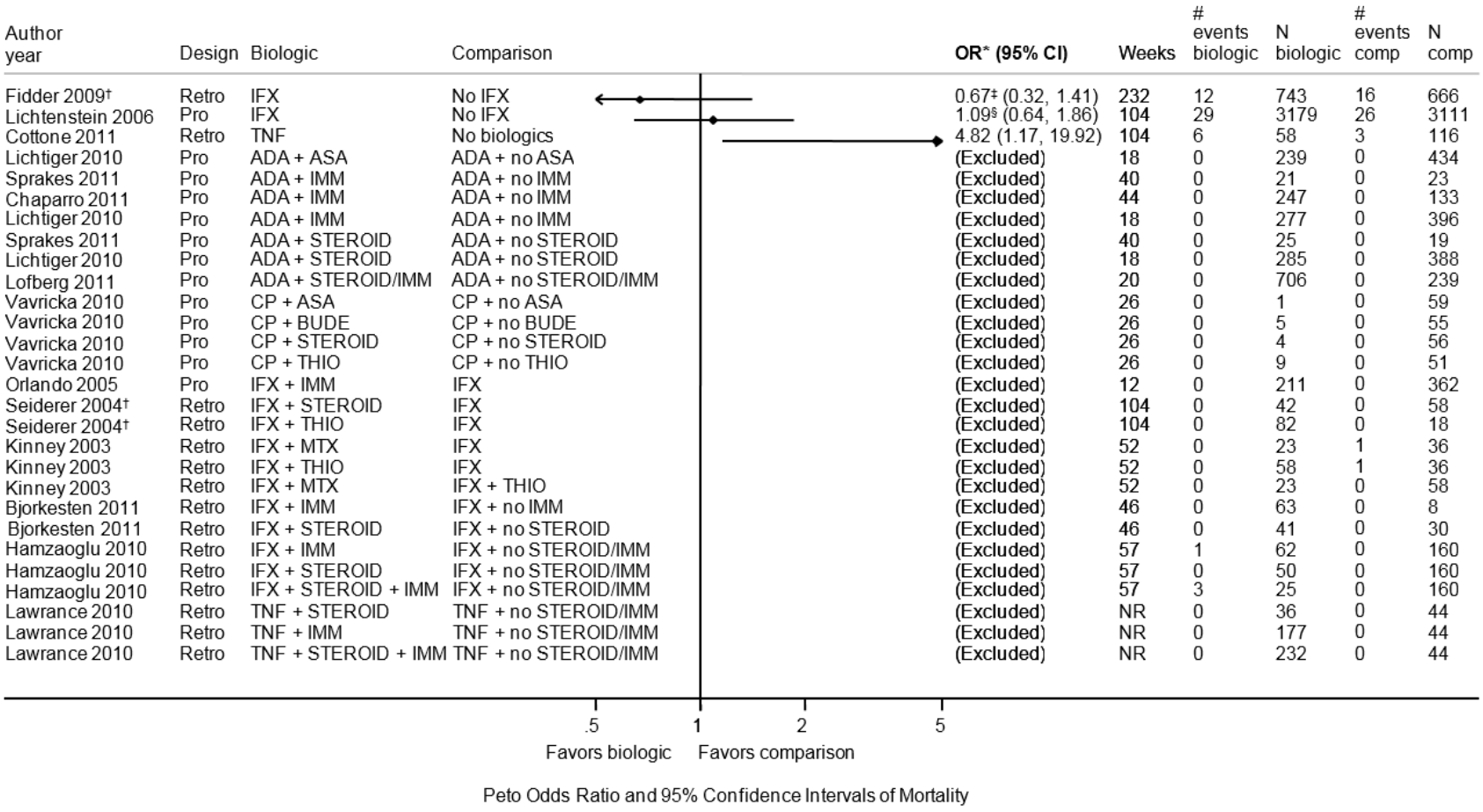
Author, Year	Followup (Weeks)	Biologic	Comparison	# of Deaths in Biologic Group	# of Patients in Biologic Group	# of Deaths in Comparison Group	# of Patients in Comparison Group
Rutgeerts, 1999[85]	36	Infliximab	Placebo	0	37	1	36
Hanauer, 2002[86]	52	Infliximab	Placebo	3	193	0	188
Sandborn, 2005[33]	48	Natalizumab	Placebo	2	723	0	181
Colombel, 2010[45]	54	Infliximab + placebo	Azathioprine + placebo	0	163	1	161
Van Assche, 2008[89]	104	Infliximab + immunomodulators	Infliximab	0	40	1	40
Colombel, 2010[45]	54	Infliximab + azathioprine	Azathioprine + placebo	0	179	1	161

Table 36. Summary of randomized controlled trials that reported no deaths when comparing the effectiveness of a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease*

Biologic	Comparison	# of Trials Reporting no Deaths	Range of Followup (Weeks)	# of Participants (Estimated Person-Years) in Biologic Group	# of Participants (Estimated Person-Years) in Comparison Group
Natalizumab	Placebo	2[32 81]	12	474 (109)	464 (107)
Adalimumab	Placebo	4[37 38 82 83]	4-52	938 (584)	519 (297)
Certolizumab pegol	Placebo	4[39-41 84]	12-26	833 (284)	638 (243)
Infliximab	Placebo	3[44 86 87]	18-52	363 (310)	362 (309)
Infliximab + azathioprine	Infliximab + placebo	1[45]	54	179 (186)	163 (169)
Infliximab+ azathioprine	Infliximab + hydrocortisone	1[88]	104	23 (46)	23 (46)
Infliximab + thiopurine	Thiopurine + placebo	1[46]	52	57 (57)	56 (56)

*Eight RCTs compared a biologic to another medication and did not report on mortality.[33-35 42 43 47 48 80]

Figure 10. Summary of Peto odds ratios of mortality among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease



ADA = adalimumab; ASA = aminosalicylates; BUDE = budesonide; CI = confidence interval; Comp = comparison; CP = certolizumab pegol; IFX = infliximab; IMM = immunomodulator; MTX = methotrexate; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

†Inflammatory bowel disease population

‡Adjusted OR, 0.8 (95% CI, 0.3 to 1.8)

§Adjusted OR, 1.0 (95% CI, 0.5 to 1.9)

Adalimumab Versus Placebo

Four RCTs compared adalimumab with placebo in 1,457 patients and reported mortality.[37,38,83,95] The 4- or 52-week trials reported no deaths during the study periods. However, one person died during an induction period prior to randomization after receiving adalimumab.[95]

Other Combinations With Adalimumab

Four prospective studies (n=2,042) reported no deaths in patients taking adalimumab alone or in combination with aminosalicylates, corticosteroids, or immunomodulators.[158-161] There were two deaths after the study period in one study.[161] One death was from aminosalicylates toxicity (the study did not report any other concomitant medications). The study also did not report any concomitant medications for the other patient who died.

Certolizumab Pegol Versus Placebo

Four RCTs compared certolizumab pegol with placebo in 1,472 patients and reported mortality.[39-41 84] Three studies were induction trials lasting 12- or 26-weeks.[39-41] The trials did not report any deaths during the study periods. One 26-week trial reported one death after the study period in the certolizumab pegol group.[39]

An 18-week trial of 428 responders from an 8-week induction phase compared certolizumab pegol with placebo among patients without obstruction, stricture, or abscess.[84] One patient died of an accidental fentanyl overdose during the induction phase (1 percent), but the trial did not report any deaths during the randomization period.[84]

Other Combinations With Certolizumab Pegol

One prospective study (n=60) reported no deaths in patients taking certolizumab pegol with or without concomitant aminosalicylates, budesonide, other corticosteroids, or thiopurine.[132]

Infliximab Versus Placebo

Four RCTs including 1,022 patients compared infliximab with placebo and reported mortality.[44,85-87] An 18-week induction trial of 94 fistulizing Crohn's disease patients compared infliximab infusion with placebo.[44] It reported no deaths during the study period.

A 36-week maintenance trial[85] compared retreatment with infliximab or placebo among 73 responders to a single induction dose in a previous 12-week trial.[43] The trial reported no deaths in the infliximab group, but reported one death in the placebo group. The deceased patient received infliximab during the induction period.[85] The trial corresponding to the induction period did not report on mortality and did not report this death.[43]

A 40-week maintenance trial of 282 responders and non-responders to a 14-week induction period with infliximab, compared infliximab with placebo.[87] They reported no deaths during the study period, but did report two deaths after the completion of the study. (The deaths occurred in 1 percent of the 306 given an induction dose prior to randomization.)

In a 52-week maintenance trial, 573 responders and non-responders to a 2-week induction period of a single infliximab dose were given either infliximab or a placebo in 5 and 10 mg/kg doses administered intravenously every 8 weeks.[86] They reported three deaths in the 5 mg/kg infliximab group (2 percent), but reported no deaths in the 10 mg/kg infliximab and placebo groups.[86]

Infliximab Versus No Infliximab

One prospective study of 6,290 Crohn's disease patients compared no infliximab use during the observation period with infliximab use within 12 weeks of enrollment, after 30 days of enrollment, or any other time during the observation period.[131] The study followed mortality through June 30, 2004, instead of August 2004, because there was incomplete information on medication usage after June 30, 2004. There was no statistically significant increase in mortality comparing infliximab with no infliximab during the study period in the relative rate (incidence rate ratio [IRR], 1.2; 95% CI, 0.7 to 2.1), unadjusted OR (OR, 1.1; 95% CI, 0.6 to 1.9), or OR adjusted for demographic factors and ever having used prednisone, immunomodulators, or narcotic analgesics (1.0; 95% CI, 0.5 to 1.9). The OR analysis excluded two deaths because they occurred after June 30, 2004. The relative rate appears to have included these deaths.

Infliximab Versus Immunomodulators

One RCT including 324 patients compared infliximab with immunomodulators and reported mortality. A 50-week induction trial compared infliximab with azathioprine among patients who were naïve to TNF-alpha inhibitors, azathioprine, 6-mercaptopurine, and methotrexate.[45] The trial collected safety information through week 54. There was one death among the 161 azathioprine patients, and no deaths among the 163 infliximab patients.

Combination of Infliximab and Immunomodulators Versus Infliximab

Three RCTs and three observational studies including 1,296 patients compared a combination of infliximab and immunomodulators with infliximab alone, and reported mortality.[45,46,89,128,162,163] Three RCTs including 535 patients compared a combination of infliximab and immunomodulators with infliximab alone. A 50-week induction trial compared infliximab and concomitant azathioprine with infliximab alone, among patients who were naïve to TNF-alpha inhibitors, azathioprine, 6-mercaptopurine, and methotrexate.[45] The trial collected safety information through week 54. One patient died prior to randomization of the 817 patients assessed for eligibility (less than 1 percent). The trial did not report any deaths in the 179 combination infliximab and azathioprine patients or 161 infliximab patients during the study period. An open-label 104-week RCT of 80 patients compared retreatment with infliximab with or without continuation of the current immunomodulators.[89] One patient who discontinued immunomodulators died during the study period (1 percent). A 52-week induction trial, of 113 steroid-dependent patients with luminal Crohn's disease reported no deaths in the combination infliximab and thiopurines or infliximab alone treatment groups.[46]

Two retrospective studies including 761 Crohn's disease patients compared a combination of infliximab and immunomodulators with infliximab alone and reported mortality. A single-center retrospective study of 122 patients administered a mean of three infliximab infusions per patient and followed them for an average of 40 to 65 weeks.[162] The trial did not record any deaths in the charts of the 58 patients treated with infliximab with concomitant azathioprine or 6-mercaptopurine, nor did it record any deaths in the charts of the 23 patients treated with concomitant methotrexate. The trial recorded one death in the medical records of 36 patients who received infliximab without concomitant thiopurines or methotrexate (3 percent). Another single-center study reported no deaths in either treatment group.[163]

One study reported no deaths among 362 patients treated with infliximab without immunomodulators, and no deaths among 211 patients who received infliximab and an immunomodulator during the 12-week treatment period.[128] Researchers describe the study as a

large series. It was likely retrospective in design because another study at the same center (reporting cancer outcomes) was retrospective.[149] The study reporting cancer outcomes compared infliximab with no infliximab and reported that three patients treated with infliximab died from their cancer through September 2004. Because the 12-week study reporting on mortality did not report these deaths, they likely did not occur during the first 12 weeks of followup, or occurred after the end of followup of the mortality study.[128]

Combination of Infliximab and Immunomodulators Versus Immunomodulators

One 50-week trial including 340 patients naïve to TNF-alpha inhibitors, azathioprine, 6-mercaptopurine, and methotrexate compared infliximab and concomitant azathioprine with azathioprine alone and reported on mortality.[45] The trial reported no deaths in the 169 combination infliximab and azathioprine patients. One of 170 azathioprine patients died during the study period (less than 1 percent).

Combination of Infliximab and Immunomodulators Versus Corticosteroids

One 2-year trial studied 46 corticosteroid-dependent patients with luminal Crohn's disease who achieved remission during the 8-week induction period. The trial compared infliximab and concomitant azathioprine given daily with infliximab and hydrocortisone given at the time of the infusion.[88] The trial reported no deaths during the study period. One retrospective study of 71 patients reported no deaths in either the infliximab combined with corticosteroids group, or the infliximab combined with no previous use of corticosteroids group.[163]

Other Combinations With Infliximab

Three retrospective cohorts including 954 patients reported on the safety profile of infliximab use at their study centers.[137 145 164] For all Crohn's disease patients, the studies reported concomitant medications at the time of the first infliximab infusion given at the center. However, the studies only reported on concomitant medication use between infusion and the time of death for patients who died. They classified patients with unavailable information as infliximab without concomitant medication. Because of the potential misclassification, we did not include these studies in the tables or the strength of evidence grading, but we did report them here because they met our inclusion criteria.

When studies categorized patients who had received infliximab but were not taking concomitant medications through the time of death as infliximab with no concomitant medications at infliximab initiation, they had the greatest mortality in two of three studies (11 and 32 percent) compared with infliximab with corticosteroids (9 and 3 percent) or compared with infliximab with an immunomodulator with or without corticosteroids (less than 5 percent). The other study reported no deaths in the groups including infliximab without concomitant medication, 2 percent mortality when patients received infliximab combined with an immunomodulator, and 12 percent mortality when patients received infliximab combined with immunomodulators and corticosteroids.[164] A previous study from one of the centers reported on the infliximab outcomes among the first 100 patients, and included one death from chronic pancreatitis 16 weeks after last infliximab infusion.[138] Based on the age at death, this patient is likely the same patient who died of organ failure 8 weeks after the last infusion as reported in the first 500 infliximab patients.[137]

One of these studies also reported mortality among 30 of the 157 patients who used adalimumab after infliximab.[145] The study did not observe any deaths among the 30 adalimumab patients, compared with seven deaths among 127 infliximab users who did not subsequently use adalimumab (6 percent). The Peto OR comparing infliximab followed by adalimumab, with infliximab not followed by adalimumab, in terms of risk of mortality, was 0.3 (95% CI, 0 to 3.5).[145]

Natalizumab Versus Placebo

Three RCTs from two articles reported mortality for natalizumab versus placebo in 1,414 patients.[32 33] The two trials (reported in the same publication) included an initial induction trial of 904 patients followed for 8 weeks, and a subsequent maintenance trial of 428 responders from that initial trial.[33] One death occurred during the induction trial study period in the natalizumab group (less than 1 percent) and an additional death from progressive multifocal leukoencephalopathy occurred in the natalizumab group after the study ended during the open-label extension (less than 1 percent).[33] No deaths occurred in the placebo groups. A 12-week trial of 510 patients did not report any deaths in the induction or study periods.[32]

Other Combinations With TNF-Alpha Inhibitors

One retrospective study reported no deaths from infection in 489 patients who received adalimumab, certolizumab pegol, or infliximab alone or in combination with steroids or immunomodulators.[165] A 104-week retrospective study reported that 10 percent of adalimumab or infliximab users died during the study period compared to 3 percent of patients who had never used a biologic. The corresponding Peto OR is 4.3 (95% CI, 0.9 to 27.6).[150]

Immunomodulators

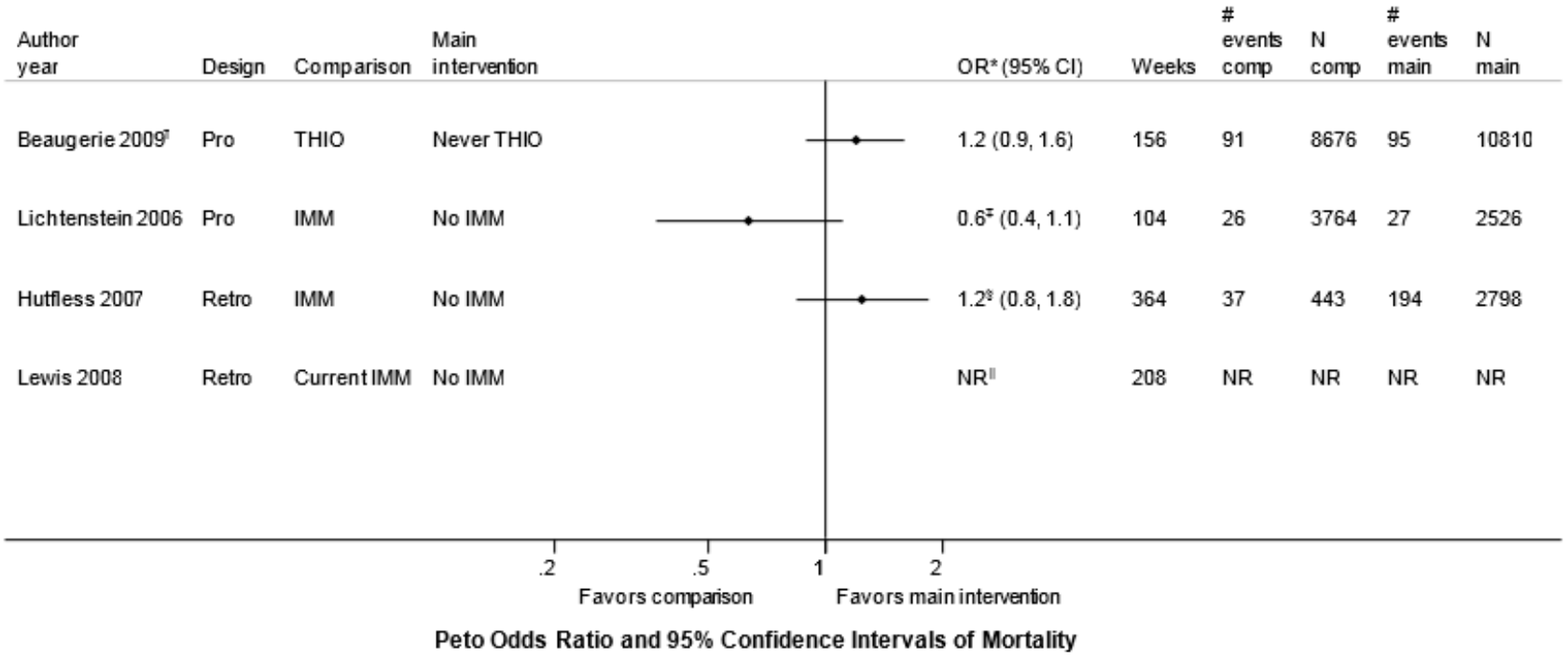
We summarized the effects of immunomodulators on mortality in patients with Crohn's disease in Table 37 (for RCTs) and Figure 11 (for observational studies). We provided additional details about the studies below.

Table 37. Summary of reported mortality results in randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, Year	Follow-up (Weeks)	Immuno-modulator	Comparison	# Deaths in IMM Group	# of Patients in IMM Group	# of Deaths in Comparison Group	# of Patients in Comparison Group
O'Donoghue, 1978[100]	52	Azathioprine	Placebo	1	24	0	27
Lemann, 2005[98]	48	Azathioprine	Placebo	1	40	0	43
Summers, 1979[56]	104	Azathioprine	Placebo	0	113	0	178
Mantzaris, 2009[102]	52	Azathioprine	Budesonide	0	112	0	83
Summers, 1979[56]	104	Azathioprine	Prednisolone	0	113	0	146
Summers, 1979[56]	104	Azathioprine	Sulfasalazine	0	113	0	132
Reinisch, 2008[51]	28	Azathioprine + prednisone	Prednisone	0	52	0	28

IMM = immunomodulator

Figure 11. Summary of Peto odds ratios of mortality among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease



CI = confidence interval; Comp = comparison; IMM = immunomodulator; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; THIO = thiopurine

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

† Inflammatory bowel disease population

‡ Adjusted OR, 0.7 (95% CI, 0.4 to 1.3)

§ Adjusted OR, 1.3 (95% CI, 0.9 to 1.9)

‖ Adjusted hazards ratio, 0.8 (95% CI, 0.4 to 1.9); the total number of mortality events for all treatment groups combined is 264 out of 5,537 patients. The studies did not report the number of events by treatment group.

Azathioprine Versus Placebo

Three RCTs compared azathioprine with placebo in 425 patients and reported on mortality. One RCT reported no deaths due to Crohn's disease in either group.[56] Two RCTs compared continuation of azathioprine with placebo among 134 prevalent users of azathioprine. Researchers conducted one RCT at multiple centers and powered it as a non-inferiority trial to assess recurrent Crohn's disease among those who had used azathioprine and been in remission for at least 42 months. This trial reported one death in the 40 azathioprine patients (3 percent) compared with zero deaths in the 43 placebo patients.[98] One RCT required at least 6 months of azathioprine-induced remission before randomizing patients to azathioprine or placebo.[100] One patient, who had been randomized to continue azathioprine after 10 years of azathioprine use, died during the study period. The trial did not report any deaths in the placebo group.

Azathioprine Versus Aminosalicylates

One 2-year RCT including 245 patients compared azathioprine with sulfasalazine. The trial reported no deaths due to Crohn's disease during the study period.[56]

Azathioprine Versus Corticosteroids

Two RCTs reported on mortality when comparing azathioprine with prednisone in 336 patients.[56,102] One RCT compared 113 azathioprine patients and 146 prednisone patients over 2 years. The RCTs reported no deaths due to Crohn's disease during the study period.[56] Another RCT compared 112 azathioprine with 83 budesonide patients, and reported no deaths during the study period.[102]

Combination of Azathioprine and Prednisone Versus Prednisone

One RCT including 81 patients compared three separate treatment regimens: 2.5 mg/kg per day azathioprine with concomitant 1 mg/kg per day of prednisone or at least 40 mg per day of prednisone (n=52), the same dose of prednisone and a placebo (n=29); and a medication not of interest for this report, everolimus (n=63).[51] Researchers stopped the study early due to lack of efficacy with everolimus, and reported no deaths within 7 months of followup.

Immunomodulators Versus No Immunomodulators

One prospective study and two retrospective studies including a total of 11,829 Crohn's disease patients reported on mortality. One prospective and one retrospective study reported on mortality comparing immunomodulators with no immunomodulators.[131,151] The prospective study reported 1 percent mortality among 3,764 persons who had taken immunomodulators during the study period, compared with 1 percent mortality among 2,526 who had not taken immunomodulators during the study period.[131] The OR was 0.7 (95% CI, 0.4 to 1.3) comparing immunomodulators with no immunomodulators, after adjusting for age; sex; race; disease location; duration of disease; severity; and having ever used infliximab, prednisone, and narcotic analgesics.[131] The retrospective study compared current use of thiopurine with no use of thiopurine during the study period. The hazard ration (HR) was 0.8 (95% CI, 0.4 to 1.9) comparing current thiopurine use versus no use (no recorded use, or no use within 182 days of death), after adjusting for age, sex, comorbidity, and time from registration.[134] In contrast, the third retrospective study reported an OR of 1.3 (95% CI, 0.9 to 1.0), comparing immunomodulators with no immunomodulators, after adjusting for age, sex, and smoking.[151] This retrospective studies did not adjust for use of other Crohn's disease medications or disease

characteristics.

Corticosteroids

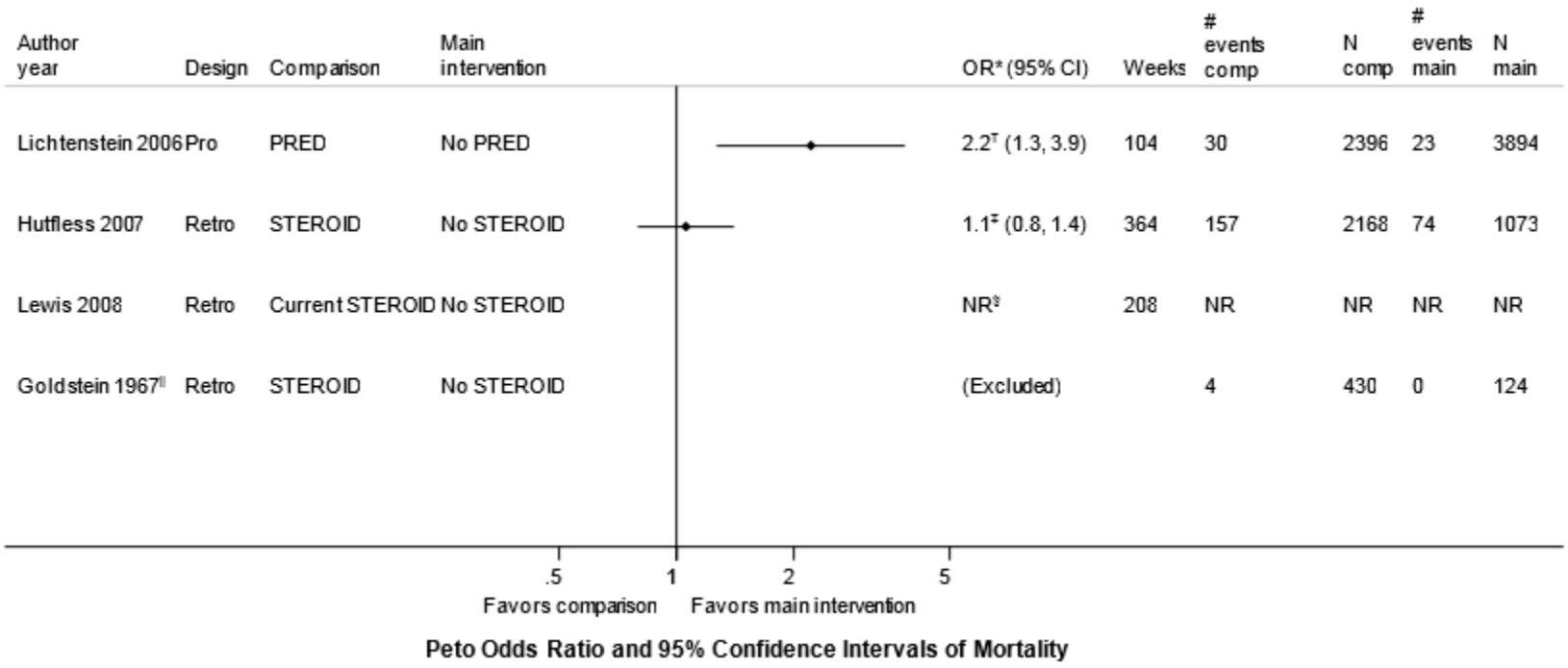
We summarized the effects of corticosteroids on mortality in patients with Crohn's disease in Table 38 (for RCTs) and Figure 12 (for observational studies).

Table 38. Summary of reported mortality results in randomized controlled trials comparing prednisone alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, Year	Followup (Weeks)	Corticosteroid	Comparison	# of Deaths in Steroid Group	# of Patients in Steroid Group	# of Deaths in Comparison Group	# of Patients in Comparison Group
Summers, 1979[56]	104	Prednisone	Placebo	0	146	0	178
Malchow, 1984[64]	104	Prednisone	Placebo	3	113	0	110
Summers, 1979[56]	104	Prednisone	Sulfasalazine	0	146	0	132
Malchow, 1984[64]	104	Prednisone	Sulfasalazine	3	113	0	117
Malchow, 1984[64]	104	Prednisone + sulfasalazine	Placebo	1	112	0	110
Malchow, 1984[64]	104	Prednisone + sulfasalazine	Sulfasalazine	1	112	0	117
Malchow, 1984[64]	104	Prednisone + sulfasalazine	Prednisone	1	112	3	113

Steroid = corticosteroid.
Note: One trial did not report on mortality.[74]

Figure 12. Summary of Peto odds ratios of mortality among observational studies comparing a corticosteroid alone or in combination with another treatment in patients with Crohn's disease



CI = confidence interval; Comp = comparison; NR = not reported; OR = odds ratio; PRED = prednisone; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroid

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

†Adjusted OR, 2.1 (95% CI, 1.1 to 3.8)

‡Adjusted OR, 1.0 (95% CI, 0.7 to 1.4)

§Adjusted hazards ratio, 2.5 (95% CI, 1.9 to 3.3); the total number of mortality events for all treatment groups combined is 264 out of 5537 patients. The studies did not report the number of events by treatment group.

‖Inflammatory bowel disease population

Corticosteroids Versus Placebo

Two RCTs including 547 patients compared corticosteroids with placebo and reported on mortality.[56,64] A 2-year RCT compared prednisone with placebo and reported no deaths due to Crohn's disease during the study period.[56] An RCT that included a 6-week corticosteroid taper for patients with active disease and a 2-year maintenance phase for inactive disease reported three deaths in the prednisolone group during the 2-year period.[64] An additional prednisolone patient died after the study period.

Corticosteroids Versus No Corticosteroids

Three observational studies including 15,070 Crohn's disease patients compared corticosteroids with no corticosteroids and reported mortality.[131,134,151] One prospective study of 6,290 Crohn's disease patients compared mortality rates among patients who used prednisone during the study period versus those who did not.[131] After adjusting for demographics, disease characteristics, and use of other Crohn's disease medications and narcotic analgesics, patients who used prednisone had a 2-fold increased odds of mortality compared with those who did not use prednisone during the study period (OR, 2.1; 95% CI, 1.1 to 3.8).

A retrospective study that observed 3,241 Crohn's disease patients for a median of 7 years reported no difference in mortality between those who used steroids during the study period and those who did not (age, sex, and smoking adjusted OR, 1.0; 95% CI, 0.7 to 1.4).[151] A retrospective study that observed Crohn's disease patients for a mean of 4 years compared those who used corticosteroids currently, recently, or never during the study period. The HR was 2.5 (95% CI, 1.9 to 3.3) comparing current (within 91 days) corticosteroid use versus no use (no recorded use or use more than 182 days prior to death), after adjusting for age, sex, comorbidity, and time from registration.[134] The adjusted HR comparing recent use (92 to 182 days prior to death) with no use (no recorded use or use more than 182 days prior to death) was 1.2 (95% CI, 0.6 to 2.4).[134] The retrospective studies did not adjust for use of other Crohn's disease medications or disease characteristics.

Corticosteroids Versus Aminosalicylates

Two RCTs including 508 Crohn's disease patients compared corticosteroids with sulfasalazine and reported on mortality.[56,64] One RCT compared prednisone with sulfasalazine and reported no deaths due to Crohn's disease during the study period.[56] The other RCT reported three deaths in the prednisolone group during the study period and an additional death after the study period in both the prednisolone and sulfasalazine groups.[64]

Combination of Corticosteroids and Aminosalicylates Versus Other Treatment

One RCT of 452 Crohn's disease patients compared a combination of prednisolone and sulfasalazine with placebo, prednisolone, or sulfasalazine and reported on mortality. During the study period, there were three deaths on prednisolone, one death on prednisolone and sulfasalazine, and no deaths on sulfasalazine or placebo. After the study period, the trial reported an additional death in each group except the placebo group.[64]

Aminosalicylates

We summarized the effects of aminosalicylates on mortality in Table 39.

Table 39. Summary of reported mortality results in randomized controlled trials and observational studies comparing an aminosalicylate alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, Year	Followup (Weeks)	Study Design	ASA	Comparison	# of Deaths in ASA Group	# of Patients in ASA Group	# of Deaths in Comparison Group	# of Patients in Comparison Group	Unadjusted OR* (95% CI)
Lennard-Jones, 1977[166]	52	RCT	Sulfasalazine	Placebo	0	6	0	2	NA
Summers, 1979[56]	104	RCT	Sulfasalazine	Placebo	0	132	0	178	NA
Malchow, 1984[64]	104	RCT	Sulfasalazine	Placebo	0	117	0	110	NA
Modigliani, 1996[119]	48	RCT	Mesalamine	Placebo	0	65	1	64	NA
Hutfless, 2007[151]	364	Retrospective cohort	ASA	No ASA	175	2566	56	675	0.8 (0.6 to 1.1)†

ASA = aminosalicylates; CI = confidence interval; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.
†Adjusted OR, 0.7 (95% CI, 0.5 to 1.1)

Aminosalicylates Versus Placebo

Four RCTs including 674 patients compared aminosalicylates with placebo and reported on mortality.[56,64,119,166] One RCT treated 150 patients with prednisolone for 3 to 7 weeks. Those patients who entered clinical remission were then randomized to receive either mesalamine or placebo until weaned from prednisolone. The trial included an additional year of followup.[119] One of 37 placebo patients died in the year after prednisolone discontinuation.

Three RCTs compared sulfasalazine with placebo. The first included eight patients who had not undergone intestinal resection within the preceding 6 months.[166] No patients died. The second reported no deaths due to Crohn's disease during the study period.[56] The third reported no deaths during the study period. However, one sulfasalazine patient died after the study period.[64]

Aminosalicylates Versus No Aminosalicylates

One retrospective study of 3,241 Crohn's disease patients reported 1 percent fewer deaths in the aminosalicylates-treated group compared with those who did not fill a prescription for aminosalicylates during the study period (age, sex, and smoking adjusted OR, 0.7; 95% CI, 0.5 to 1.1).[151]

Studies Evaluating Patients With IBD

Five studies reported on mortality in the treatment of IBD. The studies did not separate Crohn's disease from ulcerative colitis or indeterminate colitis. In general, the results were consistent between the studies. We provided details about those studies in Appendix F.

Studies Reporting Results for Crohn's Disease and IBD

One study (using administrative data) looked at the relationship between medications and mortality and did not find meaningful difference between Crohn's disease and IBD.[151] The mortality ORs (adjusting for age, sex, and smoking) were similar in Crohn's disease and IBD for patients who used corticosteroid during the study period versus patients who did not (Crohn's disease OR, 1.0; IBD OR, 0.9); the same was true for aminosalicylate versus no aminosalicylate (Crohn's disease OR, 0.7; IBD OR, 0.8). The OR for mortality was greater than 1 for Crohn's disease patients who used immunomodulators during the study period versus those who did not, (OR, 1.3; 95% CI, 0.9 to 1.9) and less than 1 for IBD patients who used immunomodulators versus those who did not (OR, 0.9; 95% CI, 0.7 to 1.2), although neither finding was statistically significant. The study did not adjust ORs for use of the other medications that the study examined.

A collection of referral centers reported on mortality for patients with Crohn's disease or ulcerative colitis.[150] In both the Crohn's disease and ulcerative colitis groups, there were more deaths in the patients treated with adalimumab or infliximab compared with those who never received a biologic.

Progressive Multifocal Leukoencephalopathy

We identified one case of Progressive Multifocal Leukoencephalopathy (PML) associated with treatment of Crohn's disease.[167] A 60-year-old man with a 28-year history of Crohn's disease was experiencing confusion and disorientation on July 2003. The patient expired three months later from PML. Subsequent immunohistochemical analysis of the brain tissue demonstrated positive staining for polyomavirus John Cunningham genotype 2, confirming the

diagnosis of PML. The patient had received 5 doses of natalizumab over a 16-month interval. The last natalizumab dose was in May or June 2003, within 2 months of symptom presentation. The patient had also previously received infliximab starting in September 1998 (prior to European approval of infliximab in August 1999). The patient received the last infliximab infusion in September 2001, 20 months prior to the PML diagnosis. The patient had also used corticosteroids, antibiotics, and azathioprine (discontinued 8 months prior to suspected PML due to refractory anemia with low platelet counts and lymphopenia). The authors of the study linked the timing of the PML diagnosis to the use of natalizumab because John Cunningham virus appeared in serum samples (available from the IBD center's serum bank from March 1999) only after this patient received natalizumab. A randomized trial reported on this case during the period when the patient first received natalizumab.[33] And an observational study reported the safety of infliximab at the study center.[153] A search of the Adverse Events Reporting System did not identify additional cases.

Lymphoma

Thirteen RCTs including 4,956 Crohn's disease patients reported on lymphoma risk by comparison group (Appendix D, Evidence Table 14). Three prospective studies (n=20,219), 12 retrospective studies (n=32,056), and one case-control study (n=15,471) reported lymphoma as an outcome. Lymphoproliferative disorders (including lymphoma) were a primary interest of outcome in one prospective study.[130] No trials of immunomodulators, corticosteroids, or aminosalicylates reported on lymphoma risk. The total number of patients in the RCTs was 71,554.

Biologics

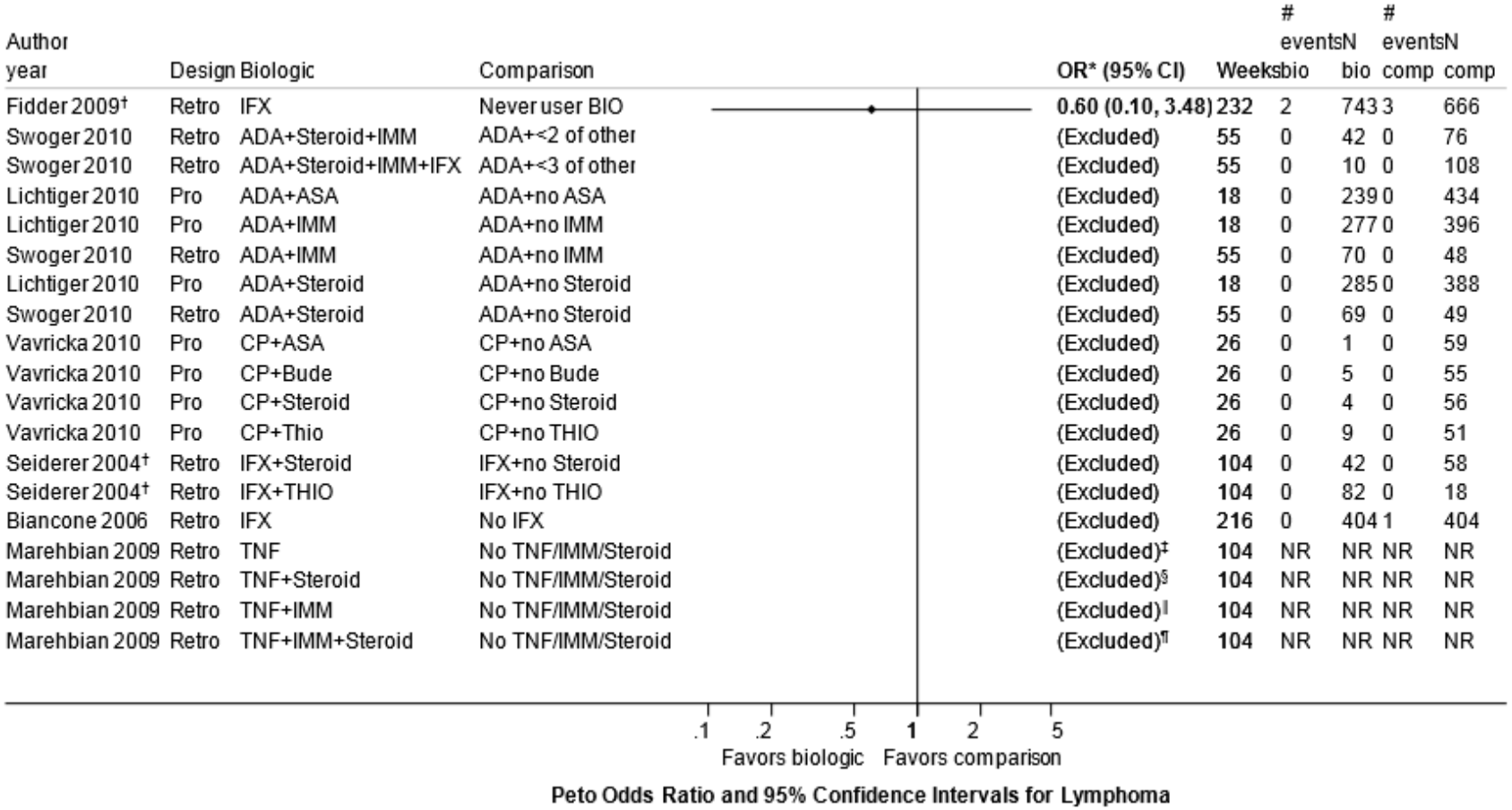
We summarized the risk of lymphoma associated with use of biologics in Crohn's disease in Table 40 (for RCTs) and Figure 13 (for observational studies). We also provided additional details regarding related studies.

Table 40. Summary of lymphoma risk in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease*

Author, Year	Followup (Weeks)	Biologic	Comparison	# of Lymphoma Cases in Biologic Group	# of Patients in Biologic Group	# of Lymphoma Cases in Comparison Group	# of Patients in Comparison Group
Rutgeerts, 1999[85]	36	Infliximab	Placebo	0	37	1	36
Hanauer, 2002[86]	52	Infliximab	Placebo	0	385	1	188
Schreiber, 2005[40]	20	Certolizumab pegol	Placebo	0	218	0	73
Schreiber, 2007[84]	18	Certolizumab pegol	Placebo	0	216	0	212
Sandborn, 2007[39]	26	Certolizumab pegol	Placebo	0	331	1	329
Sandborn, 2007[38]	4	Adalimumab	Placebo	0	159	0	166
Hanauer, 2006[37]	4	Adalimumab	Placebo	0	225	0	74
Sandborn, 2007[83]	52	Adalimumab	Placebo	0	37	0	18
Sandborn, 2005[33]	48	Natalizumab	Placebo	0	723	0	181
Targan, 2007[32]	8	Natalizumab	Placebo	0	260	0	250
Sands, 2007[35]	20	Natalizumab + infliximab	Infliximab	0	52	0	27

*Three RCTs compared a biologic with placebo or another medication and did not report on lymphomas.[42 45 89]

Figure 13. Summary of Peto odds ratios of lymphoma among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease



ADA = adalimumab; ASA = aminosalicylates; BIO = biologics; Bude = budesonide; CI = confidence interval; Comp = comparison; CP = certolizumab pegol; IFX = infliximab; IMM = immunomodulator; Main = main intervention; NR = not reported; OR = odds ratio; Retro = retrospective cohort; STEROID = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

†Inflammatory bowel disease population

‡Incidence rate ratio, 1.7 events per person-year (95% CI, 0.2 to 6.3)

§Incidence rate ratio, 0 events per person-year (95% CI, 0 to 6.5)

‖Incidence rate ratio, 1.5 events per person-year (95% CI, 0.04 to 8.7)

¶ Incidence rate ratio, 0 events per person-year (95% CI, 0 to 30.0)

Adalimumab Versus Placebo

Three RCTs including 679 patients compared adalimumab with placebo and reported no cases of lymphoma.[37,38,83]

Other Combinations With Adalimumab

One prospective (n=673)[161] and one retrospective (n=118)[140] study reported no cases of lymphoma in patients who used adalimumab alone or in combination with aminosalicylates, corticosteroids, or immunomodulators.

Certolizumab Pegol Versus Placebo

Three RCTs including 1,379 patients compared certolizumab pegol with placebo and reported on lymphoma risk.[39,40,84] One trial reported one lymphoma case in a placebo group (less than 1 percent).[39] The other two RCTs reported no cases of lymphoma.[40 84]

Other Combinations With Certolizumab Pegol

One prospective study (n=60) reported no deaths in patients who used certolizumab pegol alone or in combination with aminosalicylates, corticosteroids, or immunomodulators.[132]

Infliximab Versus Placebo

Two RCTs including 646 patients compared infliximab with placebo and reported on lymphoma risk.[85,86] One study randomized infliximab responders and non-responders after a single infusion of infliximab or placebo.[86] The other study[85] compared retreatment with infliximab with placebo among responders to a single infusion from a previous RCT.[43] The two trials reported no lymphoma cases in the infliximab groups (0 percent of 385 and 37 patients, respectively). However, in the placebo groups, one trial reported one lymphoma among 188 patients (less than 1 percent),[86] and the other study saw one lymphoma in 36 patients (4 percent).[85] The retreatment RCT reported that one lymphoma patient received infliximab in the induction period and later died from sepsis, although the induction study did report lymphoma or death.[43]

Natalizumab Versus Placebo

Three RCTs (published in two articles) included 1,414 patients and reported no cases of lymphoma in any natalizumab or control group during the study periods.[32,33] One trial reported lymphoma after the study in a patient who had received natalizumab induction, placebo maintenance, and natalizumab during the open-label extension period.[32]

Combination of Natalizumab and Infliximab Versus Infliximab

One 20-week RCT including 79 infliximab non-responders randomized patients to additional treatments with natalizumab or placebo.[35] The trial followed patients for up to 6 months. It reported no lymphoma cases.

TNF-Alpha Inhibitor Versus No TNF-Alpha Inhibitor

Two retrospective studies including 9,389 Crohn's disease patients compared a TNF-alpha inhibitor with no TNF-alpha inhibitor and reported on lymphoma risk.[149,153,168]

One study reported no lymphoma cases among 404 Crohn's disease patients with a record of

infliximab in their charts, compared with one case of lymphoma among 404 Crohn's disease patients who did not have a record of infliximab in their charts. The study matched both sets of patients with respect to age, sex, followup, immunomodulator use, Crohn's disease location and duration, and study center.[149] Because the non-Hodgkin's lymphoma patient did not use infliximab, the patient did not meet the inclusion criteria for another infliximab study at the center.[128]

A claims-based study of health plan members included 8,581 patients with one or more encounter with Crohn's disease. The study reported two lymphoma cases in TNF-alpha inhibitor users (1 per 100 person-years) and 64 lymphoma cases in patients who received no TNF-alpha inhibitor, immunomodulator, or corticosteroid (less than one per 100 person-years).[168] Although the authors did not report a rate ratio; the unadjusted rate ratio comparing TNF-alpha inhibitor use with no therapy (based on the provided information) was 1.7 (95% CI, 0.2 to 6.3).[168]

Combination of TNF-Alpha Inhibitors, Immunomodulators, and Corticosteroids Versus No Therapy

The same claims-based study reported no lymphoma cases among 31 person-years of exposure to combination therapy with TNF-alpha inhibitors, immunomodulators, and corticosteroids, compared with 64 cases among 15,673 person-years of no therapy.[168]

Combination of TNF-Alpha Inhibitors and Immunomodulators Versus No Therapy

The same claims-based study reported one lymphoma case among 162 person-years of exposure to combination therapy with TNF-alpha inhibitors and immunomodulators (with or without corticosteroids), compared with 64 cases among 15,673 person-years of no therapy (less than one per 100 person-years in both groups).[168] The corresponding unadjusted rate ratio was 1.5 (95% CI, 0 to 8.7).

Combination of TNF-Alpha Inhibitor and Corticosteroids Versus No Therapy

The same claims-based study reported no lymphoma cases among 142 person-years of exposure to combination therapy with TNF-alpha inhibitor and corticosteroids (with or without immunomodulators), compared with 64 cases among 15,673 person-years of no therapy.[168]

Other Combinations With Infliximab

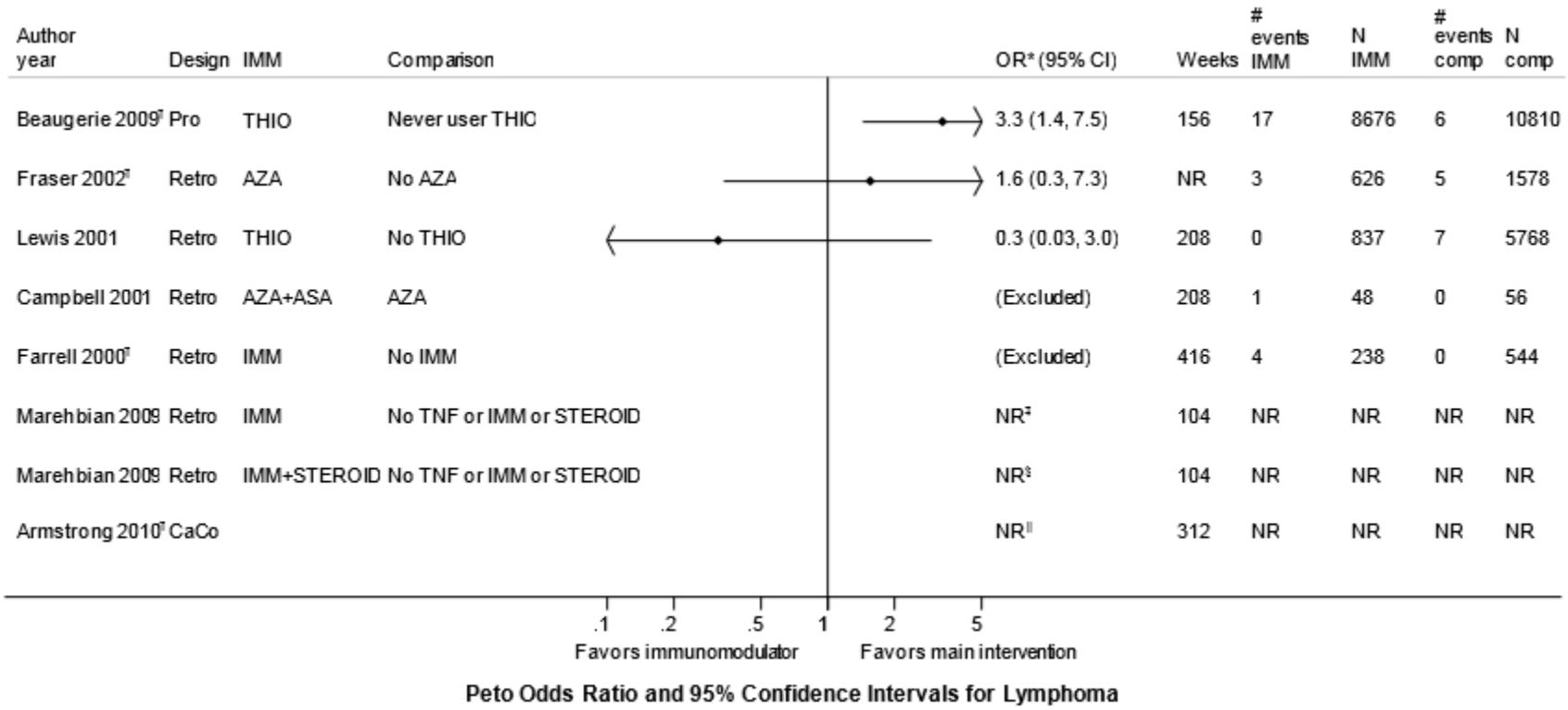
Three retrospective cohorts including 954 patients described the safety profile of infliximab use at their study centers.[137,145,164] As described in the mortality section, it is unclear if we have accurately classified patients by medication exposures. When these studies categorize patients who had received infliximab and immunomodulators at the time of lymphoma diagnosis as users of infliximab with immunomodulators at infliximab initiation, the three studies report four lymphomas. One of the studies reported four lymphomas among the 25 patients receiving infliximab in combination with immunomodulators and corticosteroids.[164] The study reported no other lymphomas for the other treatment combinations (combination of infliximab, immunomodulators, and corticosteroids, combination of infliximab and corticosteroids, or infliximab alone).

Immunomodulators

Figure 14 summarizes the risk of lymphoma in observational studies evaluating

immunomodulators in patients with Crohn’s disease.

Figure 14. Summary of Peto odds ratios of lymphoma among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease



ASA = aminosalicylates; AZA = azathioprine; CaCo = case-control study; CI = confidence interval; Comp = comparison; IMM = immunomodulator; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitors

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

†Inflammatory bowel disease population

‡Incidence rate ratio, 0.8 events per person-year (95% CI, 0.2 to 2.5)

§Incidence rate ratio, 0 events per person-year (95% CI, 0 to 48.9)

‖Adjusted OR, 3.2 (95% CI, 1.0 to 10.2)

Immunomodulators Versus No Immunomodulators

Two retrospective studies including 15,186 Crohn's disease patients reported lymphoma risk from immunomodulator use.[136,168] A claims-based study including 8,581 Crohn's disease patients reported less than one lymphoma case per 100 person-years in both the no therapy group and the immunomodulator group (with or without corticosteroids or TNF-alpha inhibitors) (unadjusted relative rate, 0.8; 95% CI, 0.2 to 2.5).[168] In one study comparing at least one prescription for a thiopurine with no thiopurine prescription, none of the 837 thiopurine users developed lymphoma, compared with seven of 5,768 non-users (less than 1 percent). The corresponding Peto OR was 0.3 (95% CI, 0 to 2.9).[136]

Combination of Immunomodulators and Corticosteroids Versus No Therapy

A claims-based study reported no lymphoma cases among patients receiving a combination of immunomodulators and corticosteroids (with or without TNF-alpha inhibitors), compared with less than one lymphoma per 100 person-years among patients receiving no therapy.[168]

Combination of Azathioprine and Aminosalicylates Versus Azathioprine

One retrospective study of 104 Crohn's disease patients reported a case of Waldenstrom's macroglobulinemia in the azathioprine and aminosalicylate group, compared with no lymphoma in the azathioprine-alone group.[146]

Corticosteroids

No trials that included corticosteroids reported on lymphoma. Table 41 summarizes the risk of lymphoma in observational studies evaluating corticosteroids in patients with Crohn's disease. We also provided additional details regarding related studies.

Table 41. Summary of risk of lymphoma in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, Year	Followup (Weeks)	Study Design	Corticosteroid	Comparison	# of Lymphoma Cases in Steroid Group	# of Patients in Steroid Group	# of Lymphoma Cases in Comparison Group	# of Patients in Comparison Group	Unadjusted Relative Measure (95% CI)	Adjusted Relative Measure (95% CI)
Lewis, 2001[136]*	208	Retrospective cohort	Steroid	No steroid	4	4064	11	11100	OR, 1.0 (0.3 to 3.1)	NR
Marehbian, 2009[168]	104	Retrospective cohort	Steroid	No TNF or IMM or steroid	NR†	NR	NR‡	NR	IRR, 0 (0 to 2.5)	HR, 1.0 (0.4 to 2.4)

CI = confidence interval; HR = hazards ratio; IMM = immunomodulator; IRR = incidence rate ratio; NR = not reported; OR = odds ratio; Steroid = corticosteroid; TNF = tumor necrosis factor-alpha inhibitor

*Inflammatory bowel disease population

†There were 0 events during 379 person-years.

‡There were 64 events during 15,673 person-years.

Corticosteroids Versus No Therapy

A claims-based study, that included 8,581 Crohn's disease patients, reported no lymphoma cases among the corticosteroid users (with or without immunomodulators or TNF-alpha inhibitors), compared with the no therapy group.[168] The study reported a HR of 1.0 (95% CI, 0.4 to 2.4) comparing use of corticosteroids alone with no therapy, after adjustment for age, gender, geographic region, health plan, and comorbidity.

Studies Evaluating Patients with IBD

Seven studies reported on lymphoma risk in IBD patients without separating Crohn's disease from ulcerative colitis or indeterminate colitis patients. In general, the results were consistent between the studies. See Appendix F for more information about these studies.

Studies Reporting Results for Crohn's Disease and IBD

One retrospective study reported similar results for IBD patients as Crohn's disease patients, one lymphoma (less than 1 percent) among 1,465 thiopurine users compared with 14 lymphomas (less than 1 percent) among 15,531 non-users.[136] The incidence density ratio comparing thiopurine to no thiopurine use was 0.8 for IBD, compared with the Peto OR of 0.3 for Crohn's disease. Neither was statistically significant. The study excluded a lymphoma case with diagnosis codes for both Crohn's disease and ulcerative colitis, according to the exclusion criteria. The patient had also received a liver transplant 4 months before the lymphoma diagnosis.

Hepatosplenic T-Cell Lymphoma

The medical community first identified hepatosplenic T-cell lymphoma (HSTCL) as a diagnosis distinct from other T-cell lymphomas in 1996.[169] HSTCL is a very rare type of lymphoma that is generally fatal.[169] To assess the risk of HSTCL associated with treatment for Crohn's disease, we supplemented the primary search strategy by searching for case reports or case series published in the literature, or cases reported to the Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS). A search of the publicly available AERS data files through March 2011 yielded 132 patient identification numbers representing 48 unique FDA-ascribed case numbers. From the literature and AERS search results, we considered 37 HSTCL cases unique based on age, sex, medications, country of origin, and length of survival. We considered two cases duplicative. We considered the remaining nine cases possibly unique. The case studies reported two of the 37 unique cases survived and none of the nine possibly unique cases survived (4 percent of 46 cases).

Tables 42 and 43 summarize the demographic and medication characteristics of the unique and possibly unique cases of HSTCL in patients with Crohn's disease. Of the 37 unique cases with Crohn's disease-associated HSTCL, most were young (86 percent younger than 40 years of age) and male (86 percent). Most cases (70 percent) had reported exposure to both a TNF-alpha inhibitor and thiopurines. Almost all cases (95 percent) had reported exposure to thiopurines compared with 75 percent who had exposure to at least one TNF-alpha inhibitor. Two cases (4 percent) reported exposure to a TNF-alpha inhibitor without thiopurines.

Table 42. Demographic and survival characteristics of patients with Crohn's disease who developed hepatosplenic T-cell lymphoma

Patient Characteristic	Unique Cases (n=37)	Possibly Unique Additional Cases (n=9)
Age at HSTCL diagnosis (in years)	N=36*	N=0
Mean	30	--
Median	26	--
Range	12 to 79	--
Crohn's disease duration (in years)	N=16	N=0
Mean	10	--
Median	6	--
Range	4 to 35	--
Sex, number of cases (%)	N=36	N=6
Female	5 (14%)	1 (17%)
Survival, number of cases (%)	N=37	N=9
Died	24 (65%)	4 (44%)
Survived	2 (5%)	0 (0%)
Outcome unclear or not reported	11 (30%)	5 (56%)

HSTCL = hepatosplenic T-cell lymphoma
*Number with report of characteristic. Mean and percentages based on this denominator.

Table 43. Medications used prior to diagnosis of hepatosplenic T-cell lymphoma in 37 unique patients with Crohn's disease

Medication	Number of Cases With Exposure (%)	Mean Cumulative Dose in Mg* (Range)	Mean Duration of Drug Use in Years (Range)	Mean Number of Injections or Infusions (Range)
Biologics	28 (76%)	--	--	--
Adalimumab	8 (22%)	920 (800-1040)	1.5 (120 days-2.6 years)	11.5 (10-13)
Infliximab	27 (73%)	41 (10-120) mg/kg	1.8 (1 day-6 years)	9 (1-24)
Natalizumab	1 (3%)	NR	NR	3 (n=1)
Certolizumab pegol	0	NR	NR	NR
Thiopurines	35 (95%)	--	--	--
6-mercaptopurine	19 (51%)	55,290 (3900-93530)	4.5 (39 days-8 years)	NA
Azathioprine	23 (62%)	151,288 (1450-301,125)	5.8 (39 days-13.5 years)	NA
Aminosalicylates	15 (41%)	--	--	--
Balsalazide	1 (3%)	NR	NR	NA
Mesalamine	13 (35%)	NR	5 (n=1)	NA
Salazopyrine	2 (5%)	NR	10 (n=1)	NA
Corticosteroids	21 (57%)	--	--	--
Budesonide	2 (5%)	NR	NR	NA
Hydrocortisone	1 (3%)	NR	NR	NA
Prednisone	14 (38%)	NR	NR	NA
Prednisolone	4 (11%)	NR	13 (n=1)	NA
Corticosteroid, unspecified	6 (16%)	NR	10 (n=1)	NA
Antibiotics†	7 (19%)	NR	NR	NA
Cyclosporine	1 (3%)	NR	NR	NA

kg = kilograms; mg = milligrams; NA = not applicable; NR = not reported
*Reported as mg/kg for infliximab only
†The antibiotics used include ciprofloxacin, doxycycline, metronidazole, nitrofurantoin, and piperacillin/tazobactam.

Cervical Cancer

One trial (n=660) reported on cervical cancer risk associated with medications for treatment of Crohn's disease. No trials of infliximab, adalimumab, natalizumab, immunomodulators, corticosteroids, or aminosalicylates reported on cervical cancer.

Certolizumab Pegol Versus Placebo

One RCT reported one carcinoma in situ of the cervix (grade 0) in a placebo patient (less than 1 percent of 197 females) and no cervical cancer in the 174 female certolizumab pegol patients during followup.[39]

Studies Evaluating Patients With Inflammatory Bowel Disease

Four observational studies reported on cervical cancer risk in IBD patients without separating Crohn's disease from ulcerative colitis or indeterminate colitis patients. We provided a summary of these studies in Appendix F.

Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease

We did not identify any studies that reported on the comparative safety, in terms of cervical cancer, for patients with Crohn's disease and IBD.

Other Cancers

Twenty-one RCTs including 7,149 Crohn's disease patients reported on other cancers by comparison group (Appendix D, Evidence Table 14). No methotrexate trial reported on cancer. One prospective (n=19,486), 12 retrospective (n=15,015), and one observational study of unclear study design (n=573)[128] reported cancer as an outcome by comparison group.

Biologics

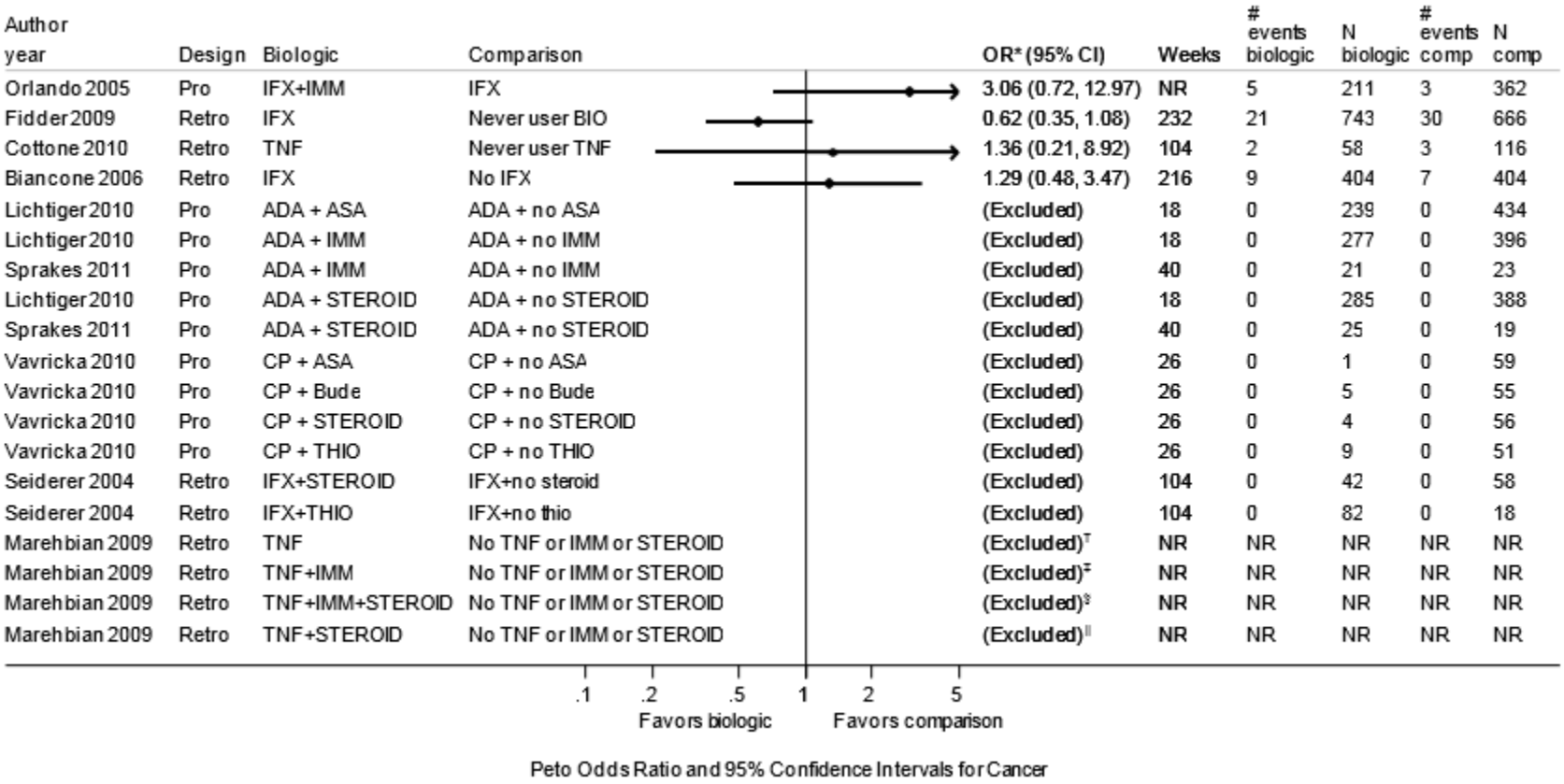
We summarized the risk of other cancers associated with treatment of Crohn's disease in Table 44 (for RCTs) and Figure 15 (for observational studies). We also provided additional details regarding related studies.

Table 44. Summary of the risk of other cancers in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease*

Author, Year	Followup (Weeks)	Biologic	Comparison	# of Cancer Cases in Biologic Group	# of Patients in Biologic Group	# of Cancer Events in Comparison Group	# of Patients in Comparison Group
Sands, 2004[87]	40	Infliximab	Placebo	0	139	0	143
Hanauer, 2002[86]	52	Infliximab	Placebo	4	385	2	188
Sandborn, 2011[42]	6	Certolizumab pegol	Placebo	1	223	0	215
Schreiber, 2007[84]	18	Certolizumab pegol	Placebo	0	216	0	212
Sandborn, 2007[39]	26	Certolizumab pegol	Placebo	2	331	2	329
Schreiber, 2005[40]	12	Certolizumab pegol	Placebo	0	219	0	73
Sandborn, 2007[38]	4	Adalimumab	Placebo	0	159	0	166
Sandborn, 2007[83]	52	Adalimumab	Placebo	0	37	1	18
Colombel, 2007[82]	52	Adalimumab	Placebo	0	517	1	261
Targan, 2007[32]	12	Natalizumab	Placebo	1	260	0	250
Sandborn, 2005[33]	48	Natalizumab	Placebo	1	723	7	181
Colombel, 2010[45]	54	Infliximab	Azathioprine	0	163	2	161
Lemann, 2006[46]	24	Infliximab + thiopurine	Thiopurine	0	57	0	56
Colombel, 2010[45]	54	Infliximab + azathioprine	Infliximab	0	179	0	163
Colombel, 2010[45]	54	Infliximab + azathioprine	Azathioprine	0	179	2	161
Van Assche, 2008[89]	104	Infliximab + immunomodulator	Infliximab	0	40	2	40
Schroder, 2006[47]	48	Infliximab + methotrexate	Infliximab	0	11	0	8
Sands, 2007[35]	20	Natalizumab + infliximab	Infliximab	0	52	0	27

*Seven randomized controlled trials evaluating biologics did not report on any cancer outcomes.[34,41,43,44,48,81,88]

Figure 15. Summary of Peto odds ratios of cancer risk among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease



BIO = biologics; CI = confidence interval; Comp = comparison; IFX = infliximab; IMM = immunomodulator; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

†Incidence rate ratio, 0.1 events per person-year (95% CI, 0.01 to 0.2)

‡Incidence rate ratio, 0.9 events per person-year (95% CI, 0.6 to 1.4)

§Incidence rate ratio, 0.7 events per person-year (95% CI, 0.1 to 2.1)

‖Incidence rate ratio, 0.6 events per person-year (95% CI, 0.3 to 1.0)

Adalimumab Versus Placebo

Three RCTs including 1,158 Crohn's disease patients compared adalimumab with placebo and reported on cancer.[37,38,82] A 4-week induction trial, including 325 patients randomized to adalimumab or placebo among patients who had lost response or were intolerant to infliximab, reported no cancers during the study period.[38] A 52-week maintenance trial reported one cancer case in 261 placebo patients (less than 1 percent) and no cancer cases in 517 adalimumab patients.[82] A 52-week maintenance trial of 276 responders to induction in a previous trial[37] reported one cancer in 18 placebo patients, compared with no cancers in the 37 adalimumab patients who remained on randomized treatment during the entire study period.[83]

Other Combinations With Adalimumab

Two prospective (n=717)[159,161] and one retrospective (n=118)[140] study reported no deaths in patients who used adalimumab alone or in combination with aminosalicylates, corticosteroids, or immunomodulators.

Certolizumab Pegol Versus Placebo

Four RCTs including 1,818 Crohn's disease patients compared certolizumab pegol with placebo and reported on cancer.[39,40,42,84] A 6-week induction trial reported one cancer (less than 1 percent) in the certolizumab pegol patients and no cancers in placebo.[42] A 12-week induction trial (followed an additional 8 weeks for safety) reported no cancers in the 292 included patients.[40] A 26-week induction trial reported two cancers in placebo patients (1 percent of 329) and two cancers in certolizumab pegol patients (1 percent of 331) during the study period.[39] An 18-week maintenance trial reported no cancers during the study period.[84] The trial reported one benign, malignant, or unspecified neoplasm (including cyst or polyp) during the 8-week induction phase which included 668 patients, but the trial did not provide specifics of the event.[84]

Other Combinations With Certolizumab Pegol

One prospective study (n=60) reported no deaths in patients who used certolizumab pegol alone or in combination with aminosalicylates, corticosteroids, or immunomodulators.[132]

Infliximab Versus Placebo

Two trials including 855 Crohn's disease patients reported on cancer risk.[86,87] A maintenance trial reported one case of cancer in the 10 mg/kg intravenous every 8 weeks infliximab group, three cases in the 5 mg/kg intravenous every 8 weeks infliximab group, and two cases in the placebo group over 52 weeks of followup.[86] A maintenance trial of fistulizing Crohn's disease reported no cancers during the 40-week trial period.[87] Two cancers occurred after the trial ended. Both patients had received infliximab.

Infliximab Versus No Infliximab

One retrospective study including 808 Crohn's disease patients reported on cancer, comparing infliximab use with no use.[149] The study reported nine cancers among 404 infliximab users followed for 48 months, compared with seven cancers among 404 no infliximab users followed for 60 months (2 percent in both groups). The study matched the two groups by factors including age, sex, followup, immunomodulator use, Crohn's disease site, Crohn's disease duration, and study center.[149] The OR was 1.3 (95% CI, 0.5 to 3.8) comparing infliximab users

with infliximab non-users accounting for the matching factors.[149] Another study reporting results from the same infliximab patients,[128] compared a combination of infliximab and immunomodulators with infliximab alone and reported one additional case of cancer among infliximab users.

Infliximab Versus Immunomodulators

One induction trial of 324 Crohn's disease patients, naïve to TNF-alpha inhibitors and immunomodulators, compared infliximab with azathioprine and reported mortality.[45] The trial did not report any cancers in the 163 infliximab patients, and reported two cancers in the 161 azathioprine patients during the 50-week study period.

Combination of Infliximab and Immunomodulators Versus Infliximab

Three RCTs[45,47,89] and two observational studies[128,129] reporting on cancer risk (1,135 Crohn's disease patients total) compared a combination of infliximab and immunomodulators versus infliximab alone. The RCTs included 441 patients. One induction trial of 342 patients, naïve to TNF-alpha inhibitors and immunomodulators, reported no cancers during the 50-week study period in the combination infliximab and azathioprine, and infliximab alone groups.[45] An open-label trial of 19 azathioprine intolerant or resistant patients compared a combination of infliximab and methotrexate with infliximab alone, and reported no malignancies during the 48-week study period.[47] An 104-week open-label RCT of 80 non-fistulizing Crohn's disease patients, retreated with infliximab while continuing or discontinuing immunomodulators, reported two cancers in the infliximab group and no cancers in the combination infliximab and immunomodulators group.[89]

In the observational studies, one retrospective study of 573 Crohn's disease patients, followed for 12 weeks or 6 months, reported five cancers among 211 combination infliximab and immunomodulator patients and three cancers in 362 patients using infliximab without immunomodulators.[128] The corresponding Peto OR was 2.9 (95% CI, 0.6 to 18.9). The other study reported no cancers.[129]

Combination of Infliximab and Immunomodulators Versus Immunomodulators

Two RCTs including 453 Crohn's disease patients compared a combination of infliximab and immunomodulators with immunomodulators alone and reported on cancer.[45,46] One induction trial of Crohn's disease patients naïve to TNF-alpha inhibitors and immunomodulators reported no cancers in the 179 patients taking infliximab and azathioprine and two cancers in the 161 patients taking azathioprine during the 50-week study period.[45] A 52-week induction trial of 113 steroid-dependent Crohn's disease patients with luminal disease reported no cancers during the study period, comparing combination infliximab and thiopurines with thiopurines alone.[46]

Other Combinations With Infliximab

Four retrospective trials including 1,069 Crohn's disease patients studied the safety profile of infliximab use at their centers.[137,145,147,164] The trials met the inclusion criteria but may have misclassified the cancer cases' concomitant medications. We described this in detail in the mortality section. The trials reported one cancer in patients receiving a triple combination of infliximab, immunomodulators, and corticosteroids, or a combination of infliximab and corticosteroids. One trial reported cancers in three of 51 patients (6 percent) taking infliximab

and an immunomodulator and one of 19 patients (5 percent) taking infliximab.[145] One study reported one cancer among 30 patients who used adalimumab after infliximab, compared with four cancers among 127 who did not subsequently use adalimumab.[145] The other three studies reported eight cancers in patients taking infliximab and an immunomodulator, one cancer in patients taking infliximab with corticosteroids, and five cancers in patients not receiving concomitant medications.[137,147,164]

Natalizumab Versus Placebo

Three RCTs including 1,414 Crohn's disease patients reported on cancer risk comparing natalizumab with placebo (reported in two publications).[32 33] A 12-week induction trial reported one basal cell carcinoma in the natalizumab group (1 out of 260) and no cancers in the 250 placebo patients.[32] A 12-week induction trial, followed by randomization of the responders to a 48-week maintenance trial, reported no cancers during the induction trial.[33] In the maintenance trial, one natalizumab patient (out of 214) and one placebo patient (out of 214) developed cancer.[33]

Combination of Natalizumab With Infliximab Versus Infliximab

One RCT including 79 Crohn's disease patients compared a combination of natalizumab and infliximab with infliximab alone and reported on cancer. The 20-week trial reported that no cancers occurred.[35]

TNF-Alpha Inhibitors Versus No Therapy

A claims-based study, that included 8,581 Crohn's disease patients, reported two solid tumor cancer cases among 92 person-years of exposure to TNF-alpha inhibitors (with or without immunomodulators or corticosteroids), compared with 2,115 cases among 15,673 person-years of no therapy.[168] The study reported an adjusted HR of 1.0 (95% CI, 0.7 to 1.3) for TNF-alpha inhibitors (with or without immunomodulators or corticosteroids) compared with no therapy, and an adjusted HR of 1.0 (95% CI, 0.8 to 1.3) for TNF-alpha inhibitors compared with no therapy (HRs adjusted for age, gender, geographic region, health plan, and comorbidity). An unadjusted rate ratio of 0.2 (95% CI, 0 to 0.6) favored TNF-alpha inhibitors (with or without immunomodulators or corticosteroids) over no therapy using the cancer cases and person-time provided.

TNF-Alpha Inhibitors Versus Never User of Biologic

A collection of referral centers reported 3 percent of adalimumab or infliximab patients and 3 percent of patients who never used biologics developed cancer over 104 weeks of followup.[150]

Combination of TNF-Alpha Inhibitors, Immunomodulators, and Corticosteroids Versus No Therapy

A claims-based study that included 8,581 Crohn's disease patients reported three cancer cases among 31 person-years of exposure to TNF-alpha inhibitors with immunomodulators and corticosteroids, compared with 2,115 cases among 15,673 person-years of no therapy.[168] The study reported an adjusted HR of 0.9 (95% CI, 0.3 to 2.4), comparing the 10 cancers per 100 person-years in the combination TNF-alpha inhibitor, immunomodulators, and corticosteroids group with 13 cancers per 100 person-years in the no therapy group. These estimates are consistent with an unadjusted rate ratio of 0.7 (95% CI, 0.1 to 2.1).

Combination of TNF-Alpha Inhibitors and Immunomodulators Versus No Therapy

The same claims-based study reported 20 cancer cases among 162 person-years of exposure to TNF-alpha inhibitor with immunomodulators (with or without corticosteroids), compared with 2,115 cases among 15,673 person-years of no therapy.[168] The study reported an adjusted HR of 1.1 (95% CI, 0.7 to 1.8). The corresponding unadjusted rate ratio was 0.9 (95% CI, 0.6 to 1.4).

Combination of TNF-Alpha Inhibitors and Corticosteroids Versus No Therapy

The same claims-based study reported 11 cancer cases among 142 person-years of exposure to TNF-alpha inhibitors with corticosteroids (with or without immunomodulators), compared with 2,115 cases among 15,673 person-years of no therapy.[168] The study reported an adjusted HR of 0.3 (95% CI, 0 to 2.3). The corresponding unadjusted rate ratio was 0.6 (95% CI, 0.3 to 1.0).

Immunomodulators

We summarized the risk of other cancers associated with use of immunomodulators for Crohn's disease in Table 45 (for RCTs) and Figure 16 (for observational studies). We also provided additional details regarding related studies.

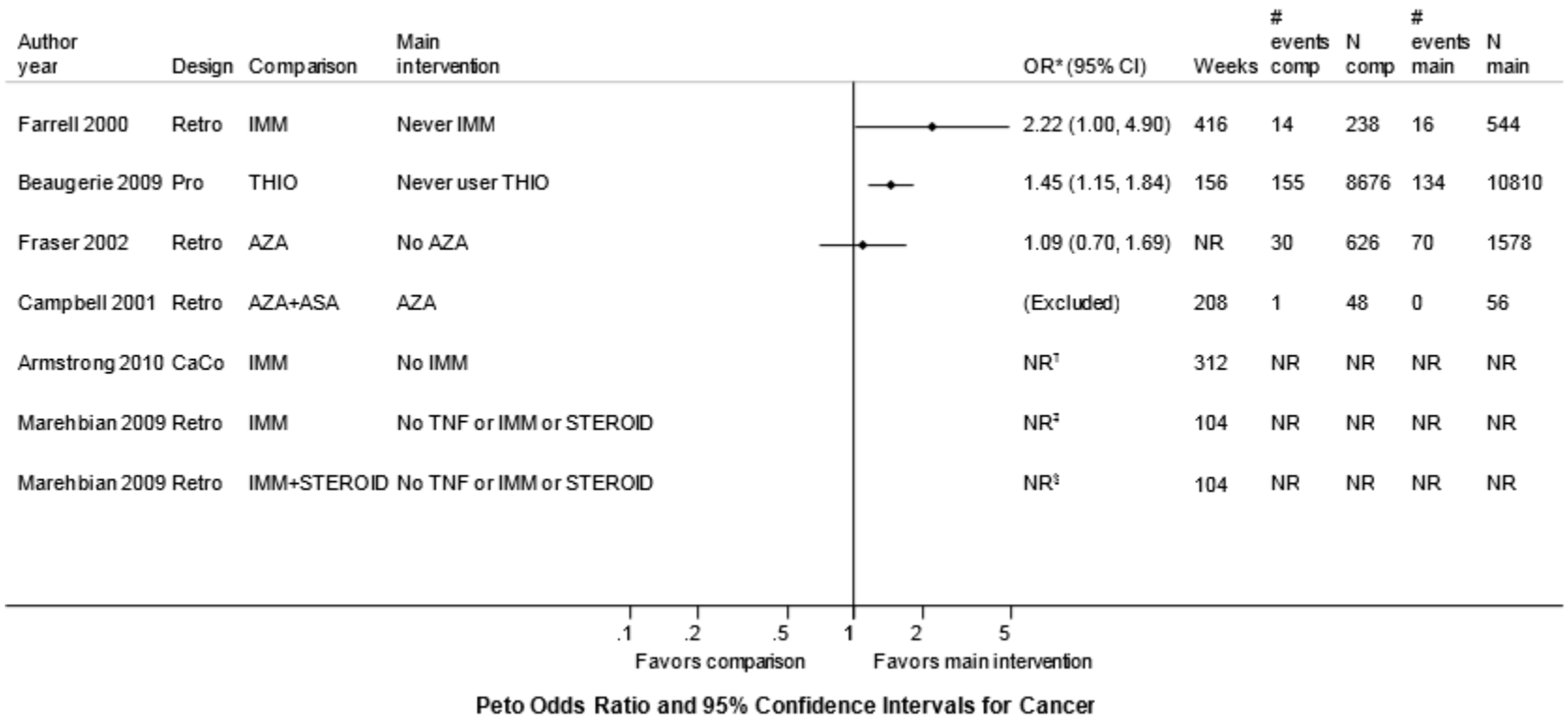
Table 45. Summary of the risk of other cancers in randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease*

Author, Year	Follow-up (Weeks)	IMM	Comparison	# of Cancer Cases in IMM Group	# of Patients in IMM Group	# of Cancer Cases in Comparison Group	# of Patients in Comparison Group
Summers, 1979[56]	104	Azathioprine	Placebo	0	113	0	178
Summers, 1979[56]	104	Azathioprine	Prednisone	0	113	1	146
Summers, 1979[56]	104	Azathioprine	Sulfasalazine	0	113	0	132

IMM = immunomodulator

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Figure 16. Summary of Peto odds ratios of cancer among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease



ASA = aminosalicylates; AZA = azathioprine; CaCo = case-control study; CI = confidence interval; Comp = comparison; IMM = immunomodulator; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitors

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

† Adjusted OR, 2.1 (95% CI, 1.3 to 3.3)

‡ Incidence rate ratio, 0.02 events per person-year (95% CI, 0.005 to 0.07)

§ Incidence rate ratio, 0 events per person-year (95% CI, 0 to 1.4)

Azathioprine Versus Placebo

One RCT including 291 Crohn's disease patients compared azathioprine with placebo and reported on cancer risk.[56] The trial did not report any cancers during the 2-year period.

Azathioprine Versus Prednisone

One 2-year RCT included 259 Crohn's disease patients in an azathioprine versus prednisone comparison and reported no cancers in 113 azathioprine and one cancer in 146 prednisone patients.[56]

Azathioprine Versus Sulfasalazine

The same 2-year RCT included 245 patients in an azathioprine versus sulfasalazine comparison and reported no cancers in either group.[56]

Combination Azathioprine and Aminosalicylates Versus Azathioprine

A retrospective chart review in 104 Crohn's disease patients compared a combination of azathioprine and aminosalicylates with azathioprine and reported on cancer risk.[146] The review required that all patients have at least 6 months of azathioprine use, no side effects to azathioprine, and be in remission to be eligible. The reviews reported one Waldenstrom's macroglobulinemia among 48 patients on a combination of azathioprine and aminosalicylates, compared with no cancers among 56 patients receiving azathioprine without aminosalicylates. The review also reported Waldenstrom's macroglobulinemia in its lymphoma section.

Immunomodulators Versus No Therapy

A claims-based study that included 8,581 Crohn's disease patients reported three cancer cases among 911 person-years of exposure to immunomodulators (with or without corticosteroids or TNF-alpha inhibitors), compared with 2,115 cases among 15,673 person-years of no therapy.[168] The study reported an adjusted HR of 1.2 (95% CI, 1.0 to 1.4). The corresponding unadjusted rate ratio is 0 (95% CI, 0 to 0.1). The study also reported an adjusted HR of 1.2 (95% CI, 1.0 to 1.4) comparing immunomodulators (with no corticosteroids and no TNF-alpha inhibitor) with no therapy.[168]

Combination of Immunomodulators and Corticosteroids Versus No Therapy

The same claims-based study reported no cancer cases among 19 person-years of exposure to immunomodulators with corticosteroids (with or without TNF-alpha inhibitors), compared with 2,115 cases among 15,673 person-years of no therapy.[168] The study reported an adjusted HR of 1.0 (95% CI, 0.7 to 1.4). The corresponding unadjusted rate ratio is not estimable because of the absence of events in the group receiving a combination of immunomodulators and corticosteroids.

Corticosteroids

Table 46 summarizes the risk of other cancers in RCTs and observational studies evaluating corticosteroids in patients with Crohn's disease.

Table 46. Summary of the risk of other cancers in randomized controlled trials and observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, Year	Followup (Weeks)	Study Design	Corticosteroid	Comparison	# of Cancer Cases in Steroid Group	# of Patients in Steroid Group	# of Cancer Cases in Comparison Group	# of Patients in Comparison Group	Unadjusted Relative Measure* (95% CI)	Adjusted Relative Measure (95% CI)
Summers, 1979[56]	104	RCT	Prednisone	Placebo	1	146	0	178	(Excluded)	NR
Summers, 1979[56]	104	RCT	Prednisone	Sulfasalazine	1	146	0	132	(Excluded)	NR
Marehbian, 2009[168]	104	Retrospective cohort	Steroid	No TNF or IMM or Steroid	NR†	NR	NR‡	NR	IRR, 0 (0 to 0.7)	HR, 1.1 (0.9 to 1.3)

CI = confidence interval; HR = hazards ratio; IMM = immunomodulator; IRR = incidence rate ratio; NR = not reported; RCT = randomized controlled trial; Steroid = corticosteroid; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate relative measures when there were fewer than five events total in the main intervention and comparison arms.

†There were 0 events during 379 person-years.

‡There were 2115 events during 15,673 person-years.

Prednisone Versus Placebo

One 2-year RCT, that included 324 Crohn's disease patients in a prednisone versus placebo comparison, reported one cancer in 146 patients on prednisone and no cancers in 178 patients taking placebo.[56]

Prednisone Versus Sulfasalazine

The same 2-year RCT that included 278 Crohn's disease patients in a prednisone versus sulfasalzine comparison reported one cancer in 146 patients on prednisone and no cancers in 132 patients taking sulfasalazine.[56]

Corticosteroids Versus No Therapy

A claims-based study, that included 8,581 Crohn's disease patients, reported no cancer cases among 379 person-years of exposure to corticosteroids (with or without immunomodulators or TNF-alpha inhibitors), compared with 2,115 cases among 15,673 person-years of no therapy.[168] The study reported an adjusted HR of 1.1 (95% CI, 0.9 to 1.3). The corresponding unadjusted rate ratio is not estimable because of a lack of events in the corticosteroids group. The study also reported a HR comparing corticosteroids (with no immunomodulators and no TNF-alpha inhibitors) with no therapy (adjusted HR, 1.0; 95% CI, 0.8 to 1.3).[168]

Aminosalicylates

Table 47 summarizes the risk of other cancers in the one RCT reporting on cancer risk associated with use of aminosalicylates in patients with Crohn's disease.

Table 47. Summary of the risk of other cancers in a randomized controlled trial comparing an aminosalicylate with placebo in patients with Crohn's disease

Author, Year	Followup (Weeks)	ASA	Comparison	# of Cancer Cases in ASA Group	# of Patients in ASA Group	# of Cancer Cases in Comparison Group	# of Patients in Comparison Group
Summers, 1979[56]	104	Sulfasalazine	Placebo	0	132	0	178

ASA = aminosalicylates

Sulfasalazine Versus Placebo

A 2-year RCT including 310 Crohn's disease patients reported no cancers in the sulfasalazine and placebo groups.[56]

Studies Evaluating Patients With IBD

Seven studies reported other cancers in IBD patients without separating Crohn's disease from ulcerative colitis or indeterminate colitis patients. We provided information about these studies in Appendix F.

Studies Reporting Results for Crohn's Disease and IBD

The retrospective chart review that reported a Waldenstrom's macroglobulinemia in a Crohn's disease patient reported no additional cancers among the 82 ulcerative colitis patients who received azathioprine with or without aminosalicylates.[146]

Case-Control Studies Designed To Examine Specific Cancers

Four case-control studies including 3,554 patients examined specific cancers. Two studies included only Crohn's disease patients.[143,170] Two studies conducted nested-case control studies using a claims databases.[170,171] A study of small bowel cancer risk included only patients with small bowel Crohn's disease.[143] A study of colon cancer risk included only patients with colonic IBD.[172]

Comparisons Including TNF-Alpha Inhibitor

A claims database study of TNF-alpha inhibitors and immunomodulators included 1,935 Crohn's disease patients and followed them for a median of 484 days. The study reported on the relationship between the risk of non-melanoma skin cancer and either recent medication use (a pharmacy claim within 90 days of diagnosis) or persistence use (recent medication use plus a pharmacy claim greater than 365 days prior to diagnosis).[170] The TNF-alpha inhibitors included infliximab and adalimumab. The immunomodulators included thiopurines, methotrexate, calcineurin inhibitor, and mycophenolate mofetil. Sixty-five percent of non-melanoma skin cancer cases and 86 percent of controls did not have a TNF-alpha inhibitor or immunomodulator claim within 90 days of the index date. Six percent of 387 cases and 1 percent of 1,548 controls were recent users of both TNF-alpha inhibitors and immunomodulators (Medicaid insurance adjusted OR compared with no use of TNF-alpha inhibitors or immunomodulators, 5.9; 95% CI, 3.2 to 10.8). Five percent of 228 cases and 1 percent of 913 controls had persistent use of a TNF-alpha inhibitor and immunomodulator (Medicaid insurance adjusted OR, 6.8; 95% CI, 2.7 to 16.7). Comparing TNF-alpha inhibitor use with no TNF-alpha inhibitor and no immunomodulator use, 4 percent of 387 cases and 2 percent of 1,548 controls were recent users of a TNF-alpha inhibitor (Medicaid insurance adjusted OR, 2.5; 95% CI, 1.3 to 4.7) and 3 percent of 228 cases and 1 percent of 913 controls were persistent users of a TNF-alpha inhibitor (Medicaid insurance adjusted OR, 3.2; 95% CI, 1.2 to 8.5). Comparing TNF-alpha inhibitor use versus no use, cases were more likely to be recent (immunomodulators and Medicaid insurance adjusted OR, 2.1; 95% CI, 1.3 to 3.3) and persistent (immunomodulators and Medicaid insurance adjusted OR, 2.2; 95% CI, 1.1 to 4.5) users of TNF-alpha inhibitor.

Comparisons Including Immunomodulators

Four case-control studies including 3,554 patients compared an immunomodulator with other medications.[143,170-172] One of these was the claims database study that included 1,935 Crohn's disease patients. This study evaluated the relationship between thiopurine use and non-melanoma skin cancer risk.[170] Cases were more likely to be recent (OR adjusted for Medicaid insurance and use of other immunomodulators and TNF-alpha inhibitors, 3.8; 95% CI, 2.9 to 5.2) and persistent (OR adjusted for Medicaid insurance and other immunomodulators and TNF-alpha inhibitors, 4.3; 95% CI, 2.8 to 6.4) users of thiopurines, compared with controls. This study also compared methotrexate with no methotrexate use. Cases were more likely to be recent (OR adjusted for Medicaid insurance and other immunomodulators and TNF-alpha inhibitors, 1.6; 95% CI, 0.6 to 4.3) and persistent (OR adjusted for Medicaid insurance and other immunomodulators and TNF-alpha inhibitors, 2.7; 95% CI, 0.6 to 11.6) users of methotrexate compared with controls, although these associations were not statistically significant.

A case-control study of 35 Crohn's disease patients compared seven small bowel adenocarcinoma cases with controls matched on age, sex, and small bowel Crohn's disease.[143] The medical charts for two of seven (29 percent) cases showed at least 6 months of 6-

mercaptopurine use, compared with one of 28 controls (4 percent; OR, 10.8; 95% CI, 1.1 to 108.7).

A case-control study of 48 patients with colonic IBD compared thiopurines use with non-use.[172] One of 18 colorectal cancer cases and four of 30 controls had thiopurine use in their paper or electronic medical record. The corresponding Peto OR is 0.4 (95% CI, 0 to 4.4). None of the patients in the study had a record of TNF-alpha inhibitor and methotrexate use.

A case-control study using International Classification of Diseases, Ninth Revision, Clinical Modification claim codes, and outpatient pharmacy claims identified 364 colorectal cancer cases and 1,172 controls without a record of colorectal cancer or bowel surgery.[171] In the 12 months prior to or on the date of the colorectal cancer diagnosis, 41 of 364 cases (11 percent) and 101 of 1,172 controls (9 percent) had a pharmacy claim for immunomodulators. The study reported a crude OR of 1.4 (95% CI, 0.9 to 2.0), comparing immunomodulator use with no immunomodulator use.

Comparisons Including Corticosteroids

Three case-control studies including 1,619 patients compared corticosteroid with other medications.[143,171,172] A case-control study of 35 Crohn's disease patients compared prednisone with no prednisone.[143] Five of seven cases (71 percent) had a record of prednisone use for at least 6 months prior to small bowel adenocarcinoma diagnosis, compared with 17 of 28 controls (61 percent). The corresponding Peto OR was 1.6 (95% CI, 0.2 to 19.6). The case-control study of 48 IBD patients reported that 15 of 18 colorectal cancer cases (83 percent) and 25 of 30 controls (83 percent) had a record of corticosteroids use.[172] The corresponding Peto OR was 1.0 (95% CI, 0.2 to 7.4). A claims-based study of colorectal cancer in IBD reported 28 percent of 364 colorectal cancer cases, and 21 percent of 1,172 controls had a pharmacy claim for corticosteroids in the 12 months prior to or on the date of the colorectal cancer diagnosis.[171] The study reported a crude OR of 1.4 (95% CI, 1.1 to 1.9).

Comparisons Including Aminosalicylates

Three case-control studies including 1,619 patients reported a comparison of outcomes related to aminosalicylate use.[143,171,172] A case-control study of 35 Crohn's disease patients reported four of seven cases (57 percent) had a record of sulfasalazine use for at least 6 months prior to small bowel adenocarcinoma diagnosis, compared with 19 of 28 controls (68 percent).[143] The corresponding Peto OR was 0.6 (95% CI, 0.1 to 5.3). A case-control study of 48 IBD patients reported 15 of 18 colorectal cancer cases (83 percent), and 29 of 30 controls (97 percent) had a record of mesalamine use.[172] The corresponding Peto OR was 0.2 (95% CI, 0 to 2.4).

A claims-based case-control study of colorectal cancer in IBD reported 43 percent of 364 colorectal cancer cases, and 44 percent of 1,172 controls had a pharmacy claim for aminosalicylates in the 12 months prior to or on the date of the colorectal cancer diagnosis (crude OR, 1.0; 95% CI, 0.8 to 1.2).[171] The comparison of aminosalicylates with colorectal cancer risk was the primary aim of the study. They also reported relationships with colorectal cancer risk for the different aminosalicylate formulations (mesalamine OR, 0.9; 95% CI, 0.7 to 1.2; sulfasalazine OR, 1.2; 95% CI, 0.8 to 1.7; and balsalazide OR, 1.3; 95% CI, 0.7 to 2.4). When they performed a test for trend to examine a relationship between number of aminosalicylate prescription claims in the 12 months prior to diagnosis and odds of colorectal cancer, they observed a p-value for trend of borderline statistical significance for any aminosalicylate (P=0.11) and mesalamine (P=0.08) but not sulfasalazine (P=0.27). They did not report a test of

trend p-value for balsalazide.

Studies Reporting for Crohn's Disease and IBD

A claims-based study of non-melanoma skin cancer reported results for all IBD patients, and also reported results exclusively for Crohn's disease patients.[170] The results for thiopurine use versus no thiopurine use in IBD patients were similar in direction for the Crohn's disease patients, (IBD OR, 3.1; 95% CI, 2.1 to 4.5; Crohn's disease OR, 3.9; 95% CI, 2.9 to 5.2), when adjusted for other classes of medications and Medicaid insurance status. The authors stated that because infliximab was approved for ulcerative colitis after the study period ended in June 2005, they did not calculate TNF-alpha inhibitor and combination TNF-alpha inhibitor and immunomodulators versus no immunomodulators ORs for all IBD patients. They also stated that they did not report the methotrexate relationship, because methotrexate use is not indicated for the treatment of ulcerative colitis in the U.S.[170]

Infections

Immune suppression caused by medications to treat Crohn's disease or the disease itself might increase the risk of infection. These infections can range from relatively mild to life threatening. Because serious infections, that may be life threatening or associated with hospitalization, have different implications for clinical care and patient quality of life, we have indicated when studies reported serious infections compared with any infection, regardless of severity. We have also indicated when the study considered an infection opportunistic.

Sixty-one studies including 42,008 patients reported on infections (Appendix D, Evidence Table 14). Thirty-eight RCTs including 8,435 patients reported infections as an outcome by comparison of interest. Four prospective studies (n=7,253), 17 retrospective studies (n=23,782), and two case-control studies (n=2,538) reported infections by a comparison of interest. Infections were a primary outcome of interest in 17 studies.

Natalizumab

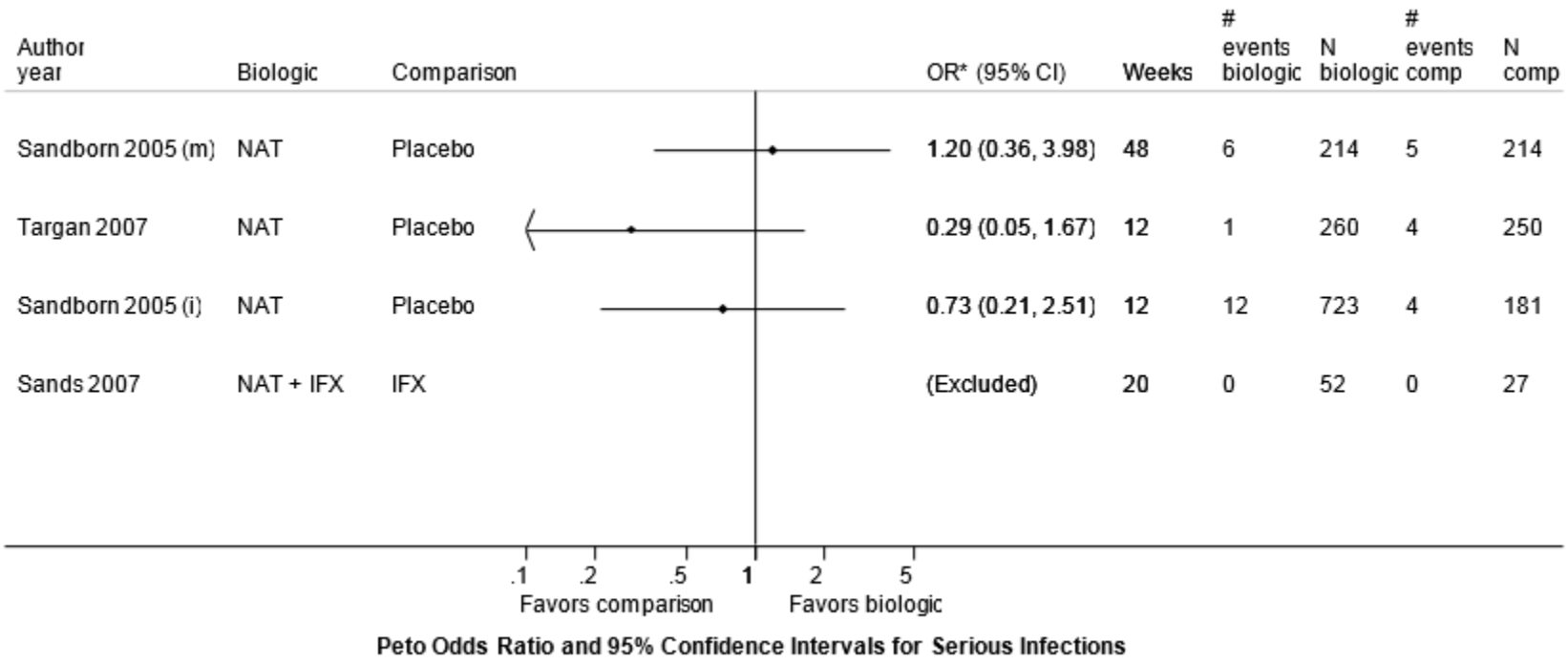
In Figures 17 and 18 we summarize the serious infections and any infections reported by RCTs evaluating natalizumab. In Table 48 we listed the RCTs evaluating natalizumab that reported no opportunistic infections. We also provided additional details regarding related studies.

Table 48. Summary of the randomized controlled trials reporting no opportunistic infections when comparing the effectiveness of a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease

Biologic	Comparison	# of Trials Reporting No Events	Range of Followup (Weeks)	# Participants in Biologic Group	# Participants in Comparison Group
Natalizumab	Placebo	1[32]	8	260	250
Natalizumab + infliximab	Infliximab	1[35]	NR	52	27

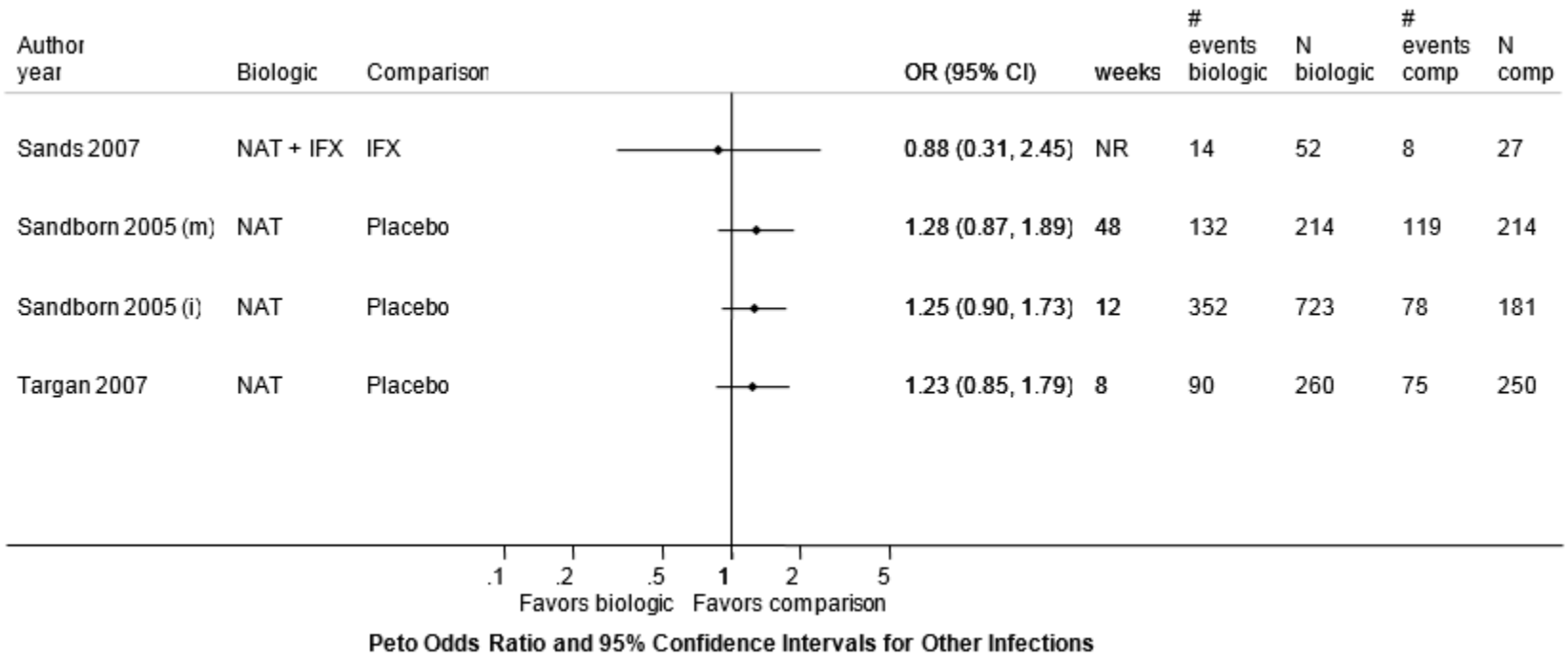
NR = not reported

Figure 17. Summary of Peto odds ratios of serious infections among randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease



CI = confidence interval; Comp = comparison; i = induction trial; IFX = infliximab; m = maintenance trial; Main = main intervention; NAT = natalizumab; OR = odds ratio
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Figure 18. Summary of Peto odds ratios of other infections among randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease



CI = confidence interval; Comp = comparison; i = induction trial; IFX = infliximab; m = maintenance trial; Main = main intervention; NAT = natalizumab; NR = not reported; OR = odds ratio

Natalizumab Versus Placebo

Three natalizumab versus placebo RCTs including 1,414 Crohn's disease patients reported on infections in two publications.[32,33]

Serious Infections

All three trials reported on serious infections.[32,33] Serious infections were rare with natalizumab patients (less than 1 to 3 percent) and placebo patients (2 percent).

Opportunistic Infections

One RCT including 510 patients reported no opportunistic infections (including PML) during the study period.[32]

Any Infection

Three trials including 1,414 patients reported on any infection.[32,33]
Infections (including serious) were more common in natalizumab patients (35 to 62 percent) than placebo patients (30 to 56 percent).

Combination of Natalizumab and Infliximab Versus Infliximab

One RCT including 79 Crohn's disease patients reported on infections comparing a combination of natalizumab and infliximab with infliximab alone in initial non-responders to infliximab.[35]

Serious Infections

There were no trials that reported serious infections during the study period.[35]

Opportunistic Infections

There were no trials that reported opportunistic infections during the study period.[35]

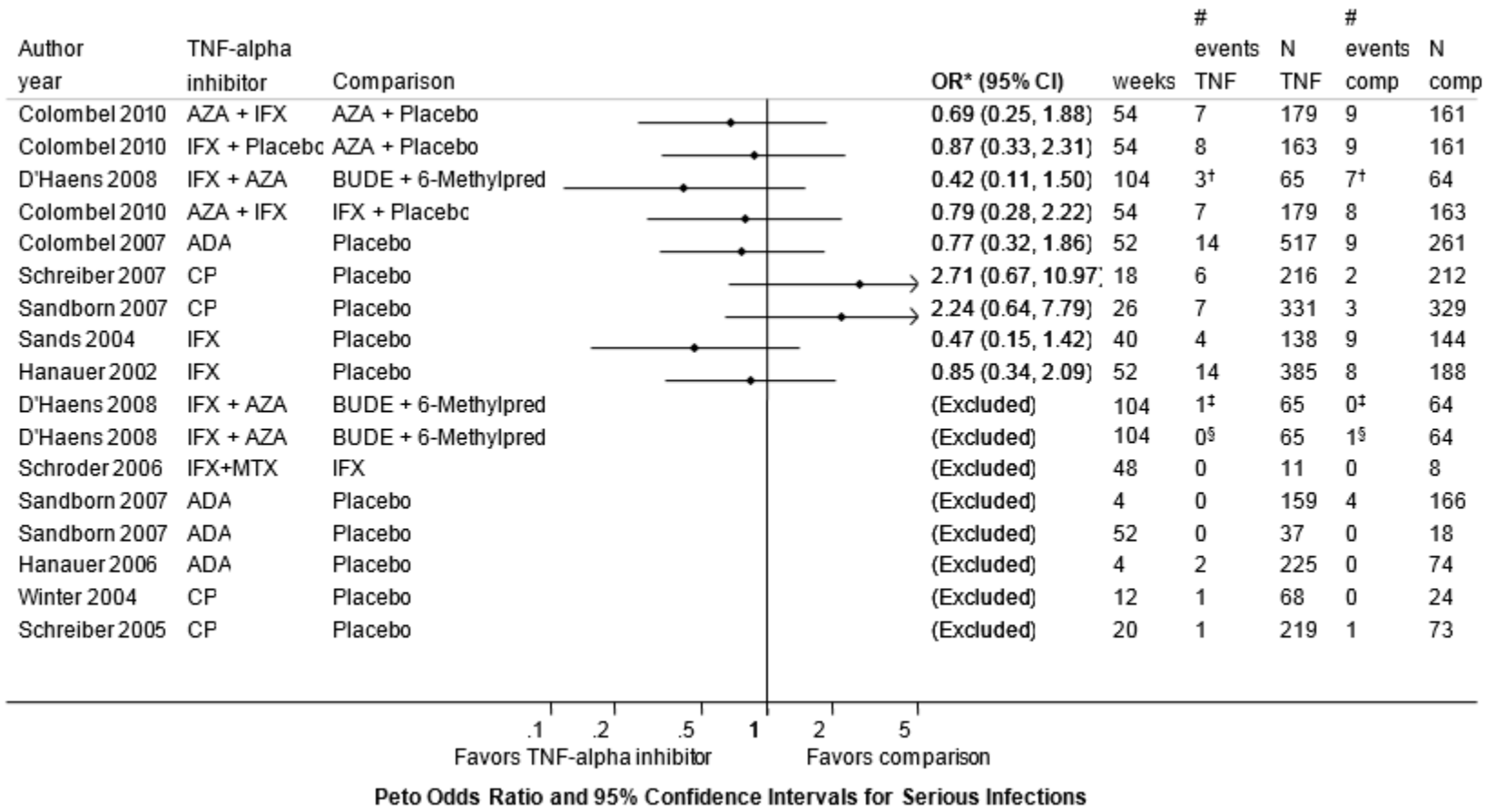
Any Infection

One trial reported infections in 14 out of 52 patients taking natalizumab and infliximab (27 percent) and eight out of 27 patients taking infliximab (30 percent).[35]

TNF-Alpha Inhibitors

We did not conduct a meta-analysis of the RCTs comparing TNF-alpha inhibitors with placebo in terms of serious infections, because four out of the five trials had fewer than five events. Figures 19 and 20 summarize the RCTs and observational studies evaluating TNF-alpha inhibitors in terms of serious infections. Figure 21 summarizes the opportunistic infections reported in RCTs evaluating TNF-alpha inhibitors. Figure 22 and Table 49 summarize any infections reported in RCTs and observational studies evaluating TNF-alpha inhibitors. We also provided additional details regarding related studies.

Figure 19. Summary of Peto odds ratios of serious infections among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease



6-Methylpred = 6-methylprednisolone; ADA = adalimumab; AZA = azathioprine; BUDE = budesonide; CI = confidence interval; Comp = comparison; CP = certolizumab pegol; IFX = infliximab; MTX = methotrexate; OR = odds ratio; TNF = tumor necrosis factor-alpha inhibitor

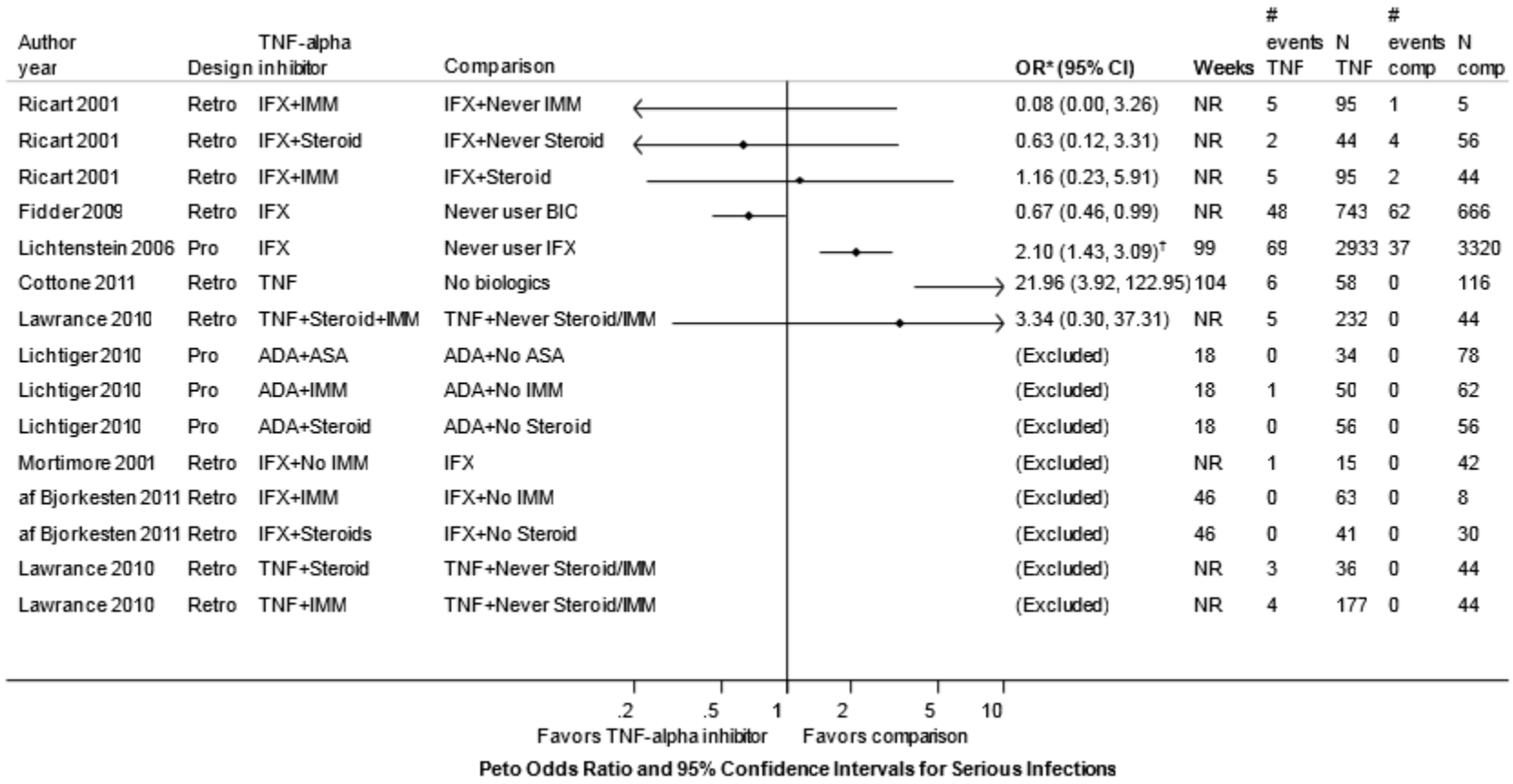
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

†The number of events is for serious cases of perianal abscess or fistula.

‡The number of events is for serious cases of pneumonia.

§The number of events is for serious cases of hepatitis C.

Figure 20. Summary of Peto odds ratios of serious infections among observational studies comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease

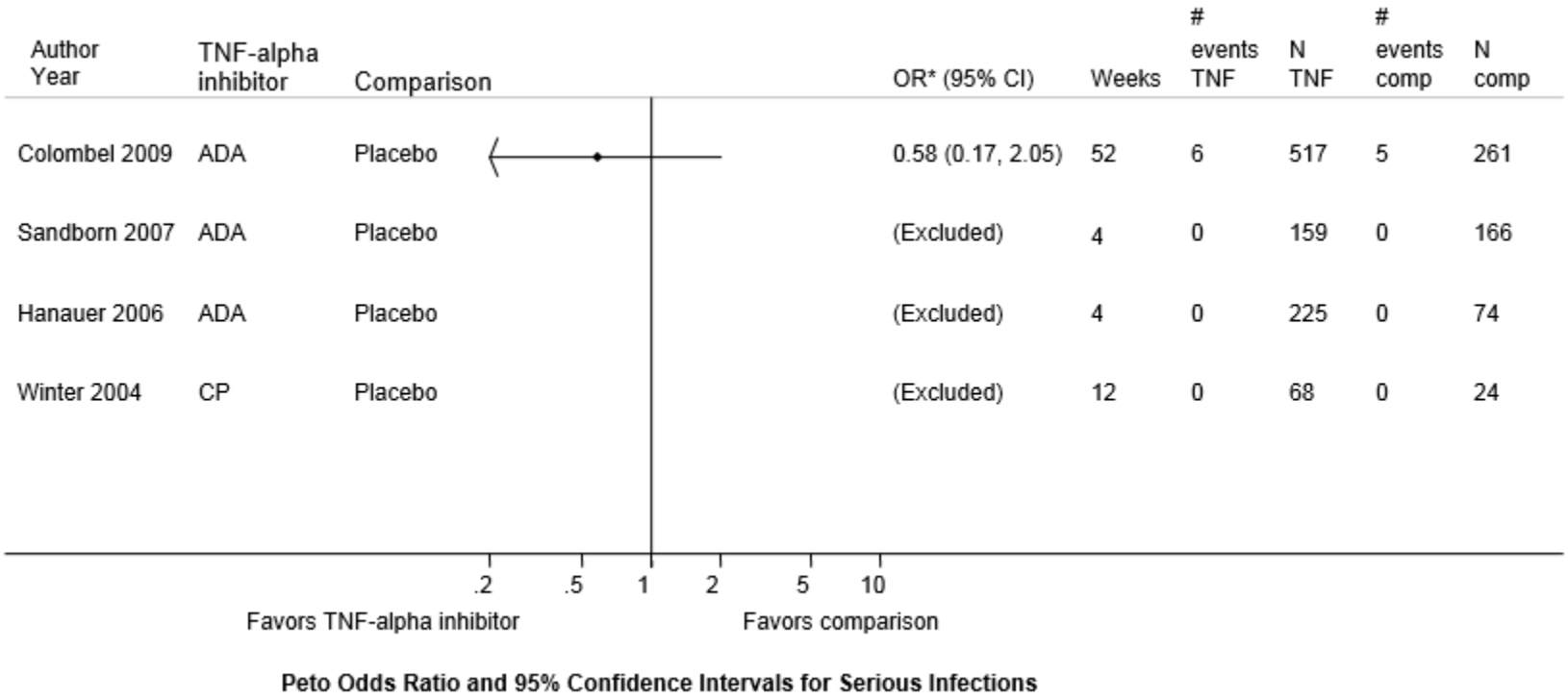


ADA = adalimumab; ASA = aminosalicylates; BIO = biologics; CI = confidence interval; Comp = comparison; IFX = infliximab; IMM = immunomodulator; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroids; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

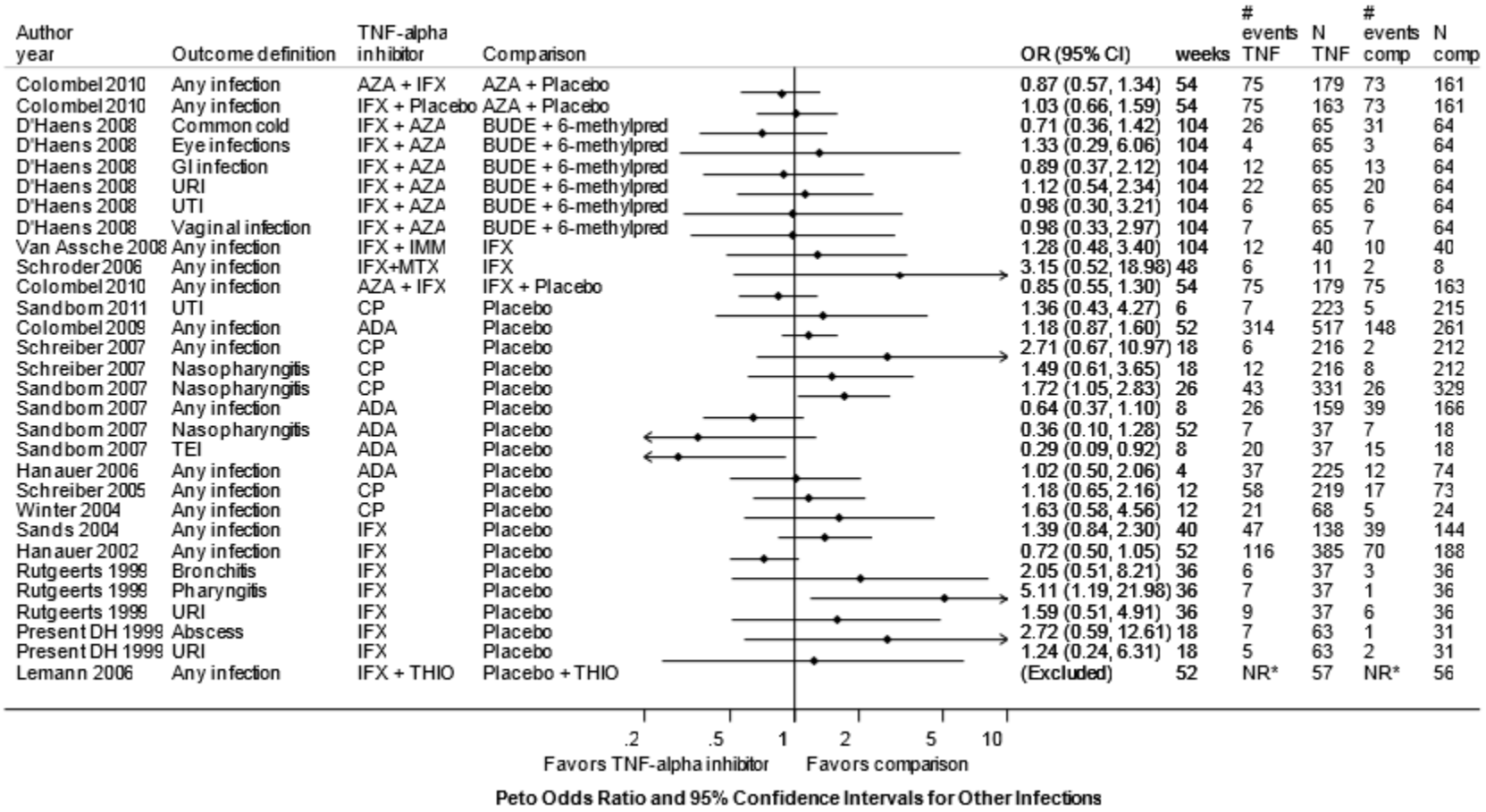
†Adjusted relative risk, 2.2 (95% CI, 1.4 to 3.2)

Figure 21. Summary of Peto odds ratios of opportunistic infections among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease



ADA = adalimumab; CI = confidence interval; Comp = comparison; CP = certolizumab pegol; OR = odds ratio; TNF = tumor necrosis factor-alpha inhibitor
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Figure 22. Summary of Peto odds ratios of other infections among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease



6-methylpred = 6-methylprednisolone; ADA = adalimumab; AZA = azathioprine; BUDE = budesonide; CI = confidence interval; Comp = comparison; CP = certolizumab pegol; GI = gastrointestinal; IFX = infliximab; IMM = immunomodulator; MTX = methotrexate; NR = not reported; OR = odds ratio; TEI = treatment-emergent infections; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor; URI = upper respiratory infection; UTI = urinary tract infection
*There were 18 events in the combination infliximab and thiopurine arm and 16 events in the thiopurine arm.

Table 49. Summary of other infections reported in observational studies comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, Year	Followup (Weeks)	TNF-Alpha Inhibitor	Comparison	# of Other Infections in TNF Group	# of Patients in TNF Group	# of Other Infections in Comp Group	# of Patients in Comp Group
Seiderer, 2004[173]	NR	Infliximab + thiopurine	Infliximab + no thiopurine	4	82	0	18
Seiderer, 2004[173]	NR	Infliximab + corticosteroids	Infliximab + no corticosteroids	0	42	3	58

Comp = comparison; NR = not reported; TNF = tumor necrosis factor-alpha inhibitor

Adalimumab Versus Placebo

Four RCT's appearing in five publications included 1,457 Crohn's disease patients and compared infections with adalimumab or placebo.[37,38,82,83,95]

Serious Infections

Four RCTs including 1,457 patients reported on serious infection. Serious infections were rare in adalimumab patients (0 to 4 percent) and placebo patients (0 to 5 percent).[37,38,82,83]

One of these trials allowed patients to switch medications after 12 weeks and reported on infections separately for patients who maintained randomized therapy and unblinded patients. A maintenance trial of those who achieved remission in a previous trial[37] reported no infections in 37 adalimumab patients and 18 placebo patients who stayed on their randomized treatment for the duration of the 52-week period.[83] Nine of 221 patients (4 percent) who elected to switch to adalimumab from placebo, increase the adalimumab dose, or discontinue at week 4, experienced a serious infection. A 52-week maintenance trial reported 3 percent of adalimumab and placebo patients experienced serious infections during the study period.[82] Another publication of the same trial reported serious infections in 4 percent of adalimumab patients and 5 percent of placebo patients.[95] The corresponding Peto OR was 0.8 (95% CI, 0.3 to 1.9). During the adalimumab induction period prior to randomization, serious infections occurred in 1 percent of 854 patients.[82]

Opportunistic Infections

Three RCTs including 1,402 patients reported on opportunistic infections.[37,38,82] The two induction trials reported that no opportunistic infections occurred.[37,38] A 52-week maintenance trial reported six (1 percent) opportunistic infections in the adalimumab patients compared with five (2 percent) opportunistic infections in the placebo group.[82] The corresponding Peto OR was 0.6 (95% CI, 0.2 to 2.1).

Any Infection

Three RCTs including 679 patients reported on any infections.[37,38,83] Infections were common in adalimumab patients (16 to 57 percent) and placebo patients (16 to 83 percent).

Other Combinations With Adalimumab

A prospective study of 112 patients who used adalimumab combined with aminosalicylates, corticosteroids, or immunomodulators reported one serious infection in a patient who used concomitant immunomodulators.[161]

Certolizumab Pegol Versus Placebo

Five RCTs including 1,910 Crohn's disease patients compared certolizumab pegol with placebo and reported on infections.[39-42,84]

Serious Infections

Four RCTs including 1,472 patients reported on serious infections.[39-41,84] Serious infections were rare (1 to 3 percent of certolizumab pegol patients and 0 to 1 percent of placebo patients). Two trials, that excluded patients with abscesses related to Crohn's disease, reported gastrointestinal and perianal abscesses as serious infections.[40,41]

Opportunistic Infections

Two RCTs including 384 patients reported on opportunistic infections.[40,41] One 12-week induction trial did not report any opportunistic infections.[41] Another reported "no increase" in opportunistic infections but did not specify the infections considered.[40]

Any Infection

Five RCTs including 1,910 patients reported on any infections.[39-42,84] Infections were common in certolizumab pegol patients (3 to 31 percent) and placebo patients (2 to 23 percent).[40-42]

An induction trial, followed by maintenance trial, reported on specific infections. Both trials reported on nasopharyngitis. The induction trial reported 13 percent of certolizumab pegol patients and 8 percent of placebo patients had nasopharyngitis (Peto OR, 1.7; 95% CI, 1.0 to 2.8).[39] The maintenance trial may have randomized some of these patients; it reported that 12 of 216 certolizumab pegol patients (6 percent) and eight of 212 placebo patients (4 percent) had nasopharyngitis (Peto OR, 1.5; 95% CI, 0.6 to 3.7).[84]

Infliximab Versus Placebo

Five RCTs including 1,130 Crohn's disease patients compared infliximab with placebo and reported on infections.[43,44,85-87]

Serious Infections

Three RCTS including 963 patients reported on serious infections.[43,86,87] Serious infections were uncommon in the maintenance trials (3 to 4 percent of infliximab and 4 to 6 percent of placebo patients).[86,87] A 12-week trial of a single infusion reported one case of salmonella colitis requiring hospitalization among 83 infliximab patients and one case of abdominal abscess requiring hospitalization among 25 placebo patients.[43]

Opportunistic Infections

No study reported on opportunistic infections.

Any Infection

Four RCTs including 1,022 patients reported on any infections.[44,85-87] Infections requiring antimicrobial treatment (including serious in infections) were common in the maintenance trials (30 to 34 percent of infliximab patients and 27 to 37 percent of placebo patients).[86,87]

The other trials reported specific infections in at least 10 percent of patients. An 18-week induction trial including a single infusion reported adverse events occurring in at least 10 percent of the population (63 infliximab patients and 31 placebo patients with fistulizing disease).[44]

Infectious adverse events included gastrointestinal abscess (seven infliximab patients versus one placebo patient; Peto OR, 2.7; 95% CI, 0.6 to 12.6), and upper respiratory infection (five infliximab patients vs. two placebo patients; Peto OR, 1.6; 95% CI, 0.5 to 8.2).[44] A 36-week retreatment trial subsequent to another trial[43] reported adverse events occurring in at least 10 percent of any group including 37 infliximab patients and 36 placebo patients.[85] Infectious adverse events included bronchitis (six infliximab patients vs. three placebo patients; Peto OR, 2.1; 95% CI, 0.5 to 8.2); pharyngitis (seven infliximab patients vs. one placebo patient; Peto OR, 5.1; 95% CI, 1.2 to 22.0); and upper respiratory infection, which may or may not have included bronchitis and pharyngitis (nine infliximab patients vs. six placebo patients; Peto OR, 1.6; 95% CI, 0.5 to 8.2).[85]

Infliximab Versus Azathioprine

One RCT including 324 Crohn's disease patients compared infliximab with azathioprine and reported on infections.[45]

Serious Infections

The same RCT reported eight serious infections in 163 infliximab patients (5 percent) compared with nine serious infections in 161 azathioprine patients (6 percent).[45] The corresponding Peto OR was 0.9 (95% CI, 0.3 to 2.3).

Opportunistic Infections

This trial did not report on opportunistic infections.[45]

Any Infection

This RCT reported a serious or non-serious infection in 46 percent of infliximab patients and 45 percent of azathioprine patients. The corresponding Peto OR was 1.0 (95% CI, 0.7 to 1.6).[45]

Combination of Infliximab and Corticosteroids Versus Infliximab

One retrospective study of 71 patients reported no serious infections.[163] The study did not report on opportunistic infections or other infections.

Combination of Infliximab and Immunomodulators Versus Infliximab

Three RCTs including 607 Crohn's disease patients compared a combination of infliximab and immunomodulators with infliximab and reported on infections.[45,47,89] Two observational studies including 128 Crohn's disease patients compared a combination of infliximab and immunomodulators with infliximab and reported on infections.[163,174]

Serious Infections

Two RCTs including 527 patients reported on serious infections.[45,47] The trials reported serious infections in less than 5 percent of patients in any study arm.

Two observational studies including 128 Crohn's disease patients reported on serious infections. A study of the early experience with infliximab at several centers reported one case of pneumocystis carinii pneumonia among 42 patients on infliximab and immunomodulator (thiopurines, methotrexate, or mycophenolate mofetil), and one episode of sepsis among 15 users of infliximab without an immunomodulator.[174] The other study reported no serious infections in either the infliximab combined with immunomodulators group, or the infliximab group that never used immunomodulators.[163]

Opportunistic Infections

None of the RCTs reported on opportunistic infections.

Any Infection

All three RCTs including 607 patients reported and included serious and non-serious infections.[45,47,89] Infections were common in patients who used infliximab combined with an immunomodulator (30 to 55 percent) and infliximab alone (25 to 46 percent).

Other Combinations With Infliximab

Five retrospective studies including 1,267 Crohn's disease patients met the inclusion criteria but the studies might have misclassified the concomitant medications (as described in the mortality section). Four studies evaluated the safety profile of infliximab use at their centers,[137,145,164,175] and one study focused specifically on the role of concomitant immunomodulators on outcomes.[147]

Serious Infections

Four studies including 1,152 patients reported on serious infections in five manuscripts.[137,138 145,164,175] The four retrospective studies reported serious infections in patients who received (at baseline) either a triple combination of infliximab, immunomodulators, and corticosteroids; a combination of infliximab and immunomodulators; a combination of infliximab and corticosteroids; or infliximab alone. The studies reported serious infections in 0 to 7 percent of patients receiving the combination of infliximab, immunomodulator, and corticosteroid; 3 to 18 percent of patients receiving infliximab and an immunomodulator; 0 to 9 percent of patients receiving infliximab and corticosteroids; and 0 to 16 percent of patients receiving only infliximab. A previous report on 500 patients from one center reported on outcomes for the first 100 patients using infliximab.[138] The report included six "significant" infections in five of the six patients using concomitant immunomodulators (with or without corticosteroids) and two of the six patients using concomitant corticosteroids (with or without immunomodulators).[138] The study of 157 patients also reported on 30 patients who received adalimumab after infliximab.[145] Of the 30 adalimumab patients, two experienced sepsis-related complications.

Opportunistic Infections

Two studies including 657 patients reported on opportunistic infections.[137,145] One study (157 patients) reported no opportunistic infections.[145] The other study (500 patients) considered three non-serious varicella-zoster infections "probably" opportunistic.[137] The study treated two of these patients with a combination of infliximab, azathioprine, and corticosteroids and treated the other with a combination of infliximab and azathioprine.

Any Infection

Four studies including 970 patients reported on any infection in five manuscripts.[137,138,145,147,175] The two retrospective studies included 157 and 500 Crohn's disease patients and reported infections (respectively) in 16 and 3 percent of patients receiving the combination of infliximab, immunomodulator, and corticosteroid; 33 and 9 percent of patients receiving infliximab and an immunomodulator; 6 and 13 percent of patients receiving infliximab and corticosteroids; and 26 and 14 percent of patients receiving only infliximab.[137,145] The reported infections included serious infections. A previous study on 500 patients from the center reported on the infliximab outcomes among the first 100 patients and did not report other

infections.[138] The study of 157 patients also reported on 30 patients who received adalimumab after infliximab.[145] Of the 30 adalimumab patients, seven patients (23 percent) had an infection.

A retrospective study with a mean followup of 29 months reported one pneumonia in 127 patients receiving infliximab and an immunomodulator, compared with no infections in 71 patients receiving infliximab without concomitant immunomodulators (this came from a database that included most of the patients treated with infliximab at the center).[175] A followup study, with a median followup of 9 years, reported two "atypical" infections in 53 patients receiving infliximab with no concomitant thiopurine use, compared with no infections among those with concomitant thiopurine use.[147] The infections reported were necrotizing pneumonia and methicillin-resistant Staphylococcus aureus skin abscess.

Combination of Infliximab and Immunomodulators Versus Immunomodulators

Two RCTs including 340 Crohn's disease patients compared the combination of infliximab and immunomodulators with immunomodulators alone and reported on infections.[45 46]

Serious Infections

The two studies reported serious infections in less than 5 percent of patients in any study arm.[45 46]

Opportunistic Infections

Neither of the RCTs reported on opportunistic infections.

Any Infection

Infections were common in all study arms (32 to 42 percent of infliximab combined with thiopurines patients and 29 to 45 percent of thiopurines patients).[45,46]

Combination of Infliximab and Immunomodulators Versus Corticosteroids

A 104-week open-label trial including 129 Crohn's disease patients compared a combination of infliximab and immunomodulators with corticosteroids and reported on infections.[48]

Serious Infections

Six percent of the combination of infliximab and azathioprine or methotrexate patients had a serious infection, compared with 13 percent of patients on prednisone or budesonide.[48]

Opportunistic Infections

This RCT did not report on opportunistic infections.

Any Infection

The trial reported 77 infectious events in 65 patients on infliximab and azathioprine or methotrexate, compared with 80 infectious events in 64 patients on prednisone or budesonide.[48]

TNF-Alpha Inhibitor Versus No TNF-Alpha Inhibitor

One prospective study and two retrospective observational studies including 15,045 Crohn's disease patients reported on infections comparing patients who had used a TNF-alpha inhibitor with those who had not used a TNF-alpha inhibitor or never used a biologic.[131,150,168]

Serious Infections

Two observational studies including 6,464 patients reported on serious infections.[131,150] An observational study (with 2 mean years of followup) reported serious infections (undefined) in 2 percent of 3,179 infliximab users, compared with 1 percent of non-users during the study period. The study reported an OR of 1.0 (95% CI, 0.6 to 1.5) when comparing infliximab with no infliximab (excluding infliximab used in the 6-month period during which the infection occurred); this is after adjusting for age, sex, race, disease location, severity of Crohn's disease, duration of followup and possibly other medication use. The relative rate comparing number of infections by person-years of exposure (unadjusted for potential confounders) was 2.2 (95% CI, 1.4 to 3.2). A 104-week prospective study reported 10 serious infections requiring hospitalization among patients who used adalimumab or infliximab, and no serious infections among those who never used a biologic.[150]

Opportunistic Infections

A claims-based study that included 8,581 Crohn's disease patients reported on opportunistic infections, candidiasis, and tuberculosis together.[168] The study reported 11 of these infections in 292 infliximab person-years, compared with 305 in 15,673 person-years with no associated Crohn's disease pharmacy claims. The study reported a HR of 2.0 (95% CI, 1.1 to 3.7) comparing infliximab (with or without corticosteroids or immunomodulators) with no therapy, adjusted for age, gender, geographic region, health plan, and comorbidity. They also reported an adjusted HR of 2.1 (95% CI, 1.1 to 3.8), comparing infliximab alone (without corticosteroids or immunomodulators) with no therapy.

Any Infection

The study also reported four additional infections that the authors did not specifically identify as serious.[168] For herpes simplex, herpes zoster, and encephalopathy, encephalitis, or meningitis; the unadjusted rate ratios and adjusted hazard ratios ranged from 0.9 to 1.7 without statistical significance. There was an increased risk of sepsis among infliximab users, compared with those without therapy. There were 48 sepsis events reported in 292 person-years of infliximab use, compared with 1,833 events among 15,673 person-years of no therapy (adjusted HR comparing infliximab [with or without corticosteroids and immunomodulators] with no therapy, 1.5; 95% CI, 1.1 to 2.0; HR for infliximab alone vs. no therapy, 1.5; 95% CI, 1.1 to 2.0).

Combination of TNF-Alpha Inhibitors, Immunomodulators, and Corticosteroids Versus No Therapy

The same claims-based study compared a triple combination of TNF-alpha inhibitors, immunomodulators, and corticosteroids with no therapy; the study reported on opportunistic and other specific infections.[168]

Opportunistic Infections

The study reported two opportunistic infections among 31 person-years of exposure to combination therapy with TNF-alpha inhibitors, immunomodulators, and corticosteroids, compared with 305 opportunistic infections among 15,673 person-years of no therapy.[168] The study reported an adjusted HR of 3.6 (95% CI, 0.9 to 14.6), comparing triple combination therapy with no therapy.

Any Infection

The study also reported four additional infections that the authors did not specifically identify as serious. The study compared 31 person-years of triple combination therapy of infliximab, immunomodulators, and corticosteroids with 15,673 person-years of no therapy over an average of 2 years per person. The study did not identify claims associated with herpes simplex in any of the triple therapy patients, compared with 134 in the no therapy patients.[168] The study reported one herpes zoster infection in the triple therapy group, compared with 123 infections in the no therapy group (unadjusted rate ratio, 4.1; 95% CI, 0.1 to 23.3). The study reported nine claims for sepsis in the triple therapy group, compared with 1,833 claims in the no therapy group (study reported adjusted HR, 2.4; 95% CI, 1.2 to 4.7). The study reported four encephalopathy, encephalitis, or meningitis infections in the triple therapy group, compared with 499 infections in the no therapy group (unadjusted rate ratio, 4.1; 95% CI, 1.1 to 1.4).

Combination of TNF-Alpha Inhibitors and Immunomodulators Versus No Therapy

The same claims-based study compared a combination of TNF-alpha inhibitors and immunomodulators with no therapy and reported on opportunistic and specific other infections.[168]

Opportunistic Infections

The study reported 15 opportunistic infections among 162 person-years of exposure to combination therapy with TNF-alpha inhibitors and immunomodulators (with or without corticosteroids), compared with 305 opportunistic infections among 15,673 person-years of no therapy.[168] The corresponding unadjusted rate ratio was 4.8 (95% CI, 2.6 to 8.0).

Any Infection

The study reported three herpes simplex infections among the patients receiving a TNF-alpha inhibitor and immunomodulator and 134 infections among patients receiving no therapy. The corresponding rate ratio was 2.2 (95% CI, 0.4 to 6.5). The study reported four herpes zoster infections among patients receiving a TNF-alpha inhibitor and immunomodulator, compared with 123 infections among patients receiving no therapy (unadjusted rate ratio, 3.1; 95% CI, 0.8 to 8.3). The study reported sepsis claims in 23 patients receiving the combination therapy and 1,833 patients receiving no therapy (adjusted HR, 1.9; 95% CI, 0.8 to 1.8). The study reported encephalopathy, encephalitis, or meningitis claims in 12 patients receiving the combination therapy and 499 patients receiving no therapy (unadjusted rate ratio, 2.3; 95% CI, 1.2 to 4.1).[168]

Combination of TNF-Alpha Inhibitor and Corticosteroids Versus No Therapy

The same claims-based study compared no therapy with a combination of TNF-alpha inhibitors and corticosteroids and reported on opportunistic and specific other infections.[168]

Opportunistic Infections

The study reported two opportunistic infections among 142 person-years of exposure to combination therapy with TNF-alpha inhibitors and corticosteroids (with or without immunomodulators), compared with 305 opportunistic infections among 15,673 person-years of no therapy.[168] The corresponding unadjusted rate ratio was 0.7 (95% CI, 0.1 to 2.6).

Any Infection

The study reported one herpes simplex infection in the group receiving a TNF-alpha inhibitor and corticosteroids, compared with 134 infections in the no therapy group (unadjusted rate ratio, 0.8; 95% CI, 0 to 4.7). The study reported herpes zoster claims in three patients receiving the combination therapy and 123 patients receiving no therapy (unadjusted rate ratio, 2.7; 95% CI, 0.5 to 8.1). The study reported sepsis claims in 27 patients receiving the combination therapy and 1,833 patients receiving no therapy. The study reported an adjusted HR for sepsis of 2.8 (95% CI, 1.2 to 6.5) that differed in magnitude from the unadjusted rate ratio of 1.6 (95% CI, 1.1 to 2.4). The study reported encephalopathy, encephalitis, or meningitis in six patients receiving the combination therapy and 499 patients receiving no therapy (unadjusted rate ratio 1.3; 95% CI, 0.5 to 2.9).

Other Combinations With TNF-Alpha Inhibitors

A retrospective study reported no serious infections requiring hospitalization in the 44 people who used TNF-alpha inhibitors without concomitant corticosteroids and immunomodulators. Eight percent of patients on TNF-alpha inhibitors combined with corticosteroids, 2 percent of patients on TNF-alpha inhibitors combined with immunomodulators, and 2 percent of patients on TNF-alpha inhibitors combined with corticosteroids and immunomodulators had serious infections.[165]

Immunomodulators

Table 50 summarizes the risk of serious infections in observational studies evaluating immunomodulators in patients with Crohn's disease. Figure 23 and Table 51 summarize the risk of any infection in RCTs and observational studies evaluating immunomodulators in patients with Crohn's disease. We also provided additional details regarding related studies.

Table 50. Summary of the risk of serious infections in observational studies comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, Year	Followup (Weeks)	Design	IMM	Comparison	# of Serious Infections in IMM Group	# of Patients in IMM Group	# of Serious Infections in Comparison Group	# of Patients in Comparison Group	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Lichtenstein, 2006[131]	99	Prospective cohort	IMM	No IMM	58	3478	48	2775	1.0 (0.7 to 1.4)	0.8 (0.5 to 1.2)

CI = confidence interval; IMM = immunomodulator; OR = odds ratio

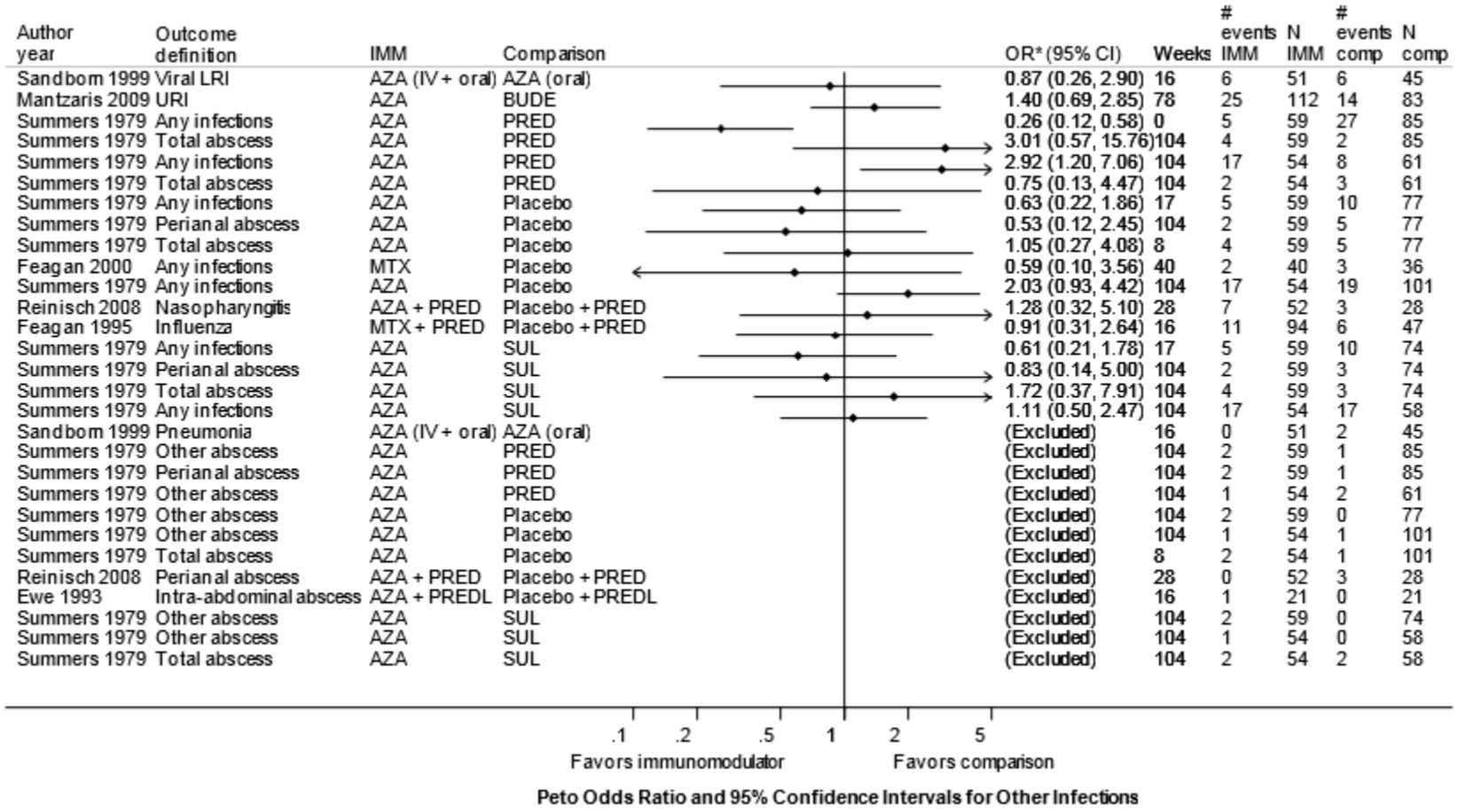
Table 51. Summary of the risk of other infections in observational studies comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, Year	Followup (Weeks)	Immunomodulator	Comparison	# of Other Infections in IMM Group	# of Patients in IMM Group	# of Other Infections in Comparison Group	# of Patients in Comparison Group
Maher, 2009[176]	NR	Azathioprine	Never azathioprine	NR*	12	NR*	60
Shah, 2008[156]	NR	Azathioprine + mesalamine	Azathioprine + never mesalamine	2	104	2	95

IMM = immunomodulator; NR = not reported

*There were two events among 12 patients in the azathioprine group and seven events among 60 patients in the never azathioprine group.

Figure 23. Summary of Peto odds ratios of other infections among randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease



AZA = azathioprine; BUDE = budesonide; CI = confidence interval; Comp = comparison; IMM = immunomodulator; IV = intravenous; LRI = lower respiratory infection; MTX = methotrexate; NR = not reported; OR = odds ratio; PRED = prednisone; PREDL = prednisolone; SUL = sulfasalazine; URI = upper respiratory infection
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Azathioprine Versus Corticosteroids

Two RCTs including 454 Crohn's disease patients compared azathioprine with corticosteroids and reported on infections.[102,177]

Serious Infections

One RCT including 259 patients reported on serious infections.[177] The study termed serious infections a "disaster" if the patient required hospitalization or suffered a disability for at least 3 months, or "serious" if the patient had to withdraw from the study or needed treatment. During induction, two of 59 patients on azathioprine (3 percent) and two of 85 patients on prednisone (2 percent) experienced a serious infection.[177] Seven percent of both groups had a serious infection during the maintenance period.

Opportunistic Infections

Neither of the RCTs reported on opportunistic infections.

Any Infection

Two RCTs including 454 patients reported on any infection. The study reported non-serious infections during induction in 8 percent of patients on azathioprine and 32 percent of patients on prednisone.[177] During maintenance, the studies reported infections in 31 percent of patients on azathioprine and 13 percent of patients on prednisone. A 1.5-year maintenance trial comparing azathioprine with budesonide reported infections in 66 percent of azathioprine and 36 percent of budesonide patients.[102] The majority of infections were upper respiratory or herpes infections.

Azathioprine Versus Sulfasalazine

One RCT including 245 Crohn's disease patients compared azathioprine with sulfasalazine and reported on infections.[177]

Serious Infections

During the induction period, 3 percent of patients on azathioprine and 0 percent of patients on sulfasalazine had serious infections.[177] During maintenance therapy, 7 percent of patients on azathioprine and no patients on sulfasalazine had a serious infection.

Opportunistic Infections

This RCT did not report on opportunistic infections.

Any Infection

The study reported non-serious infections during induction in 8 percent of patients on azathioprine and 14 percent of patients on sulfasalazine.[177] During maintenance therapy, the study reported infections in 31 percent of patients on azathioprine and 54 percent of patients on sulfasalazine.

Combination of Immunomodulators and Corticosteroids Versus Corticosteroids

Three RCTs including 263 Crohn's disease patients compared a combination of immunomodulators and corticosteroids with corticosteroids alone and reported on infections.[51,54,63]

Any Infections

Three RCTs including 263 patients reported on any infections.[51,54,63] A 4-month induction trial comparing a combination of azathioprine and prednisolone with prednisolone alone reported no infections in the 42 patients.[54] A 7-month induction trial reported adverse events that occurred in at least 10 percent of the study population.[51] The trial reported nasopharyngitis in seven of 52 patients (13 percent) receiving azathioprine and prednisone and three of 28 patients (11 percent) receiving prednisone. A 16-week induction trial reported influenza in 11 percent of patients on methotrexate and prednisone compared with 13 percent of patients on prednisone.[63] The trial reported pneumonia in one patient taking methotrexate and prednisone and no patients taking prednisone.[63] None of the RCTs reported on serious or opportunistic infections.

Immunomodulators Versus Placebo

Three RCTs including 463 Crohn's disease patients compared azathioprine with placebo and reported on infections.[56 59 105] One study included an induction and maintenance phase comparing oral azathioprine with placebo.[56] Some patients participated in induction and maintenance, whereas some patients in remission at enrollment only participated in the maintenance phase. We considered serious infections those where patients were hospitalized, suffered a disability of at least 3 months, had to withdraw from the study or needed treatment. Another study compared a single infusion of azathioprine or placebo followed by oral azathioprine in both groups.[59] A 40-week methotrexate trial included patients who were in steroid-free remission from a previous trial[63] or who responded to methotrexate within 16 to 24 weeks.[105]

Serious Infections

Two studies including 367 patients reported on serious infections.[105,177] One study reported serious infections in 3 percent of the azathioprine and 4 percent of placebo patients during induction, and 7 percent of azathioprine and 2 percent of placebo patients during maintenance.[177] The second study, a methotrexate trial, reported one infection-related severe adverse event in a placebo patient.[105]

Opportunistic Infections

No study reported on opportunistic infections for this comparison.

Any Infection

Three studies including 463 patients reported on any infection.[59 105 177] One study reported infections in 8 percent of the azathioprine patients and 13 percent of the placebo patients during the 17-week induction phase, compared with 31 percent of azathioprine patients and 19 percent of placebo patients in the 104-week maintenance phase.[177] A 16-week study that compared a single infusion of azathioprine with placebo to induce remission combined with oral azathioprine in both groups reported no pneumonia cases in the 51 azathioprine patients, compared with two pneumonia cases in the 45 placebo patients.[59] The trial reported viral lower respiratory infections in six azathioprine patients (12 percent) compared with two placebo patients (4 percent). A methotrexate trial reported two flu-like illnesses in both the methotrexate group (5 percent) and the placebo group (5 percent).[105]

Immunomodulators Versus No Immunomodulators

One prospective study including 6,290 Crohn's disease patients compared immunomodulators with no immunomodulators and reported on infections.[131]

Serious Infections

Two percent of patients using immunomodulators and 2 percent of patients not using immunomodulators had a serious infection. The study reported an OR of 0.8 (95% CI, 0.5 to 1.2), comparing immunomodulators with no immunomodulators, adjusted for age, sex, race, disease location, severity of Crohn's disease, duration of followup, and possibly other medications. The authors did not include in the analysis the medication exposure during the 6-month time period when the infection occurred. This prospective study did not report on opportunistic or any other infections.

Immunomodulators Versus No Therapy

A claims-based study that included 8,581 Crohn's disease patients reported opportunistic infections, candidiasis, and tuberculosis together.[168] The study reported 17 of these infections in 911 person-years associated with claims for immunomodulator use, compared with 305 in 15,673 person-years with no claims for medical treatment of Crohn's disease. The study reported an HR of 1.1 (95% CI, 0.6 to 1.8), comparing immunomodulators (with or without infliximab or corticosteroids) with no therapy, adjusted for age, gender, geographic region, health plan, and comorbidity. The study also reported an adjusted HR of 1.1, comparing immunomodulators alone (without infliximab or corticosteroids) with no therapy (95% CI, 0.6 to 1.8).

Any Infection

The study also reported four additional infections that were not specifically identified by the authors as serious. There were 911 immunomodulator person-years compared with 15,673 no therapy person-years.[168] The comparison between immunomodulators and no therapy did not produce any statistically significant associations for herpes simplex, herpes zoster, sepsis, encephalopathy, encephalitis, or meningitis. The HRs ranged from 0.6 to 1.0.

Combination of Immunomodulators With Corticosteroids Versus No Therapy

The same claims-based study reported opportunistic infections, candidiasis, and tuberculosis together.[168] The study reported two of these infections in 19 person-years of followup on a combination of immunomodulator and corticosteroid, compared with 305 infections in 15,673 person-years of followup without any claims for medical treatment of Crohn's disease. The study reported a HR of 4.8 (95% CI, 2.7 to 8.3), comparing a combination of immunomodulators and corticosteroids (with or without infliximab) with no therapy, adjusted for age, gender, geographic region, health plan, and comorbidity. The corresponding unadjusted rate ratio was 5.4 (95% CI, 0.7 to 19.7).

Any Infection

The study also reported four additional infections that were not specifically identified by the authors as serious. The study had 19 person-years of followup on patients receiving an immunomodulator and corticosteroid, compared with 15,673 person-years of followup on patients receiving no therapy.[168] The reported infections included herpes simplex (zero in the combination group vs. 134 in the no therapy group), herpes zoster (zero in the combination group vs. 123 in the no therapy group), sepsis (six in the combination group vs. 1,833 in the no therapy group; the adjusted HR for sepsis, comparing a combination of immunomodulators and corticosteroids [with or without infliximab] with no therapy was 1.2; 95% CI, 0.8 to 1.8; the unadjusted rate ratio was 2.7; 95% CI, 1.0 to 5.9), and encephalopathy, encephalitis, or

meningitis (three in the combination group vs. 499 in the no therapy group; the unadjusted rate ratio for encephalopathy, encephalitis, or meningitis was 5.0; 95% CI, 1.0 to 14.6).

Corticosteroids

Table 52 summarizes the risk of serious infections in studies evaluating corticosteroids in patients with Crohn's disease. Figure 24 and Table 53 summarize the risk of any infection in RCTs and observational studies evaluating corticosteroids in patients with Crohn's disease. We also provided additional details regarding related studies. We did not identify any RCT or observational study that evaluated corticosteroids in patients with Crohn's disease and reported on opportunistic infections.

Table 52. Summary of the risk of serious infections in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, Year	Followup (Weeks)	Design	Corticosteroid	Comparison	# of Serious Infections in Steroid Group	# of Patients in Steroid Group	# of Serious Infections in Comparison Group	# of Patients in Comparison Group	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Lichtenstein, 2006[131]	99	Prospective cohort	Prednisone	No prednisone	61	2142	45	4111	2.9 (1.9 to 4.3)	2.2 (1.5 to 3.3)

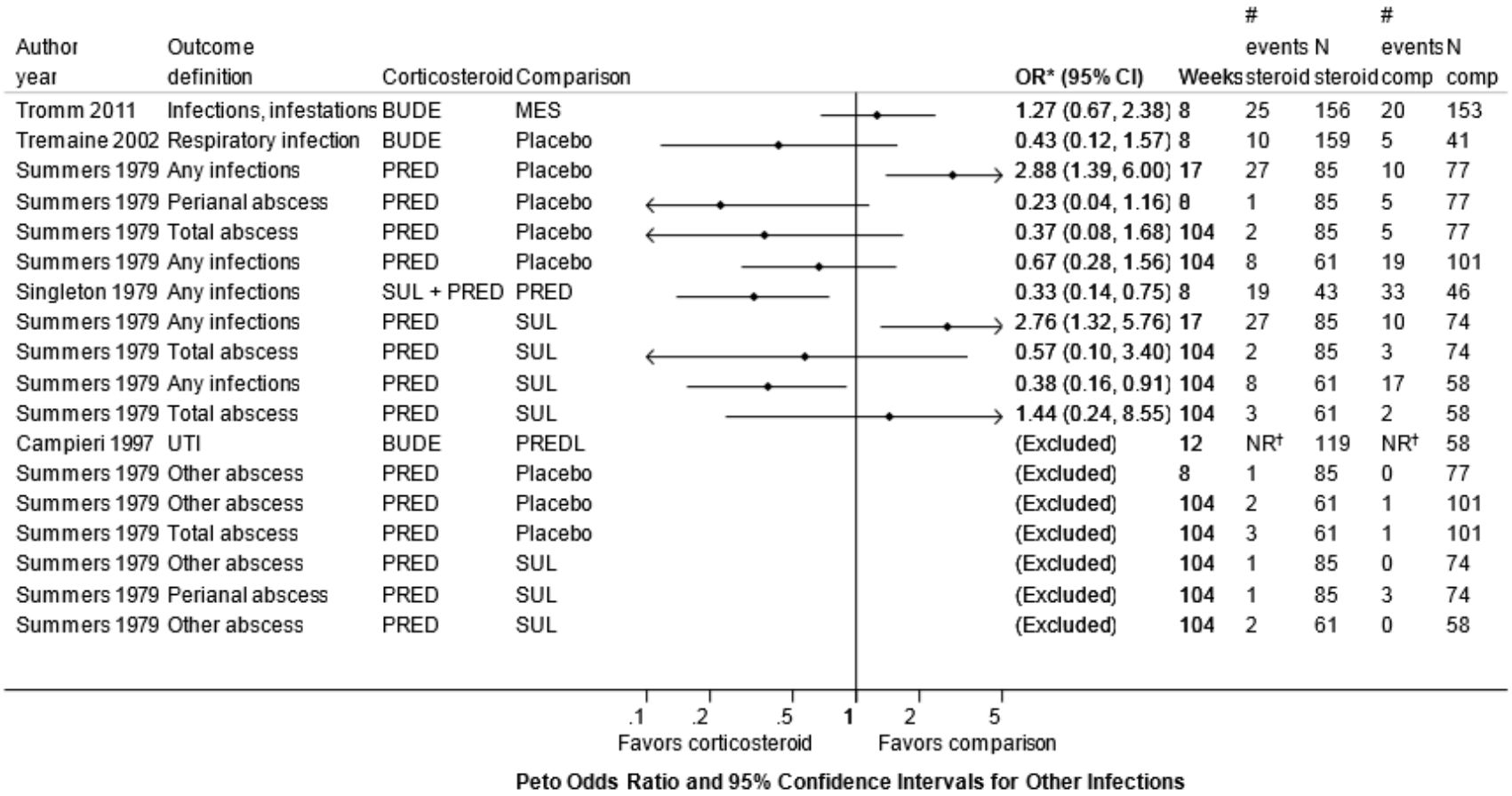
CI = confidence interval; OR = odds ratio; Steroid = corticosteroid

Table 53. Summary of the risk of other infections in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, Year	Followup (Weeks)	Design	Corticosteroid	Comparison	# of Other Infections in Steroid Group	# of Patients in Steroid Group	# of Other Infections in Comparison Group	# of Patients in Comparison Group	Unadjusted OR (95% CI)
Goldstein, 1967[142]	NR	Retrospective cohort	Corticosteroid	Never corticosteroid	95	430	17	124	1.7 (1.0 to 2.8)

CI = confidence interval; NR = not reported; OR = odds ratio; steroid = corticosteroid

Figure 24. Summary of Peto odds ratios of other infections among randomized controlled trials comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease



BUDE = budesonide; CI = confidence interval; Comp = comparison; NR = not reported; OR = odds ratio; PRED = prednisone; steroid = corticosteroid; UTI = urinary tract infections

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

†The number of patients with urinary tract infections was reported to be higher in the budesonide twice daily group.

Corticosteroids Versus Placebo

Two RCTs including 362 Crohn's disease patients compared corticosteroids with placebo and reported on infections.[65,177] They did not report on opportunistic infections.

Serious Infections

One RCT including 302 patients reported on serious infections.[177] The study reported serious infections during the induction period in 2 percent of patients on prednisone and 4 percent of patients on placebo.[177] During the maintenance trial, 7 percent of patients on prednisone and 2 percent of patients on placebo had a serious infection.[177]

Any Infection

Two trials including 362 patients reported on any infection.[65 177] The study reported non-serious infections during the induction period in 32 percent of patients on prednisone and 13 percent of patients on placebo.[177] During the maintenance trial 13 percent of patients on prednisone and 19 percent of patients on placebo had a nonserious infection.[177] A trial comparing budesonide with placebo reported common adverse events. The trial reported respiratory infections in 6 percent of patients on budesonide and 12 percent of patients on placebo (Peto OR, 0.4; 95% CI, 0.1 to 1.6).[65] The trial reported flu-like disorder in 6 percent of budesonide patients and 6 percent of placebo patients.

Corticosteroids Versus No Corticosteroids

One prospective study including 6,253 Crohn's disease patients compared corticosteroids with no corticosteroids and reported on infections.[131]

Serious Infections

The trial reported serious infections in 3 percent of patients on prednisone taken at least 6 months prior to the infection and 1 percent of patients not taking prednisone.[131] The study reported a demographics and medication adjusted OR of 2.2 (95% CI, 1.5 to 3.3). The study did not report on opportunistic or other infections.

Corticosteroids Versus No Therapy

A claims-based study that included 8,581 Crohn's disease patients reported opportunistic infections, candidiasis, and tuberculosis together.[168] The study reported 25 of these infections in 379 person-years of followup for corticosteroid use, compared with 305 infections in 15,673 person-years of followup without therapy for Crohn's disease. The study reported a HR of 3.2 (95% CI, 2.1 to 4.8), comparing corticosteroids (with or without immunomodulators and infliximab) with no therapy, adjusted for age, gender, geographic region, health plan, and comorbidity. The HR for corticosteroids only, compared with no therapy, was also 3.2 (95% CI, 2.1 to 4.8).

Any Infection

The study also reported on four additional infections that the authors did not specifically identify as serious. The study reported 379 person-years of followup for corticosteroid users and 15,673 person-years of followup for the no therapy group.[168] The reported infections included herpes simplex (three in the corticosteroid group vs. 134 in the no therapy group; the HR for corticosteroids only was 0.9; 95% CI, 0.2 to 2.8); herpes zoster (nine in the corticosteroid group

vs. 123 in the no therapy group; the HR for corticosteroids only was 3.1; 95% CI, 1.6 to 6.2); sepsis (72 in the corticosteroid group vs. 1,833 in the no therapy group; the adjusted HR comparing corticosteroids [with or without immunomodulators and infliximab] with no therapy was 1.6; 95% CI, 1.3 to 2.0; the HR for corticosteroids only was 1.6; 95% CI, 1.3 to 2.0); and encephalopathy, encephalitis, or meningitis (34 in the corticosteroid group vs. 499 in the no therapy group; the unadjusted rate ratio for corticosteroids only was 2.6; 95% CI, 1.8 to 3.7).

Corticosteroids Versus Aminosalicylates

Three RCTs including 525 Crohn's disease patients compared corticosteroids with aminosalicylates and reported on infections.[74,113,177]

Serious Infections

One trial including 159 patients reported on serious infections. The study reported serious infections during the induction period in 2 percent of patients on prednisone and 0 percent of patients on sulfasalazine.[177] During the maintenance trial, 7 percent of patients on prednisone and 0 percent of patients on sulfasalazine had a serious infection.[177]

Any Infection

Three trials including 525 patients reported on any infection.[74,113,177] One study reported non-serious infections during the induction period in 32 percent of patients on prednisone and 14 percent of patients on sulfasalazine.[177] During the maintenance trial, 13 percent of patients on prednisone and 29 percent of patients on sulfasalazine had a non-serious infection.[177] A RCT comparing 29 patients on budesonide with 28 patients on mesalamine reported 19 infections in budesonide patients and 16 infections in mesalamine patients.[113] The infections reported included upper respiratory tract infections and urinary tract infections. A larger trial of budesonide compared with aminosalicylates reported 16 percent of budesonide and 13 percent of aminosalicylates patients had an infection.[74]

Combination of Prednisone and Sulfasalazine Versus Sulfasalazine

One RCT including 89 Crohn's disease patients reported on infections.[75]

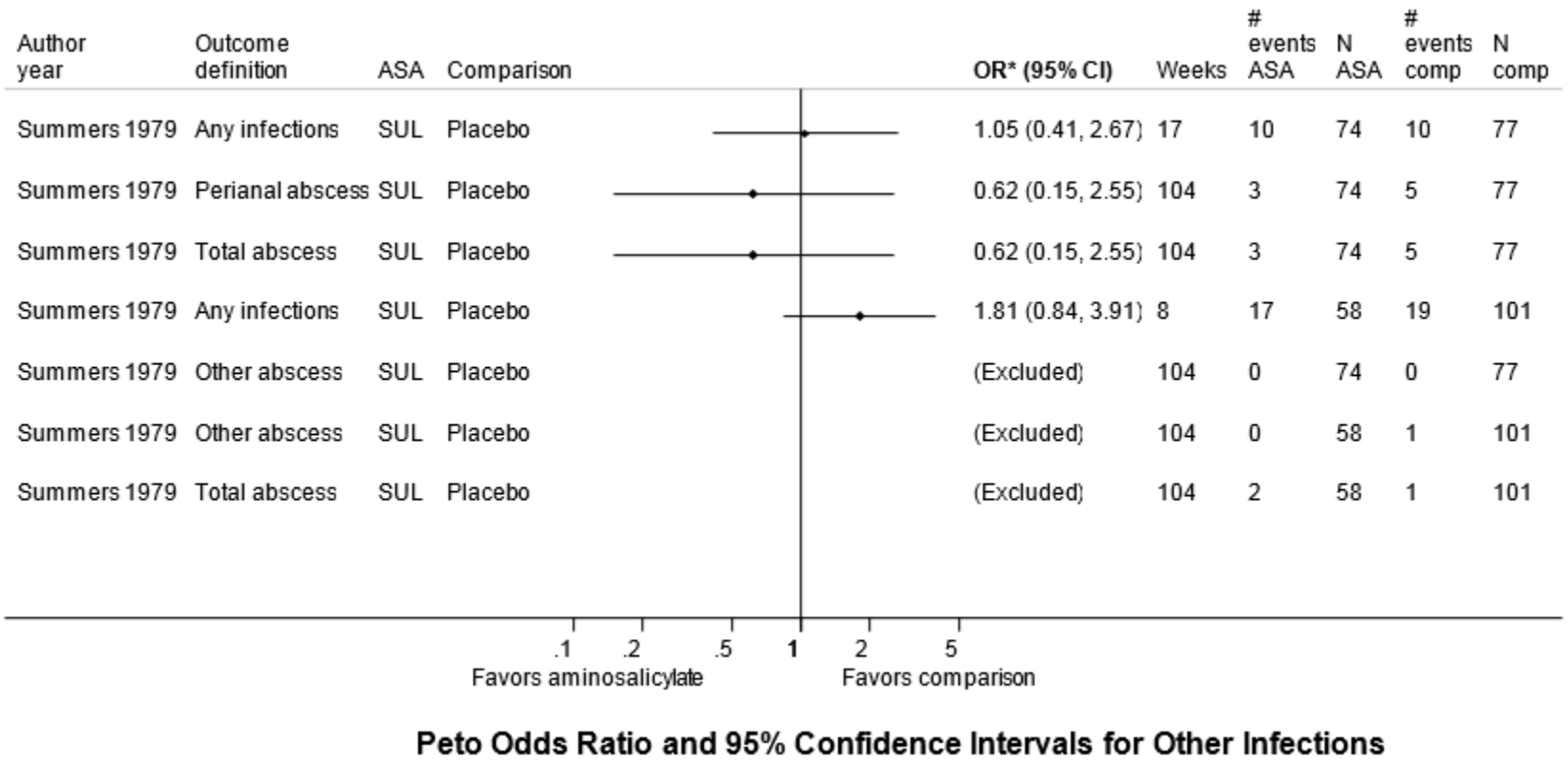
Any Infection

The 8-week induction trial reported 44 percent of patients on prednisone and 72 percent of patients on sulfasalazine had an infection[75]). It did not report serious infections and opportunistic infections.

Aminosalicylates

Figure 25 summarizes the risk of infection in the one RCT evaluating infections associated with use of aminosalicylates in patients with Crohn's disease.

Figure 25. Summary of Peto odds ratios of other infections in a randomized controlled trial comparing an aminosalicylate alone or in combination with placebo or another treatment in patients with Crohn's disease



ASA = aminosalicylate; CI = confidence interval; Comp = comparison; Main = main intervention; OR = odds ratio; SUL = sulfasalazine
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Sulfasalazine Versus Placebo

One RCT included 159 Crohn's disease patients and reported on infections.[177]

Serious Infections

The trial reported serious infections in zero of 74 patients (0 percent) on sulfasalazine and three of 55 patients (5 percent) on placebo during the induction period.[177] During maintenance therapy, the trial reported serious infections in zero of 61 patients (0 percent) on sulfasalazine and two of 101 patients (2 percent) on placebo.

Any Infection

The trial reported non-serious infections during the induction period in 14 percent of patients on sulfasalazine and 13 percent of patients on placebo.[177] During the maintenance trial, 29 percent of patients on sulfasalazine and 19 percent of patients on placebo had an infection. This RCT did not report on opportunistic infections.

Studies Evaluating Patients With Crohn's Disease and IBD

One study reported results for Crohn's disease and all IBD patients.[150] In both groups, the study reported more infections in patients who used adalimumab or infliximab, compared with patients who had never used biologics.

Studies Evaluating Patients With IBD

Eight studies reported infections in IBD patients without separating Crohn's disease from ulcerative colitis or indeterminate colitis patients. We provided details about these studies in Appendix F.

Case-Control Studies Designed To Examine Specific Infections

Two case-control studies including 2,538 IBD patients examined specific infections. One study reported on opportunistic infections[139] and the other on herpes zoster.[135] Researchers nested the case-control studies within a large primary care database covering multiple centers[135] and a single-center.[139] Both studies may have patients that contributed to other studies using these data sources.[133,134,136-138]

Combinations Including Infliximab

The single-center case-control study included 300 IBD patients and reported on specific infections associated with combination therapy including infliximab.[139]

Infliximab Versus No IBD Medication

The single-center case-control study cross-referenced the system's diagnostic index for inpatient and outpatient IBD patients with a viral, fungal, or bacterial opportunistic infection.[139] The study required microbiologic, pathologic, or physician consensus to confirm infection. The study analyzed and matched each of the first 100 consecutive infection cases diagnosed between 1998 and 2003 with two controls (patients who did not have an opportunistic infection). The study matched patients by type of IBD, sex, geographic region, and duration of visits for IBD at the center. Three of 100 opportunistic infection cases (3 percent) had used infliximab alone while being treated at the center, compared with two of 200 controls (1 percent). Compared with no use of mesalamine, corticosteroids, immunomodulators, and infliximab, the age and matching factor

adjusted OR was 11.1 (95% CI, 0.8 to 148). The study did not provide the percent of cases and controls that did not use an IBD medication. One patients developed Epstein-Barr virus lymphoma, but the study did not provide the medication history. The authors also reported that no patient died as a result of their opportunistic infection.

Combination of Infliximab, Thiopurines, and Corticosteroids Versus No IBD Medication

The single-center case-control study reported five of 100 opportunistic infection cases (5 percent), compared with zero of 200 matched controls (0 percent), used a triple combination of infliximab, thiopurines, and corticosteroids.[139]

Combination of Infliximab and Thiopurines Versus No IBD Medication

The single-center case-control study reported one of 100 opportunistic infection cases (1 percent), compared with five of 200 matched controls (2 percent), used a combination of infliximab and thiopurines.[139] Compared with no IBD medication use, the age and matching factor adjusted OR was 1.6 (95% CI, 0.1 to 19).

Combinations Including Immunomodulators

Two case-control studies including 2,538 IBD patients reported on specific infections associated with combination therapy including immunomodulators.[135,139]

Thiopurines Versus No IBD Medication

The single-center case-control study reported that 20 of 100 opportunistic infection cases (20 percent), compared with 31 of 200 matched controls (15 percent), used thiopurines alone. Compared with no IBD medication, the age and matching factor adjusted OR was 3.4 (95% CI, 1.5 to 7.5).[139]

A case-control study of herpes zoster infections looked at IBD patients within a multi-center general practice database.[135] The study matched controls to cases on sex, year of birth, and duration of followup (prior to the case's herpes zoster diagnosis date). The study matched up to four controls that did not have herpes zoster during the followup to each case. Herpes zoster cases had 4 times higher odds of having a prescription for thiopurines alone, versus no IBD medication, in the 30 days prior to the index date, compared with controls (OR, 4.1; 95% CI, 1.9 to 8.7). When the study adjusted corticosteroids and mesalamine in the model (instead of excluding them), the OR was 3.1 (95% CI, 1.7 to 5.6). When the study considered thiopurine use 31 to 90 days before herpes zoster index date, the odds of infection with thiopurine use were no longer higher (OR, 0.6; 95% CI, 0.2 to 1.8).

Combination of Thiopurines and Corticosteroids Versus No IBD Medication

The single-center case-control study reported that 16 of 100 opportunistic infection cases (16 percent), compared with six of 200 matched controls (3 percent), used a combination of infliximab and thiopurines.[139] Compared with no IBD medication use, the age and matching factor adjusted OR was 17.5 (95% CI, 4.5 to 68). The multi-center case-control study reported herpes zoster cases had 3 times higher odds of having a prescription for thiopurines alone, versus no IBD medication, in the 30 days prior to the index date, compared with controls (OR, 3.0; 95% CI, 1.2 to 7.3).[135]

Combinations Including Corticosteroids

Two case-control studies including 2,538 IBD patients reported on specific infections associated with combination therapy including corticosteroids.[135,139]

Corticosteroids Versus No IBD Medication

The single-center case-control study reported that 16 of 100 opportunistic infection cases (15 percent), compared with 27 of 200 matched controls (14 percent), used corticosteroids alone, compared with no IBD medication (the age and matching factor adjusted OR was 2.2, 95% CI, 1.0 to 4.9).[139] The multiple center case-control study reported herpes zoster cases had 60 percent higher odds of having a prescription for thiopurines alone, versus no IBD medication, in the 30 days prior to the index date, compared with controls (OR, 1.6; 95% CI, 1.1 to 2.4).[135]

Combinations Including Aminosalicylates

One multiple center case-control study including 2,238 IBD patients reported on specific infections associated with combination therapy including aminosalicylates.[135]

Mesalamine Versus No Mesalamine

The case-control study reported that herpes zoster patients did not have an increased odds of having a prescription for mesalamine, compared with controls, in the 30 days prior to the index date (OR, 0.9; 95% CI, 0.7 to 1.2).[135]

Tuberculosis

Tuberculosis is of special concern in Crohn's disease because the treatments suppress the immune system. The U.S. Food and Drug Administration has mandated a warning on adalimumab, infliximab, and certolizumab pegol regarding the risk of tuberculosis.[178-180] Nine RCTs (n=3,295), two prospective studies (n=733), and five observational studies (n=2,655) reported on the risk of tuberculosis in patients receiving treatment for Crohn's disease (Appendix D, Evidence Table 14). Four of the RCTs excluded patients with a prior history of tuberculosis or initiating treatment prior to randomization. None of the RCTs described active assessment of tuberculosis specifically.

No RCTs of natalizumab, immunomodulators, corticosteroids, or aminosalicylates reported tuberculosis as an outcome. One study randomized patients to sulfasalazine, prednisone, or azathioprine, and included isoniazid as part of the treatment regimen in patients randomized to prednisone because of the known increased risk of tuberculosis associated with prednisone.[56]

Table 54 summarizes the reported rates of tuberculosis in studies of the treatment of Crohn's disease. We also provided additional details regarding related studies.

Table 54. Summary of reported rates of tuberculosis in randomized controlled trials* comparing the safety of therapies for the management of Crohn's disease

Author, Year	Design, Duration N With CD New Users Only (Y/N)	Comparison, Dose	Specific Aim (Y/N)	Ascertainment of Tuberculosis During Study Tuberculosis Testing Before Enrollment	Concomitant Medications	Tuberculosis Results
Hanauer, 2002[86]	RCT, 52 wk 573 N	Infliximab vs. placebo	N	Not specified N	ASA Steroids IMM Antibiotics	1/385 (<1%) vs. 0/188 (0%)
Colombel, 2010[45]	RCT, 52 wk 503 Y	Infliximab vs. azathioprine vs. infliximab + azathioprine	N	Not specified Y	ASA Steroids Antibiotics NR	0/161 (0%) vs. 0/163 (0%) vs. 1/179 (1%)
Colombel, 2009[95]	RCT, 52 wk 778 N	Adalimumab vs. placebo	N	Not specified Y	ASA Steroids IMM Antibiotics NR	2/517 (<1%) vs. 0/261 (0%)
Sandborn, 2007[83]	RCT, 52 wk 55 N	Adalimumab vs. placebo	N	Not specified Y	ASA Steroids IMM Antibiotics	0/37 (0%) vs. 0/18 (0%)
Sandborn, 2007[38]	RCT, 4 wk 325 N	Adalimumab vs. placebo	N	Not specified Y		0/159 vs. 0/166
Hanauer, 2006[37]	RCT, 4 wk 299 Y	Adalimumab vs. placebo	N	Not specified Y	ASA Steroids IMM Antibiotics	0/225 (0%) vs. 0/74(0%)
Schreiber, 2007[84]	RCT, 18 wk 668 N	Certolizumab pegol vs. placebo	N	Not specified Y	ASA Steroids IMM Antibiotics	1/216 (<1%) vs. 0/212 (0%)
Schreiber, 2005[40]	RCT, 12 wk 292 N	Certolizumab pegol vs. placebo	N	Not specified Y		0/219 vs. 0/73
Winter, 2001[41]	RCT, 12 wk 92 N	Certolizumab pegol vs. placebo	N	Not specified Y		0/68 vs. 0/24

ASA = aminosalicylates; CD = Crohn's disease; IBD = inflammatory bowel disease; IMM = immunomodulators; N = no; NR = not reported; RCT = randomized controlled trial; Steroids = corticosteroids; vs. = versus; wk = weeks; Y = yes

*Four observational studies reported on tuberculosis. Two cases among 743 infliximab users compared with no cases among 666 never users of biologic.[153] No cases among 757 patients treated with combinations of medications with infliximab or infliximab alone.[137,145,173]

Adalimumab Versus Placebo

Four RCTs[37,38,82,83] including 1,447 patients compared adalimumab with placebo. One of those studies[82] reported two cases of tuberculosis, one patient receiving adalimumab 40 mg weekly and one patient receiving adalimumab 40 mg every other week, compared with no cases of tuberculosis in the placebo group. The other three studies reported no incident cases of tuberculosis. One study excluded patients with untreated tuberculosis within 3 months.[38]

Certolizumab Pegol Versus Placebo

Three RCTs including 812 Crohn's disease patients compared certolizumab pegol with placebo and reported on tuberculosis.[40,41,84] A maintenance trial after induction response reported one tuberculosis case in the certolizumab pegol group (less than 1 percent of 216 patients) during 26 weeks of followup despite having excluded purified protein derivative positive patients from the study.[84] The trials reported no other tuberculosis cases.[40,41]

Infliximab Versus Placebo

One RCT[86] including 573 patients evaluated infliximab compared with placebo. The trial detected one incident case of tuberculosis in an infliximab patient.

Other Combinations With TNF-Alpha Inhibitors

An induction trial[45] including 503 Crohn's disease patients compared infliximab, azathioprine, and the combination of infliximab and azathioprine. The trial reported one incident case of tuberculosis in the group receiving infliximab and azathioprine.

Two prospective studies (n=733) and five retrospective studies (n=2,655) reported on tuberculosis.[132,137,145,153,161,165,173] Six studies compared combinations of medications with a TNF-alpha inhibitor and reported no tuberculosis cases.[132,137,145,161,165,173] One retrospective study reported two tuberculosis cases among 743 infliximab users, compared with no cases among 666 non-users.[153]

Infusion- and Injection-Site Reactions

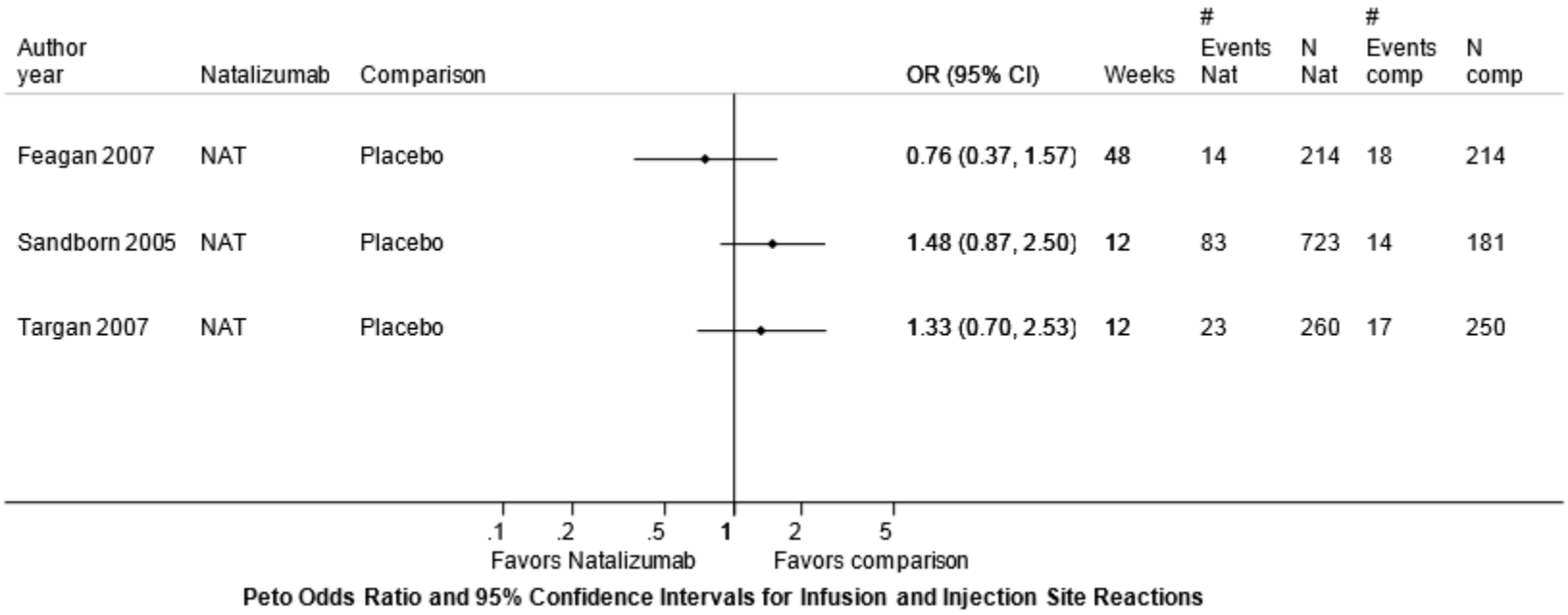
Infusion and injection-site reactions can include a wide range of symptoms (from local irritation or pain to anaphylaxis) that occur during or shortly after an infusion. This definition is generally consistent (when reported) in the studies we included. Other types of reactions can occur a few days to a few weeks after medication administration, including hypersensitivity-type reactions, delayed infusion reactions, and serum sickness. We did not address these longer-term reactions in this review. In some cases, the study authors did not define the symptoms and timing of the infusion or injection-site reactions; we included these studies in this review.

Twenty-two RCTs including 6,809 patients reported infusion reactions as an outcome by comparison group, one of which addressed infusion reactions as a primary outcome of interest (Appendix D, Evidence Table 14).[88] Four prospective studies, with 1,067 patients, and 10 retrospective studies, with 2,972 patients, reported on infusion reactions. Three observational studies mentioned active ascertainment as a means of identifying infusion reactions.[138,161,181] All retrospective studies relied on chart reviews to identify infusion reactions. Many of the prospective and retrospective studies specifically stated or implied that patients were pre-treated with medications at the infusion center to prevent infusion reactions. Most RCTs did not report pre-treating patients with medications to prevent infusion reactions.

Natalizumab

Figure 26 summarizes the data on infusion- and injection-site reactions in RCTs evaluating natalizumab in patients with Crohn's disease. We also provided additional details regarding related studies.

Figure 26. Summary of Peto odds ratios of infusion- and injection-site reactions among randomized controlled trials comparing natalizumab to placebo in patients with Crohn's disease



CI = confidence interval; comp = comparison; NAT = natalizumab; OR = odds ratio

Natalizumab Versus Placebo

Three RCTs including 1,414 Crohn's disease patients reported infusion reactions within 2 hours of the start of infusion in patients receiving natalizumab, compared with placebo. These appeared in two publications.[32,33] During the induction trials, the trials reported infusion reactions in 9 to 11 percent of natalizumab and 7 to 8 percent of placebo patients.[32,33] Researchers re-randomized 228 responders from one of these trials for a 48-week maintenance trial.[33] They reported any adverse event occurring during or within 2 hours of infusion in 7 percent of natalizumab users and 8 percent of placebo users.

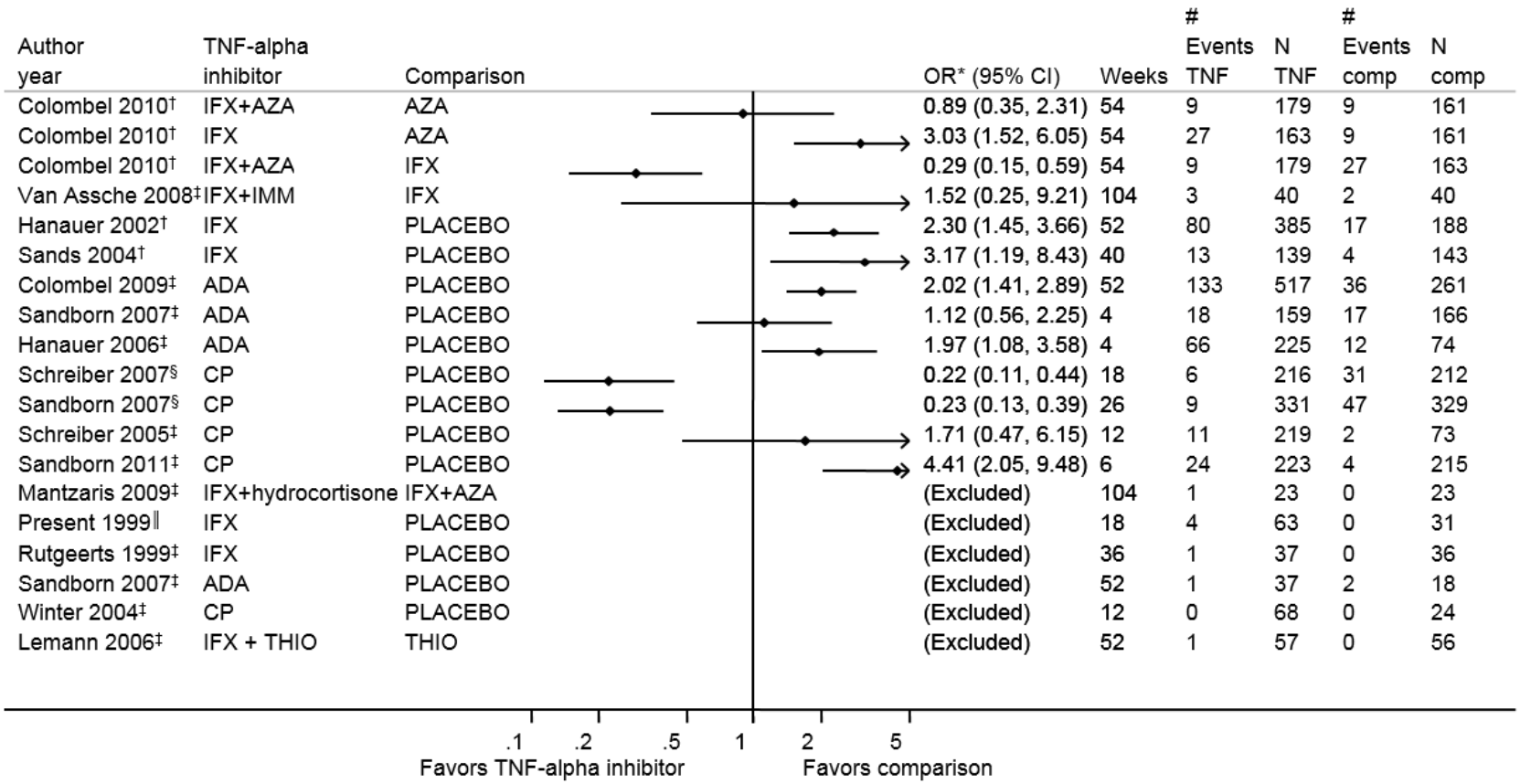
Combination of Natalizumab and Infliximab Versus Infliximab

One 20-week RCT including 79 non-responders to infliximab randomized patients to continued infliximab alone or natalizumab and infliximab. Three of 52 patients taking natalizumab and infliximab had a non-serious hypersensitivity reaction during or within 120 minutes of infusion, compared with zero of 27 patients taking only infliximab.[35]

TNF-Alpha Inhibitors

For studies that we combined in Key Questions 1 and 2 we tried to conduct meta-analyses separately for induction and maintenance RCTs comparing TNF-alpha inhibitors with placebo in terms of infusion- and injection-site reactions. However, we were unable to do so because of statistical heterogeneity (I-squared, 82 percent for induction trials and 87 percent for maintenance trials). Figures 27 and 28 summarize the data on infusion- and injection-site reactions in RCTs and observational studies evaluating TNF-alpha inhibitors in patients with Crohn's disease. We also provided additional details regarding related studies.

Figure 27. Summary of Peto odds ratios of infusion- and injection-site reactions among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with another treatment in patients with Crohn's disease



ADA = adalimumab; AZA = azathioprine; CI = confidence interval; comp = comparison; CP = certolizumab pegol; IFX = infliximab; OR = odds ratio; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor

* We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

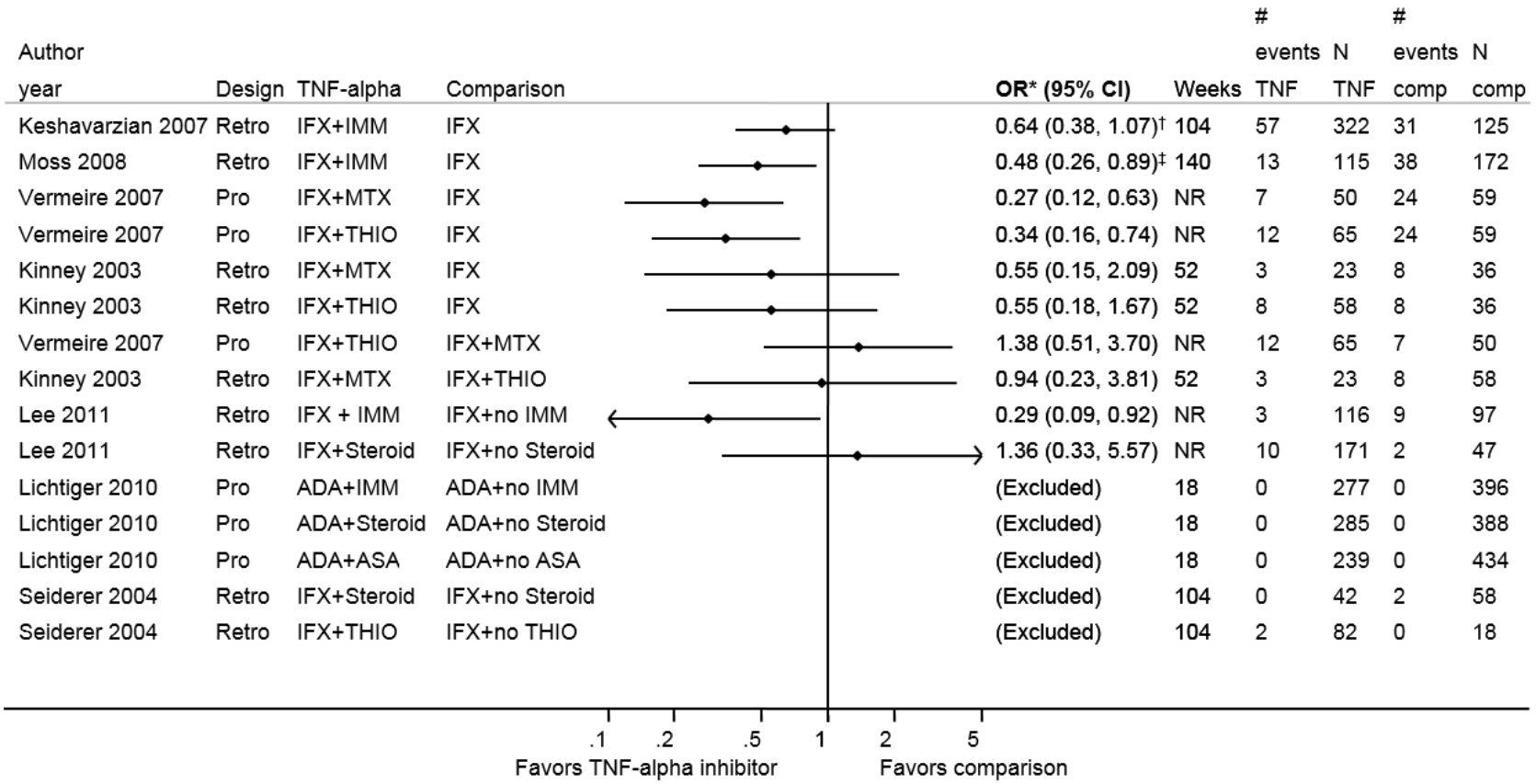
† Infusion and injection site reactions were defined as any adverse event occurring within 1 hour of infusion/injection.

‡ Infusion and injection site reactions were not defined in the study.

§ Infusion and injection site reactions were defined as any adverse event that occurred at the infusion/injection site and was temporarily related to the infusion/injection.

‖ Infusion and injection site reactions were defined as any adverse event occurring within 2 hours of infusion/injection.

Figure 28. Summary of Peto odds ratios of infusion- and injection-site reactions among observational studies comparing a TNF-alpha inhibitor alone or in combination with another treatment in patients with Crohn's disease



ADA = adalimumab; ASA = aminosalicylate; CI = confidence interval; comp = comparison; CP = certolizumab pegol; IFX = infliximab; IMM = immunomodulator; MTX = methotrexate; NR = not reported; OR = odds ratio; Pro = prospective study; Retro = retrospective study; Steroid = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

†Adjusted odds ratio, 0.7 (95% CI, 0.4 to 1.1).

‡Adjusted odds ratio, 0.3 (95% CI, 0.2 to 0.9).

Adalimumab Versus Placebo

Four RCTs including 1,457 Crohn's disease patients compared adalimumab with placebo and reported injection reactions. In two induction trials, injection-site reactions were more common in adalimumab (11 to 29 percent) and placebo (10 to 16 percent) patients.[37,38]

A 52-week maintenance trial of 55 patients who achieved remission during induction, reported injection-site reactions in one of 37 patients on adalimumab and two of 18 patients on placebo.[83] Those who the trial did not randomize for the maintenance study received adalimumab without blinding. Twenty-six of 221 (12 percent) patients who entered open-label adalimumab therapy, or were not randomized, had an injection-site reaction.[83] The publications that studied maintenance and induction reported different numbers of patients randomized in the induction trial (n=299 and n=276).

A 52-week maintenance trial of responders from a 4-week induction period reported injection-site reactions in 26 percent of patients on adalimumab and 14 percent of patients on placebo who re-initiated adalimumab after week 12 (blinding maintained).[95] Another publication of this trial reported injection-site reactions during the randomized followup in 5 percent of patients on adalimumab and less than 1 percent of the patients on placebo.[82] The publications did not define injection-site reactions.

Other Combinations With Adalimumab

A prospective cohort of 673 patients, treated with adalimumab with or without concomitant aminosalicylates, corticosteroids, or immunomodulators, reported no injection-site reactions at 18 weeks.[161]

Certolizumab Pegol Versus Placebo

Five RCTs including 1,910 Crohn's disease patients compared certolizumab pegol with placebo and reported infusion or injection-site reactions.[39-41,84] The duration of the four induction trials ranged from 6 to 26 weeks. Reactions occurred in 0 to 11 percent of certolizumab pegol and 0 to 14 percent of placebo patients.[39-42] The Peto OR ranged from 0.2 to 6.4.[39,40,42]

A maintenance trial of 428 patients who responded to certolizumab pegol induction[39] reported any local reaction to infusion in six out of 216 patients on certolizumab pegol (3 percent) and 31 out of 212 patients on placebo (15 percent), during the 18-week followup.[84] The corresponding Peto OR was the same as the induction OR (0.2; 95% CI, 0.1 to 0.4).

Infliximab Versus Placebo

Four RCTs including 1,022 patients compared infliximab with placebo and reported infusion reactions.[44,85-87] Infusion reactions, defined as an adverse event during or within 2 hours of infusion, occurred in 6 percent of infliximab and 0 percent of placebo patients, during an induction trial.[44]

A 36-week trial[85] compared retreatment with infliximab or placebo among 73 responders to a single induction dose in a previous 12-week trial.[43] The trial reported an acute infusion reaction with dyspnea in one of 36 infliximab patients. The trial did not report infusion reactions in 36 patients on placebo, although it is unclear if infusion reactions were a possible safety outcome for placebo patients. The trial corresponding to the induction period reported infusion reactions only for those who received two doses of infliximab and only during the second infusion (two of 29 patients).[43]

A 40-week maintenance trial, of 282 responders and non-responders to a 14-week induction period with infliximab for fistulizing Crohn's disease, compared infliximab with placebo.[87] They reported infusion reactions during or within 1 hour of infusion in 9 percent of patients on infliximab and 3 percent of patients on placebo, during the randomized period. During induction (among patients randomized for maintenance therapy), 7 percent of patients on infliximab and 8 percent of patients on placebo had an infusion reaction (the trial did not randomize nine of 306 given induction because of adverse events; the trial did not report the adverse events). At 22 weeks, placebo patients were eligible to crossover to 5 mg/kg intravenous every 8 weeks infliximab treatment; and patients receiving 5 mg/kg of infliximab were eligible to have the dose increased to 10 mg/kg (the trial maintained blinding after crossover). During crossover, 9 percent of those who had a dose increase to 10 mg/kg experienced an infusion reaction, compared with 23 percent of patients who crossed over to infliximab from placebo.

A 52-week maintenance trial, of 573 responders and non-responders to a 2-week induction period of a single infliximab dose, compared infliximab with placebo and reported adverse events during or within 1 hour of infusion.[86] The trial reported infusion reactions in 21 percent of infliximab patients and 9 percent of placebo patients, during the maintenance period (the trial did not report reactions during the initial infusion).

Infliximab Versus Azathioprine

One RCT including 324 Crohn's disease patients compared infliximab with azathioprine and reported on infusion reactions.[45] Seventeen percent of patients taking infliximab and 6 percent of patients taking azathioprine experienced an adverse event during or within 1 hour of infusion.

Other Combinations With Infliximab

Four retrospective studies including 1,152 Crohn's disease patients met the inclusion criteria, but the studies may have misclassified the concomitant medications (as described previously in the mortality section). The studies evaluated the safety profile of infliximab use at their centers.[137,145,164,175] A retrospective study reported infusion reactions that resulted in medication discontinuation in 5 percent of 127 patients taking infliximab and an immunomodulator, compared with 13 percent of 71 patients receiving infliximab without concomitant immunomodulators, as recorded in a database that included most of the patients treated with infliximab at the center.[175] The other studies reported infusion reactions in 2 to 5 percent of patients receiving a triple combination of infliximab, immunomodulators, and corticosteroids, 4 to 20 percent of patients receiving the combination of infliximab and immunomodulator, 0 to 7 percent of patients receiving the combination of infliximab and corticosteroid, and 5 to 21 percent of patients receiving only infliximab.[137,145,164] In a previous report from one of these centers, 19 infusion reactions occurred in the first 100 patients given infliximab.[138] However, we noted a discrepancy between the two reports from this center. One article reported concomitant medications in 18 of 19 infusion reactions among the first 100 patients,[138] but the other article reported concomitant medications in only 17 of 19 infusion reactions among the first 500 patients.[137]

Combination of Infliximab and Immunomodulators Versus Infliximab

Three RCTs including 468 Crohn's disease patients and three retrospective studies (n=1,025), compared a combination of infliximab and immunomodulators with infliximab and reported infusion reactions.[45,88,89] A 50-week induction trial compared an infliximab-azathioprine

combination with infliximab among patients who were naïve to TNF-alpha inhibitors, azathioprine, 6-mercaptopurine, and methotrexate.[45] They reported adverse events during or within 1 hour of infusion in 5 percent of 179 patients taking infliximab and azathioprine and 17 percent of 163 patients taking infliximab.[45]

A 104-week induction trial, of blinded physicians and unblinded steroid-dependent luminal Crohn's disease patients, reported severe infusion reactions in zero of 23 patients taking infliximab and azathioprine and one of 23 patients taking infliximab and hydrocortisone.[88] The group taking infliximab and azathioprine included only azathioprine-naïve patients whereas the infliximab group included both azathioprine-naïve patients as well as those who had previously taken azathioprine for less than a month (but stopped because of intolerance or severe adverse events). The infliximab group received a pre-infusion dose of hydrocortisone whereas the infliximab and azathioprine group did not.

A 104-week open-label retreatment trial of non-fistulizing Crohn's disease patients reported three unspecified infusion reactions in the 40 patients taking infliximab and an immunomodulator (it is possible that these reactions occurred in the same person), and two infusion reactions in the 40 patients taking infliximab.[89]

One prospective and three retrospective observational studies including 1,025 patients reported on infusion reactions.[148,154,162,182] The prospective study[154] included patients receiving infliximab without concomitant immunomodulators. The study occurred in 2000 and 2001, before the authors reported that concomitant immunomodulators appeared to be associated with a decreased risk of infusion reactions and changed their practice pattern.[183] During 2002 and 2003, a study treated patients with infliximab and concomitant azathioprine, 6-mercaptopurine, or methotrexate.[154] The study gave luminal disease patients a single induction infusion, and fistulizing disease patients a three-dose induction regimen (at 0, 2, and 6 weeks). If clinicians felt the patients lost response or had an acute flare, they treated patients with infliximab and considered them at risk of infusion reaction. Infusion reactions in retreated patients occurred in 16 percent of 115 patients taking infliximab and an immunomodulator, compared with 40 percent of 59 patients taking infliximab without an immunomodulator. The Peto OR was similar for both the combination of infliximab and a thiopurine (OR, 0.3; 95% CI, 0.2 to 0.7) and the combination of infliximab and methotrexate (OR, 0.3; 95% CI, 0.1 to 0.6), compared with infliximab.

The retrospective studies reported infusion reactions in 11 to 18 percent of infliximab combined with immunomodulators, compared to 22 to 25 percent in patients not receiving a concomitant immunomodulators.[148,162,182,184] The Peto OR favored infliximab combined with immunomodulators to decrease infusion reactions in all studies. We did not perform a meta-analysis because of the different time periods of followup, definitions of infusion reaction, and immunomodulators allowed.

Combination of Infliximab and Immunomodulators Versus Immunomodulators

Two RCTs[45,46] including 452 Crohn's disease patients reported infusion reactions in users of infliximab and an immunomodulator, compared with users of an immunomodulator alone.

A 52-week induction trial in steroid-dependent, luminal Crohn's disease patients reported a severe infusion reaction in one of 57 patients taking infliximab and a thiopurine, and zero of 56 patients taking a thiopurine alone.[46] A 50-week induction trial compared infliximab and azathioprine with azathioprine alone among patients who were naïve to TNF-alpha inhibitors,

azathioprine, 6-mercaptopurine, and methotrexate.[45] The trial reported adverse events during or within 1 hour of infusion in 5 percent of patients taking infliximab and azathioprine, and 6 percent of patients taking azathioprine.[45]

Combination of Infliximab and Thiopurines Versus Combination of Infliximab and Methotrexate

Two observational studies including 291 Crohn's disease patients compared a combination of infliximab and azathioprine with a combination of infliximab and methotrexate and reported infusion reactions.[154,162] A prospective study of retreated patients reported infusion reactions by type of concomitant immunomodulators. Infusion reactions occurred in 18 percent of patients taking infliximab and azathioprine, compared with 14 percent of patients taking infliximab and methotrexate.[154] A retrospective study of 1 year mean followup reported infusion reactions in 14 percent of patients taking infliximab and a thiopurine, and 13 percent of patients taking infliximab and methotrexate.[162]

Immunomodulators

Azathioprine Versus Placebo

One RCT including 96 patients evaluated infusion reactions (not defined) following a single infusion of azathioprine 40 mg/kg, compared with placebo.[59] The trial reported infusion reactions in 11 of 51 patients receiving azathioprine (22 percent) and one of 45 patients receiving placebo (2 percent). The corresponding Peto OR was 5.8 (95% CI, 1.7 to 19.2).

Studies Evaluating Patients With IBD

Four studies reported infusion- and injection-site reactions in IBD patients without separating Crohn's disease patients from ulcerative colitis or indeterminate colitis patients. We provided details about these studies in Appendix F.

Bone Fractures

We did not identify any studies comparing biologics, immunomodulators, or aminosalicylates in terms of the risk of bone fracture. Three studies including 1,032 patients with at least one corticosteroids group reported bone fractures (Table 55; Appendix D, Evidence Table 14).[127,185,186] Two of these studies excluded patients who had used medications for preventing fractures or osteoporosis,[187] such as bisphosphonates; hormone replacement therapy; and certain doses of calcium, fluoride or Vitamin D supplements, within 6 or 24 months of the study.[127,185] One of the studies that made these exclusions recruited patients with osteoporosis.[127]

Table 55. Summary of the risk of bone fracture in studies comparing the safety of therapies for the management of Crohn's disease

Author, Year	Design, Duration N CD/IBD New Users Only / Specific Aim (Y/N)	Comparison, Dose Source for Non-RCTs	Assessment of Bone Fracture	Surveillance Blinded Assessments (Y/N)	Concomitant Medications	Bone Fracture Results
Schoon, 2005[185]	RCT, 2y 271 CD N / Y	Budesonide, 9 mg qd vs. prednisolone, 40 mg qd	Vertebrae with a height reduction of >20% as measured by X-ray and traumatic fractures	Active Y	ASA, IMM, vitamin D and calcium supplementation	2/137 (2%) vs. 3/134 (2%)
Siffledeen, 2007[127]	Cross-sectional 207 CD N / Y	Steroid use vs. no steroid use in past year Questionnaire	Vertebrae with a height reduction of >20% and a loss of surface area >10% in the presence of a biconcave, crush, or wedge deformity as measured by DXA scan	Active Y	NR	25/105 (24%) vs. 17/102 (17%)
Bernstein, 2003[186]	Case-control 116 CD N / Y	Steroid use in two years prior to fracture vs. no steroid use in two years prior to fracture Electronic pharmacy record	ICD-9 codes 805, 807.0, 807.1, 813 and 820 representing fractures at the hip, spine, ribs or wrist	NA	NR	7/13 (54%) vs. 23/103 (22%)
Goldstein, 1967[142]	Retrospective cohort, NR 554 IBD N / N	Steroid non-user vs. steroid user Chart review	Pathologic fractures recorded in patient chart	Passive NR	NR*	0/124 (0%) vs. 6/430 (1%)

ASA = aminosalicylates; CD = Crohn's disease; DXA = dual energy x-ray absorptiometry; IBD = inflammatory bowel disease; ICD-9 = International Classification of Diseases, Ninth Revision; IMM = immunomodulators; mg = milligrams; N = no; NA = not applicable, secondary database analysis; NR = not reported; qd = once daily; RCT = randomized controlled trial; vs. = versus; y = year; Y = yes

* Concomitant medication use other than aminosalicylates was deemed unlikely because the last point of data collection was 1965.

Budesonide Versus Prednisolone

One 2-year RCT (n=271) specifically compared the risk of vertebral fractures between budesonide and prednisolone in ileal or ileocolonic uncomplicated Crohn's disease.[185] The study found a similar percentage of vertebral or traumatic fractures in both study groups (2 percent). The authors also reported that 14 percent of patients had non-symptomatic vertebral fractures at baseline.

Corticosteroids Versus No Corticosteroids

A cross-sectional study of 207 Crohn's disease patients compared questionnaire-reported use of corticosteroids in the year prior to a dual-energy X-ray absorptiometry (DXA) scan with no reported use of corticosteroids in the prior year.[127] Seventeen percent of 102 non-users had a vertebral fracture, compared with 24 percent of 105 corticosteroid users. The study reported a Pearson correlation coefficient *P*-value of 0.27 for this comparison. A case-control study of Crohn's disease patients reported seven out of 13 cases of hip, spine, rib, or wrist fracture had used corticosteroid within 2 years of injury (54 percent), compared with 23 corticosteroid users among 103 controls (22 percent).[186]

Studies Evaluating Patients With IBD

One retrospective cohort reported on bone fractures in the treatment of IBD without separating Crohn's disease from ulcerative colitis or indeterminate colitis (see Appendix F).

Studies Reporting Results for Crohn's Disease and IBD

A case-control study reported similar rates of bone fracture for all IBD patients (30 percent of 40 cases of bone fracture were corticosteroid users, compared with 22 percent of 276 controls; the unadjusted OR was 1.8; 95% CI, 0.6 to 3.7).[186]

Study Quality

We rated many of the studies containing data relevant to Key Question 3 as low quality for assessing the question of patient safety because they did not report on the specific safety outcomes that we sought to assess in this review. In many cases, the studies did not report their primary exposure-outcome relationship sufficiently and did not account for confounding and selection bias in the safety analyses. Another common reason we rated studies as poor quality was the inability to adjust for confounders because of the small number of events, even if all other reporting and bias adjustment categories were sufficient.

Of the prospective and retrospective observational studies, we rated all as poor quality except eight. We rated seven studies good quality and one study fair quality. Of the nine included case-control studies, we rated four good quality and five poor quality (see Appendix D, Tables 15 and 16).

Key Question 4: Effectiveness of Therapies Used To Prevent Post-Operative Recurrence as Pertains to Patient-Reported Outcomes

Studies Included

We included two studies with 120 participants, in KQ4--an RCT and a prospective cohort study (Appendix D, Evidence Tables 17-20).[188,189] These studies considered comparisons with azathioprine and mesalamine; no evidence is available for this KQ with regard to other agents.

Study Design and Population Characteristics

Randomized Controlled Trial

The RCT was a 1-year, double-blind, double-dummy, randomized trial which took place in 21 gastroenterology centers in Austria, the Czech Republic, Germany, and Israel.[188] The study participants were 78 adults with Crohn's disease who had undergone resection with ileocolonic anastomosis in the preceding 6 to 24 months without subsequent clinical recurrence. The participants had a CDAI score less than 200, but with moderate or severe endoscopic recurrence. The study drugs were azathioprine 2.0-2.5 mg/kg/day (N=41) or mesalamine 4 g/day (N=37) over 1 year.

The mean age in the groups was 35.5 years for azathioprine and 36.0 for mesalamine. Fifty-nine percent of the azathioprine group and 54 percent of the mesalamine group were male. Proportions of continuous, recurrent, and unknown course were similar in the two groups. Mean baseline IBDQ in the two groups was 191 and 175 for azathioprine and mesalamine, respectively.

Observational Study

The observational study[189] was a prospective cohort study with 42 participants, which investigated the influence of azathioprine on postoperative recurrence in a subgroup of Crohn's disease patients considered to have aggressive disease. In a nested case-control study, controls were patients selected to treatment but intolerable to azathioprine or 6-mercaptopurine; the study compared their postoperative course with that of patients receiving and tolerating the drugs postoperatively.

Twenty-eight participants received azathioprine, compared with 14 controls. The participants receiving azathioprine had a median age of 34.5 years (range, 17 to 71 years); the controls had a median age of 38.0 years (range, 19 to 64 years). Of patients receiving azathioprine, three (10 percent) were smokers, compared with none of the controls. The duration of disease among participants receiving azathioprine was a median of 13 years (range, 0 to 34 years); among controls it was a median of 12.5 years (range, 0 to 36 years). Fourteen (50 percent) of the azathioprine recipients and six (43 percent) of the controls had perianal disease. Median followup among azathioprine recipients and controls was 85.1 months (range, 23 to 139 months) and 78.7 months (range, 25.4 to 140 months), respectively.

Study Results

Randomized Controlled Trial

The RCT used the IBDQ as its patient-reported outcome.[188] The change in mean IBDQ score from baseline (azathioprine, 191; mesalamine, 175) to last on-treatment visit (azathioprine, 200; mesalamine, 180) was similar in both treatment arms (change in the azathioprine group, 9; standard deviation, 17.7, change in the mesalamine group, 5; standard deviation, 27.4; P=0.4565, two-sided Wilcoxon test).

Observational Study

The prospective cohort used as its patient-reported outcome the patients' assessment of general health according to a visual analogue scale (VAS) integrated over time.[189] The VAS used runs from 0 to 100, where 0 is the worst possible score and 100 corresponds to perfect health. The authors stated that "repeated observations on the VAS …were integrated over time as a way of describing the patients' condition during the study period."[189] The study did not offer any more details.

The study did not find any difference between the groups in perceived health over time, as evaluated on the VAS. In the azathioprine group, the mean VAS integrated over time was 65.4 (range, 0 to 99.4); in the control group it was 55.5 (range, 14.6 to 98.6). The study rated this difference as not statistically significant, although it did not provide any measures of variation.

Study Quality and Limitations

Randomized Controlled Trial

The risk of bias for the RCT[188] is low. However, one should give consideration to the fact that the study was industry-funded and that industry investigators were among the co-authors. The study did not provide any information on what role industry played in design or analysis. Consistency is unclear, given that this is a single study. With regard to directness, this study is direct. The study is precise. In summary, the quality of this study is high.

Observational Study

The risk of bias for this study is moderate to high,[189] given its small sample size and uncontrolled nature; in addition, it is unclear whether the study blinded participants to their treatment assignment, and whether the study authors (in "integrating" the VAS over time [about which no detail was given]), were blinded to the participants' treatment group. Consistency is unclear given that this is a single study. With regard to directness, this study is direct. We could not determine the precision given the lack of information. In summary, the quality of this study is low. Limitations of this study include the lack of information on variation and statistical procedures used in integrating the VAS, and that the study selected a measure of patient outcome not used in other studies (e.g., the SF-36 or IBDQ).

Pediatric Results

Few studies compared the efficacy or safety of Crohn's disease treatments in the pediatric population (younger than 18 years old).

Five randomized controlled trials (RCTs) compared the efficacy of therapies, alone or in combination, to induce or maintain remission in children with Crohn's disease. No other RCTs that included participants less than 18 years of age reported results separately for the pediatric population.

Nine studies reported the comparative safety of therapies alone or in combination in children with Crohn's disease. Of these nine studies, the majority studied height or weight change as their primary outcomes of interest. Five additional studies included both children and adults, but did not report results separately for the pediatric population.

Key Question 1: Effectiveness of Therapies To Induce Remission in Children

Key Points

Disease Activity Scales

- The combination therapy 6-mercaptopurine and prednisone was more effective than prednisone alone in reducing remission after 1 month of treatment in children with Crohn's disease (relative risk [RR], 1.18; 95% confidence interval [CI], 0.95 to 1.47). (strength of evidence [SOE]: Low)
- Budesonide and prednisolone did not differ in inducing remission at week eight in children with Crohn's disease (RR, 0.77; 95% CI, 0.49 to 1.22). (SOE: Moderate)
- Combination therapy with prednisone and mesalamine and combination therapy with budesonide and mesalamine did not differ in inducing remission at week 12 in children with Crohn's disease (RR, 0.95; 95% CI 0.47 to 1.92). (SOE: Low)
- We did not find any studies addressing the comparative effectiveness of other therapies alone or in combination to induce remission in children with Crohn's disease. (SOE: Insufficient)

Reduction of Steroids

- The drug 6-mercaptopurine was more effective than placebo in reducing the need for corticosteroids in children with Crohn's disease (observed-to-expected ratio of days on prednisone, 0.73 for the 6-mercaptopurine group, and 1.34 for the placebo group; $P < 0.001$). (SOE: Low)
- We found insufficient evidence to determine the comparative effectiveness of other therapies alone or in combination to reduce the need for corticosteroids in children with Crohn's disease. We did not find any studies evaluating the effects of biologics, azathioprine, methotrexate, corticosteroids, or aminosalicylates on the reduction of steroids in children.

Mucosal Healing, Hospitalization, Surgery, Fistula Response, and Patient-Reported Outcomes

- We found insufficient evidence to determine the comparative effectiveness of therapies alone, or in combination, with respect to mucosal healing, hospitalization, surgery, fistula response, and patient-reported outcomes, in children with Crohn's disease. No studies evaluating those outcomes in children met our inclusion criteria.

Table 56 summarizes the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix D, Table 21.

Table 56. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission in children

Comparison	Disease Activity Scale	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Patient-Reported Outcomes
6-Mercaptopurine and prednisone vs. prednisone alone	Favors 6-mercaptopurine and prednisone; Low	Insufficient	Insufficient	Favors 6-mercaptopurine; Low	Insufficient	Insufficient	Insufficient
Prednisone and mesalamine vs. budesonide and mesalamine	Neither drug combination favored; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide vs. prednisolone	Neither drug favored; Mod	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Note: We defined the strength of the evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.
We graded all other comparisons and outcomes as insufficient since there were no eligible studies.

Study Design and Population Characteristics

Three RCTs compared the effectiveness of therapies alone or in combination to induce remission in children with Crohn's disease (Appendix D, Evidence Tables 22 and 23).[190-192] None of these RCTs were crossover studies and none had a run-in period. All three RCTs were multi-centered studies (one in the United States, one in Europe, and one in Israel). The total length of followup was 8 weeks, 12 weeks, and 18 months.

All three RCTs included pediatric patients exclusively, totaling 136 children. All three studies reported the mean age of the children was 13.3 years (range: 13.0 to 13.9 years). One study (48 children) reported the mean disease duration was 0.7 years.[190] Eighty-six of the 136 children were male (63 percent, range: 60 to 69 percent). One study reported race, listing 51 of 55 children (93 percent) as white.[192]

Age, disease location, disease severity, and baseline disease activity were comparable in the RCTs. Two of the three studies reported disease location.[190,192] Twenty-five of 103 children (24 percent, range: 9 to 42 percent) had ileal disease, 65 of 103 children (63 percent, range: 50 to 75 percent) had ileocolonic disease, 12 of 103 children (12 percent, range: 6 to 16 percent) had colonic disease, and zero of 103 children had perianal disease. All three studies reported disease severity.[190-192] The mean baseline Pediatric Crohn's Disease Activity Index (PCDAI) score was consistent with moderate-to-severe disease in all three studies (range, 29.1 to 45.7]).[193] One study (48 children) reported the Crohn's Disease Activity Index (CDAI) and Harvey-Bradshaw index (HBI).[190] The mean CDAI score was 255 and mean baseline HBI score was 7.5. None of these studies reported on smoking status, age at diagnosis, disease behavior, baseline Inflammatory Bowel Disease Questionnaire (IBDQ) score, or C-reactive protein (CRP) level.

Other inclusion criteria were similar for the three studies. Individual studies further restricted their patients on disease location, disease duration, and medications allowed prior to and during the study. One study, comparing budesonide with prednisolone,[190] included children with disease of the ileum or ascending colon exclusively. One study, comparing a combination of prednisone and mesalamine with a combination of budesonide and mesalamine,[191] only included children with a disease duration of at least 2 months; while another study, comparing a combination of 6-mercaptopurine and prednisone with prednisone alone, included children with a disease duration of less than 8 weeks.[192] Two studies[191,192] did not allow children any additional treatment during the study. The third study[190] allowed children to continue taking additional aminosalicylates or antibiotics as long as they received a constant dose for the 30 days prior to randomization of budesonide or prednisolone.

Disease Activity Measures

All three RCTs used disease activity scales to measure remission (Appendix D, Evidence Table 24).[190-192] The disease activity scales were the PCDAI, CDAI, and HBI. We summarized the absolute disease activity scores in Table 57. None of these studies provided a measure of variability, thereby limiting our ability to comment of the effectiveness of these therapies on affecting these indexes.

Combination of 6-Mercaptopurine and Prednisone Versus Prednisone Alone

One RCT randomized 55 children to a combination of 1.5 mg/kg per day of 6-mercaptopurine and prednisone or prednisone alone with a scheduled taper, and evaluated inactive disease (defined as total HBI score less than 3).[192] After 1 month of treatment, 93

percent of 27 children in the combination group and 79 percent of 28 children in the prednisone alone group had inactive disease.

Budesonide Versus Prednisolone

One RCT assessed remission (defined as CDAI less than or equal to 150) in 18 children with active Crohn's disease (CDAI greater than 150). The study randomized the children to 9 mg per day of budesonide taper or 1 mg/kg per day of prednisolone taper.[190] The study saw remission at 8 weeks in 12 of 22 children (55 percent) in the budesonide treatment group, and 17 of 24 children (71 percent) in the prednisolone treatment group. The remission rate difference between the two groups was 16 percent (95% CI, 13 to 45 percent, P=0.25).

Combination of Budesonide and Mesalamine Versus Combination of Prednisone and Mesalamine

One RCT examined remission within 12 weeks (defined as PCDAI of less than or equal to 10) in 33 pediatric patients with mild-to-moderate Crohn's disease (PCDAI 12.5 to 40).[191] The percent of children in remission did not differ between the two treatment groups at 4, 8, or 12 weeks. At 12 weeks, nine of 19 children (47 percent) receiving 9 mg per day budesonide taper with mesalamine, and seven of 14 children (50 percent) receiving 40 mg per day prednisone taper with mesalamine, were in remission.

Table 57. Summary of absolute disease activity scores in studies comparing the effectiveness of medications in inducing remission in children with Crohn's disease

Author, Year	Length of Followup	Main Intervention (Dose), N	Comparison (Dose), N	Baseline Activity Score	Final Activity Score
Markowitz, 2000[192]	1 mo	6-Mercaptopurine (1.5 mg/kg daily) + prednisone taper, 27	Placebo + prednisone taper, 28	7.7 vs. 7.4 (mean HBI)	NR
Escher, 2004[190]	8 wks	Budesonide (9 mg daily x 8 wks, then 6 mg daily x 4 wks), 22	Prednisolone (1 mg/kg daily x 4 wks, then tapering for 8 wks), 24	39 vs. 45 (mean PCDAI)	149 vs. 97 (mean CDAI)
Levine, 2003[191]	12 wks	Budesonide (3 mg q 8 hours x 8 wks, then tapered wks 9-10, discontinued after 10 wks) + mesalamine, (3-4 g daily wks 11-12), 19	Prednisone (40 mg daily x 2 wks, then tapered wks 3-10, discontinued after 10 wks) + mesalamine (3-4 g daily wks 11-12), 14	29.3 vs. 28.9 (mean PCDAI)	-9.3 vs. -13.4 (change in PCDAI)

CDAI = Crohn's Disease Activity Index; HBI = Harvey-Bradshaw Index; mg = milligram; mg/kg = milligrams per kilogram; mo = month; NR = not reported; PCDAI = Pediatric Crohn's Disease Activity Index; wks = weeks

Mucosal Healing

We did not find any studies conducted among children with active Crohn's disease that evaluated mucosal healing.

Hospitalizations

We did not find any studies conducted among children with active Crohn's disease that evaluated hospitalization rates.

Surgeries

No study of children with Crohn's disease reported surgeries as an outcome of interest. One study of children with Crohn's disease did comment that four children who withdrew from the study (one patient from the 6-mercaptopurine and prednisone group and three children from the placebo and prednisone group) required surgery after withdrawal.[192]

Reduction of Steroids

6-Mercaptopurine Versus Placebo

One RCT of pediatric patients with Crohn's disease[192] looked at the reduction of corticosteroids as an outcome of interest among children. The study randomized the children to a combination of 6-mercaptopurine and prednisone or prednisone alone (Appendix D, Evidence Table 24). The study increased, decreased, or did not change prednisone dosage based on the patient's change in partial HBI score. Children in the 1.5 mg/kg per day 6-mercaptopurine group required fewer days of prednisone treatment than the children in the placebo group, with an observed-to-expected ratio of days on prednisone of 0.73 for the 6-mercaptopurine group, and 1.34 for the placebo group ($P < 0.001$). Both groups required comparable time to initially wean off prednisone, with the children in the 6-mercaptopurine group requiring a median of 121 days (95% CI, 117 to 143 days), and the children in the placebo group requiring a median of 131 days (95% CI, 120 to 178 days, $P > 0.05$).

Fistula Response

None of the studies looked at fistula response as an outcome of interest among children with active Crohn's disease.

Patient-Reported Outcomes

We did not find any studies evaluating patient-reported outcomes as an outcome of interest among children with active Crohn's disease.

Study Quality

Of the studies on treatment of children with Crohn's disease, two studies[190 192] had good quality and one study[191] had poor quality (Appendix D, Evidence Table 25). The two good-quality studies had an adequate allocation sequence and concealment, adequate blinding, and complete outcome data. The other study was unclear about the allocation sequence and concealment, blinding technique, and completeness of outcome data. Only one of the studies reported pharmaceutical support and company involvement in the design, conduct, or reporting of the trial.[190]

Key Question 2: Effectiveness of Therapies To Maintain Remission in Children

Key Points

Disease Activity Scales

- Among those who achieved remission with induction infliximab, maintenance infliximab was more effective than episodic therapy at maintaining remission at week 50 in children with Crohn's disease (RR, 1.35; 95% CI, 0.84 to 2.18). (SOE: Low)
- Mesalamine and placebo did not differ in maintaining remission at 1 year in children with Crohn's disease (RR, 0.90; 95% CI, 0.67 to 1.21). (SOE: Low)
- We found insufficient evidence to determine the comparative effectiveness of other therapies alone or in combination to maintain remission in children with Crohn's disease. We did not find any studies evaluating the effectiveness of thiopurines, methotrexate, corticosteroids, or sulfasalazine in children with Crohn's disease.

Surgeries

- Mesalamine and placebo did not differ in maintaining remission and avoiding surgeries at year one in children with Crohn's disease (no events observed in either arm). (SOE: Low)
- We found insufficient evidence to determine the comparative effectiveness of other therapies alone or in combination in maintaining remission and avoiding surgeries in children with Crohn's disease. We did not find any studies evaluating the effectiveness of biologics, thiopurines, methotrexate, corticosteroids, or sulfasalazine in children with Crohn's disease.

Mucosal Healing, Hospitalization, Reduction of Steroids, Fistula Response, and Patient-Reported Outcomes

- We found insufficient evidence to determine the comparative effectiveness of therapies alone or in combination in maintaining remission with respect to mucosal healing, hospitalizations, reduction of steroids, fistula response, and patient-reported outcomes in children with Crohn's disease. We did not find any studies evaluating the effectiveness of biologics, thiopurines, methotrexate, corticosteroids, or aminosalicylates in children with Crohn's disease.

Table 58 summarizes the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix D, Table 21.

Table 58. Key findings and strength of evidence comparing pharmacologic therapies for the management of children with Crohn's disease to maintain remission

Comparison	Disease Activity Scale	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Patient-Reported Outcomes
Infliximab (maintenance vs. episodic therapy)	Maintenance therapy favored; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Mesalamine vs. placebo	Neither drug favored; Low	Insufficient	Insufficient	Neither drug favored; Low	Insufficient	Insufficient	Insufficient

Note: We defined the strength of the evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.
We graded all other comparisons and outcomes as insufficient since there were no eligible studies.

Study Design and Population Characteristics

Two RCTs compared the effectiveness of therapies alone or in combination to maintain remission in children with Crohn's disease (Appendix D, Evidence Tables 22 and 23).[194,195] One study evaluated mesalamine versus placebo,[194] while another compared infliximab maintenance therapy versus episodic (or on-demand) therapy.[195]

One study, examining mesalamine versus placebo, took place in Europe at multiple centers; the length of follow-up was 1 year.[194] This RCT included 122 pediatric patients (18 years and younger) diagnosed with Crohn's disease before the age of 16 years. The mean age was 11.8 years. Seventy-three of 122 children (58 percent) were male. The mean disease duration was 0.8 years. Only children with active Crohn's disease were eligible (defined as HBI score greater than or equal to 5 or erythrocyte sedimentation rate (ESR) greater than or equal to 25 mm at 1 hour). The mean baseline HBI was 0.8, indicating that the study included the majority of children, based on ESR value. All disease activity levels were included in this study. However, the study excluded children if they had documented previous use of thiopurines or methotrexate. Disease locations were 12 percent ileal, 69 percent ileocolonic, and 19 percent colonic. Combining all disease locations, 32 percent of children also had perianal involvement. The study did not report smoking status, age at diagnosis, race, disease behavior, baseline IBDQ score, or CRP level.

One open-label randomized study, examining different strategies of infliximab, took place in Europe at multiple centers; the length of follow-up was 1 year.[195] The study population included 40 patients enrolled between 2002 and 2005. The study included patients if they were between 7-17 years of age with moderate-to-severe Crohn's disease, based on HBI greater than or equal to 5 and an ESR of greater than 20 mm/hour. Patients had to have prior resistance to thiopurines or methotrexate, as well as corticosteroids. The study prohibited prior anti-TNF use. All patients received induction dosing of infliximab 5 mg/kg intravenous at 0, 2, and 6 weeks. The study randomized those who achieved remission by week eight to receive maintenance infliximab at 5 mg/kg every 8 weeks (Group A), or episodic (or on-demand) infliximab for patients who relapsed (Group B). The study defined remission as an HBI less than 5, ESR less than 20 mm/h, fistula closure [where applicable], and weaning completely from steroids. It defined relapse as an HBI greater than or equal to 5 and incomplete fistula closure.

The mean age at diagnosis was 13.9, and mean duration of disease was 3.0 years. Twenty-two patients (55 percent) were male. Twenty-seven patients had nonstricturing, nonpenetrating disease, while 13 had penetrating disease. At inclusion, all but four patients were on steroids, 37 were on a thiopurine, and three were on methotrexate. Baseline HBI was 7.6. A total of 34 patients went into clinical remission after induction dosing, and the study randomized 31 to maintenance, versus on-demand therapy. The study did not provide baseline characteristics for the randomized patients.

Disease Activity Measures

Infliximab Maintenance Versus Episodic Therapy

One RCT[195] examined clinical relapse at 50 weeks after randomization. The rate of remission at 50 weeks was 83 percent in the maintenance group and 61 percent in the episodic group ($P < 0.001$). The rate of relapse over the course of the study was three of 13 (23 percent) and 11 of 12 (92 percent), respectively (not intention-to-treat analysis). Notably, almost all patients in the episodic arm received infliximab at some point during the study (mean of 3.4 infusions

compared to six infusions in the maintenance arm), although at a later point in time (mean of 150 days after randomization).

Mesalamine Versus Placebo

One RCT[194] examined clinical relapse at 1 year (defined as HBI score of greater than or equal to 5) in 122 pediatric patients with active Crohn's disease. The study randomized the patients after induction treatment (Appendix D, Evidence Table 24). The difference in relapse was not meaningful between children receiving 50 mg/kg per day of mesalamine and children receiving placebo. The 1-year relapse rate was 34 of 60 children (57 percent) receiving mesalamine, and 39 of 62 children (63 percent) receiving placebo. The average time without relapse was 8.6 months in the mesalamine group and 7.9 months in the placebo group, and was not clinically or statistically different between the two groups.

Mucosal Healing

Neither study looked at mucosal healing as an outcome of interest.

Hospitalizations

Neither study looked at hospitalizations as an outcome of interest.

Surgeries

Mesalamine Versus Placebo

One RCT[194] examined surgery for acute complications as an outcome of interest. At 1 year, the study reported no surgeries for children in either the 1 mg/kg per day mesalamine treatment group or the placebo group.

Reduction of Steroids

Neither study looked at reduction of steroids as an outcome of interest.

Fistula Response

Neither study looked at fistula response as an outcome of interest.

Patient-Reported Outcomes

Neither study looked at patient-reported outcomes as an outcome of interest.

Study Quality

The overall quality of one RCT[194] was fair (Appendix D, Evidence Table 25). The study had adequate allocation sequence and concealment and adequate blinding, but the completeness of outcome data was unclear. The authors reported no conflict of interest.

The overall quality of one RCT[195] was poor. The study had adequate allocation sequence, but there was no blinding built into the study and outcome data was unclear with regard to relapse rates. The authors reported their conflicts of interest.

Key Question 3: Safety of Therapies in Children

Key Points

Mortality, Lymphoma, Other Cancers, Tuberculosis, Infusion- and Injection-Site Reactions, and Bone Fractures

- We found insufficient evidence to determine the comparative safety of therapies alone or in combination in children with Crohn's disease. We did not find any studies reporting on mortality, lymphoma or other cancers, tuberculosis, infusion- and injection-site reactions, or bone fractures.

Serious Infections

- Infliximab maintenance therapy and episodic therapy did not differ in minimizing serious infections at 1 year in children with Crohn's disease (no events reported). (SOE: Low)
- Placebo was safer than 6-mercaptopurine in minimizing serious infections at 18 months in children with Crohn's disease (RR, 3.1; 95% CI, 0.1 to 73.1). (SOE: Low)
- We found insufficient evidence to determine the comparative safety of other therapies alone or in combination to minimize serious infections in children with Crohn's disease. We found no studies evaluating other biologics, azathioprine, methotrexate, corticosteroids, or aminosalicylates in terms of serious infections among children with Crohn's disease.

Other Infections

- Infliximab maintenance therapy and episodic therapy did not differ in minimizing other infections at 1 year in children with Crohn's disease. (SOE: Low).
- Budesonide was safer than prednisone in minimizing other infections at week eight in children with Crohn's disease (RR, 0.2; 95% CI 0.01 to 3.8). (SOE: Low)
- Budesonide and mesalamine combination therapy was safer than prednisone and mesalamine combination therapy in minimizing other infections at week 12 in children with Crohn's disease (RR, 0.3; 95% CI, 0.01 to 5.7). (SOE: Low)
- Prednisolone was safer than budesonide in minimizing other infections in children with Crohn's disease (RR, 2.4; 95% CI 0.2 to 24.4). (SOE: Moderate)
- We found insufficient evidence to determine the comparative safety of other therapies alone or in combination to minimize other infections in children with Crohn's disease.
- We did not find any studies evaluating other biologics, thiopurines, methotrexate, or aminosalicylates in children with Crohn's disease.

Height Change

- Maintenance infliximab was more effective than episodic infliximab in allowing growth at 1 year in children with Crohn's disease (z-score increased from -1.5 to -0.6 in the maintenance arm vs. -1.4 to -1.0 in the episodic arm). (SOE: Low)
- 6-mercaptopurine and placebo did not differ at 6, 12, and 18 months in allowing growth in children with Crohn's disease (6.8 cm vs. 5.3 cm after 18 months, respectively, P=0.3). (SOE: Low)

- Prednisone was more effective than placebo in allowing growth in children with Crohn's disease. (SOE: Low)
- Prednisone and budesonide did not differ in allowing growth at 6 months in children with Crohn's disease (change in height percentile, 0.25 vs. -2.35 for budesonide and prednisone, respectively; P=0.1). (SOE: Low)
- We found insufficient evidence to determine the comparative safety of other therapies alone or in combination to allow growth in children with Crohn's disease. We did not find any studies evaluating the effects of other biologics, azathioprine, methotrexate, or aminosalicylates in children with Crohn's disease.

Weight Change

- Maintenance infliximab was more effective than episodic infliximab in allowing weight gain at 1 year in children with Crohn's disease (weight gain, 4.3 kg vs. -0.1 kg; P < 0.001). (SOE: Low)
- Infliximab was more effective than placebo in allowing weight gain in children with Crohn's disease (fat mass to height z-score beta-coefficient, 0.29; 95% CI, 0.06 to 0.52). (SOE: Low)
- Methotrexate was more effective than placebo in allowing weight gain in children with Crohn's disease (fat mass to height z-score beta-coefficient, 0.30; 95% CI, 0.04 to 0.56). (SOE: Low)
- Prednisone was more effective than placebo in allowing weight gain in children with Crohn's disease (fat mass to height z-score beta-coefficient, 0.69; 95% CI, 0.12 to 1.26). (SOE: Low)
- Prednisone was more effective than budesonide in allowing weight gain after 8 weeks in children with Crohn's disease (weight gain, 4.6 vs. 2.5 kg for prednisone and budesonide, respectively; P < 0.05). (SOE: Low)
- We found insufficient evidence to determine the comparative safety of other therapies alone or in combination to allow weight gain in children with Crohn's disease. We did not find any studies evaluating the effects of natalizumab, adalimumab, certolizumab pegol, thiopurines, or aminosalicylates on weight in children with Crohn's disease.

Table 59 summarizes the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix D, Table 21.

Table 59. Key findings and strength of evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of safety

Comparison	Mortality	Lymphoma, Cervical Cancer, and Other Cancers	Serious Infections	Tuberculosis	Other Infections	Infusion- and Injection-Site Reactions	Bone Fractures	Height Change	Weight Change
Infliximab vs. placebo	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors infliximab; Low
Infliximab (maintenance vs. episodic therapy)	Insufficient	Insufficient	Neither favored; Low	Insufficient	Neither favored; Low	Insufficient	Insufficient	Maintenance infliximab favored; Low	Maintenance infliximab favored; Low
6-Mercaptopurine and prednisone vs. prednisone alone	Insufficient	Insufficient	Neither drug combination favored; Low	Insufficient	Insufficient	Insufficient	Insufficient	Neither drug combination favored; Low	Insufficient
Methotrexate vs. placebo	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors methotrexate; Low
Prednisone vs. placebo	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Conflicting evidence; Low	Favors prednisone; Low
Budesonide vs. prednisone	Insufficient	Insufficient	Insufficient	Insufficient	Neither drug favored; Low	Insufficient	Insufficient	Neither drug favored; Low	Favors prednisone; Low
Budesonide and mesalamine vs. prednisone and mesalamine	Insufficient	Insufficient	Insufficient	Insufficient	Neither drug combination favored; Low	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide vs. prednisolone	Insufficient	Insufficient	Insufficient	Insufficient	Neither drug favored; Mod	Insufficient	Insufficient	Insufficient	Insufficient

Note: We defined the strength of the evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.
We graded all other comparisons and outcomes as insufficient since there were no eligible studies.

Study Design and Population Characteristics

Nine studies compared the safety of therapies alone or in combination in children with Crohn's disease (Appendix D, Evidence Tables 22 and 23). Four studies were RCTs.[190-192,195] Two studies were prospective cohort studies,[196,197] and three studies were retrospective cohort studies.[198-200] One of the RCTs had a run-in period where both arms received induction infliximab; none of the RCTs were crossover studies. The studies took place in various countries (two in the United States, one in Canada, four in Europe, and two in Israel), and five studies were multi-centered trials.[190-192,195,198] The length of followup ranged from 8 weeks to 43 months.

The nine studies included pediatric patients exclusively, totaling 573 children. The mean age of children ranged from 12.7 to 13.9 years in seven studies (351 children).[190-192,195,196,198,199] The mean disease duration ranged from 0.6 to 3.0 years in three studies (166 children).[190,195,199] All nine studies reported the percent of male patients, which ranged from 33 to 100 percent. Two studies reported race; 51 of 55 children (93 percent) were white in one study,[192] and eight of 78 children (10 percent) were black in another study.[199] Two studies (72 children) reported the mean age at diagnosis, which ranged from 7.0 to 13.9 years.[196,197]

Five studies reported Crohn's disease characteristics as disease location, severity, and baseline disease activity.[190,192,197,199,200] The studies reported disease location for 333 children as follows: 14 percent (range: 3 to 42 percent) had ileal disease, 71 percent (range: 21 to 84 percent) had ileocolonic disease, 12 percent (range: 6 to 16 percent) had colonic disease, and 8 percent (range: 0 to 36 percent) had perianal disease. One study reported disease behavior; 27 patients had nonstricturing, nonpenetrating disease, while 13 had penetrating disease.[195] Seven studies reported disease severity[190-192,195,197-199] for 337 children as follows: 11 percent (range: 0 to 83 percent) had mild disease, 50 percent (range: 0 to 100 percent) had mild-to-moderate disease, less than 1 percent (range: 0 to 6 percent) had moderate disease, 37 percent (range: 0 to 100 percent) had moderate-to-severe disease, and less than 1 percent (range: 0 to 12 percent) had severe disease. Five studies reported a mean baseline PCDAI score ranging from 27.6 to 45.7[190-192,198,199] for 334 children. One study reported the mean baseline CDAI was 255 for 48 children.[190] Two studies reported the mean baseline HBI score was 7.5-7.6, in 95 children.[192,195] None of these studies reported on smoking status, baseline IBDQ score, or CRP level.

The inclusion criteria were mostly the same among the studies except in regards to disease severity. All studies included mostly children, with a maximum age of 22 years. Five studies used Crohn's disease severity for inclusion;[190,192,195,198,201] the studies determined severity using physician assessment, PCDAI, CDAI, and HBI. Eight studies included only children with Crohn's disease; one study included children with inflammatory bowel disease.[197] One study excluded girls;[196] all others included both sexes.

Three studies, examining 6-mercaptopurine and prednisone[192] and corticosteroids,[190,191] excluded children who had previously used thiopurines. Two studies, measuring growth,[199,200] excluded children who had an illness or were taking any other medications that could affect growth or development.

Mortality

No studies meeting our inclusion criteria reported on the outcome of mortality in children with Crohn's disease.

Cancer

No studies meeting our inclusion criteria reported on cancer rates in children with Crohn's disease.

Serious Infections

Infliximab Maintenance Versus Episodic Therapy

One RCT of 40 children reported on serious infections.[195] Over the course of 1 year, none of the children in either arm developed a serious infection.

Combination of 6-Mercaptopurine and Prednisone Versus Prednisone Alone

One RCT of 55 children reported on serious infections (Table 60; Appendix D, Evidence Table 24).[192] Over the course of the 18-month study, one of 27 children, receiving 1.5 mg/kg per day of 6-mercaptopurine and prednisone taper, developed an intra-abdominal abscess. None of 28 children receiving a prednisone taper alone developed a serious infection.

Table 60. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of serious infections

Comparison	Type of Infection	Type of Studies	Number of Studies	Results	Conclusions	Strength of Evidence
Infliximab (maintenance vs. episodic therapy)	Serious infection	RCT	1	0/18 maintenance 0/13 episodic	Neither favored	Low
6-Mercaptopurine and prednisone vs. prednisone alone	Intra-abdominal abscess	Randomized controlled trial	1	1/27 6-mercaptopurine 0/28 placebo	Neither favored	Low

RCT = randomized controlled trial

Note: We defined the strength of the evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Tuberculosis

No studies meeting our inclusion criteria reported on tuberculosis rates in children with Crohn's disease.

Other Infections

Four studies of 241 children with Crohn's disease[190,191,195,198] reported other infections during the course of their study (Table 61; Appendix D, Evidence Table 24). All but one study[195] compared some combination of corticosteroids. Two studies[191,198] of 153 patients reported herpetic infections, all three of which occurred only in patients taking prednisone; none occurred in patients taking budesonide. One study[190] on pharyngitis (48 patients) reported that two cases of pharyngitis in 22 patients in the budesonide treatment group, and one case in 26 patients in the prednisone treatment group.

Infliximab Maintenance Versus Episodic Therapy

One study[195] of 40 pediatric patients reported that there was no difference in infections (viral upper airway infections, gastroenteritis, herpes simplex lip infection, axillary bacterial abscess) between maintenance versus episodic therapy groups. They study did not provide a breakdown by treatment group.

Budesonide Versus Prednisolone

One RCT[190] of 48 pediatric patients with mild-to-moderate Crohn's disease, treated children with either budesonide or prednisolone. Over the 8-week course of the study, one of the 26 children in the 1 mg/kg per day prednisolone taper treatment group developed pharyngitis, compared with two of the 22 children in the 9 mg per day budesonide taper treatment group.

Budesonide Versus Prednisone

One retrospective cohort study[198] of 120 pediatric patients with mild-to-moderate Crohn's disease, reviewed records of patients treated with either prednisone or budesonide. The study found two of the 58 children in the prednisone treatment group developed herpetic infections, compared with zero of the 62 children in the budesonide treatment group. There was no difference in herpetic infection rates between the two groups.

Combination of Budesonide and Mesalamine Versus the Combination of Prednisone and Mesalamine

One RCT,[191] of 33 pediatric patients with mild-to-moderate Crohn's disease, treated children with either 3 to 4 g per day of mesalamine and a 40 mg-per-day prednisone taper, or 3 to 4 g per day of mesalamine and a 9 mg-per-day budesonide taper. Over the 12-week course of the study, one of 14 children in the mesalamine and prednisone treatment group developed a herpetic infection, compared with zero of 19 children in the mesalamine and budesonide treatment group. There was no difference in herpetic infection rates between the two groups.

Table 61. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of other infections

Comparison	Type of Infection	Type of Studies	Number of Studies	Results	Conclusions	Strength of Evidence
Budesonide vs. prednisolone	Pharyngitis	RCT	1[190]	2/22 budesonide 1/26 prednisone	Not statistically significant	Moderate
Budesonide vs. prednisone	Herpetic infection	Retrospective cohort study	1[198]	0/62 budesonide 2/58 prednisone	Neither favored	Low
Combination budesonide + mesalamine vs. combination prednisone + mesalamine	Herpetic infection	RCT	1[191]	0/19 budesonide + mesalamine 1/14 prednisone + mesalamine	Neither favored	Low

RCT = randomized controlled trial

Note: We defined the strength of the evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Infusion- and Injection-Site Reactions

No studies meeting our inclusion criteria reported infusion- or injection-site reactions in children with Crohn's disease.

Bone Fractures

No studies meeting our inclusion criteria reported bone fractures in children with Crohn's disease.

Height Change

Seven studies of 492 children reported on the effects on height (Table 62; Appendix D, Evidence Table 24).

Infliximab Maintenance Versus Episodic Therapy

One RCT of 40 children,[195] comparing z-score for height and absolute height gain, randomized patients who went into remission after induction infliximab to receive maintenance dosing of infliximab versus episodic dosing for patients who relapse. The study followed patients for 50 weeks after randomization. Patients in the maintenance arm improved their z-score from -1.5 to -0.6, compared with an improvement from -1.4 to -1.0 in the episodic therapy group ($P < 0.001$). Absolute height gain was 6.9 and 4.3 cm, respectively.

Combination of 6-Mercaptopurine and Prednisone Versus Prednisone Alone

One RCT of 55 children[192] compared the linear growth of children treated with 1.5 mg/kg per day of 6-mercaptopurine and prednisone taper versus those who were treated with a prednisone taper alone. This study found no significant difference in linear growth between the two groups at 6, 12, or 18 months. From 0 to 6 months, the 6-mercaptopurine group (n=26) grew an average of 3.4 cm, and the placebo group (n=25) grew an average of 1.9 cm (P=0.06). From 6 to 12 months, the 6-mercaptopurine group (n=23) grew an average of 0.7 cm, and the placebo group (n=24) grew an average of 1.3 cm (P=0.4). From 12 to 18 months, the 6-mercaptopurine group (n=23) grew an average of 2.8 cm, and the placebo group (n=24) grew an average of 2.3 cm (P=0.5). Overall, from 0 to 18 months, the 6-mercaptopurine group (n=23) grew an average of 6.8 cm, and the placebo group (n=24) grew an average of 5.3 cm (P=0.3).

Prednisone Versus Placebo

Four studies[196,197,199,200] of 277 children found mixed results when comparing the effect of prednisone versus placebo on linear growth in children. One study found children who had taken prednisone were shorter than those who had not taken prednisone, one study found that children who had taken prednisone were taller than those who had not taken prednisone, and two studies found no difference in height between children who had taken prednisone and those who had not.

One prospective cohort study of 17 children[196] compared the linear growth of nine boys with Crohn's disease who were treated with alternate day prednisone (0.3 mg per kg) for longer than 3 months, with eight boys with Crohn's disease who had not been treated with alternate day prednisone for longer than 3 months. At the end of 2 years, both groups showed similar linear growth.

One retrospective cohort study[200] looked at 135 children with an early onset of Crohn's disease. This study asked adults about their growth and medication use (men with onset of symptoms before age 22 years, and women with onset of symptoms before age 18 years). Eight

children had received corticosteroids before puberty and 19 children had received corticosteroids during puberty. Children who had received corticosteroids during puberty were significantly shorter than those who had not (P=0.005). This study also found that children with disease onset during puberty who had received corticosteroids were significantly shorter than those with disease onset during puberty that had not received corticosteroids (P=0.03).

One prospective cohort study[197] looked at 47 pediatric patients with either Crohn's disease (n=18) or ulcerative colitis (n=29). This study found no significant difference in height standard deviation score (HSDS) or the height velocity standard deviation score (HVSDS) between those children who had received prednisone, compared with those children who had not received prednisone. The HSDS for children treated with prednisone was -0.50 at diagnosis, -0.47 after 1 year, -0.24 after 2 years, -0.10 after 3 years, and +0.00 after 4 years. The HSDS for children not treated with prednisone was -0.20 at diagnosis, -0.31 after 1 year, -0.13 after 2 years, -0.09 after 3 years, and +0.13 after 4 years. The HVSDS for children treated with prednisone was -1.20 at diagnosis, +0.29 after 1 year, +0.87 after 2 years, +1.47 after 3 years, and +0.78 after 4 years. The HVSDS for children not treated with prednisone was -0.01 at diagnosis, -0.26 after 1 year, +0.63 after 2 years, +0.16 after 3 years, and +1.25 after 4 years.

One prospective cohort study[199] looked at 78 patients (ages 5 to 21 years) with Crohn's disease of varied severity and reported on height. This study performed a subgroup analysis on the 46 children who had completed four study visits, and found that children who had taken corticosteroids had a significantly lower height z-score than children who had not taken corticosteroids.

Budesonide Versus Prednisone

One retrospective cohort study[198] compared the post-remission linear growth of 41 of 120 children whose records included height measures. The children had mild-to-moderate Crohn's disease and had received either prednisone or budesonide for at least 2 weeks. This study found no significant difference in the change of height percentile at 6 months between those children who had taken prednisone, compared with those children who had taken budesonide.

Table 62. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of height change

Comparison	Height Measure	Type of Studies	Number of Studies	Results	Conclusions	Strength of Evidence
Infliximab (maintenance vs. episodic therapy)	Height z-score	RCT	1[195]	+0.9 maintenance +0.4 episodic	$P < 0.001$	Low
Infliximab (maintenance vs. episodic therapy)	Linear growth (cm)	RCT	1[195]	6.9 maintenance 4.3 episodic	$P < 0.015$	Low
6-Mercaptopurine vs. placebo	Linear growth (cm)	Randomized controlled trial	1[192]	6.8 6-mercaptopurine 5.3 placebo	$P=0.3$	Low
Prednisone vs. placebo	Linear growth over 2 years (cm)	Prospective cohort study	1[196]	9.1 prednisone 10.3 placebo	NR	Low
Prednisone vs. placebo	Height (cm)	Retrospective cohort study	1[200]	NR	$P=0.005$	Low
Prednisone vs. placebo	HSDS	Prospective cohort study	1[197]	+0.00 prednisone +0.13 placebo	No difference	Low
Prednisone vs. placebo	HVSDS	Prospective cohort study	1[197]	+0.78 prednisone +1.25 placebo	No difference	Low
Corticosteroids vs. placebo	Height z-score	Retrospective cohort study	1[199]	Beta-coefficient = -0.63; 95% CI, -1.00 to -0.28	$P=0.0005$	Low
Budesonide vs. prednisone	Change in height percentile	Retrospective cohort study	1[198]	+0.25 budesonide -2.35 prednisone	$P=0.1$	Low

cm = centimeter; HSDS = height standard deviation score; HVSDS = height velocity standard deviation score; NR = not reported
Note: We defined the strength of the evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Weight Change

Two studies[198,199] of 198 children reported on the outcome of weight (Table 63; Appendix D, Evidence Table 24).

Infliximab Versus Placebo

One prospective cohort study of 78 children with Crohn's disease of varied severity[199] reported on the interaction of body mass and height. This study performed a subgroup analysis on the 46 children who had completed four study visits, and found that children who had taken infliximab had a significantly higher lean mass–height z-score than children who had not taken infliximab. This study also found that children who had taken infliximab had a significantly higher fat mass–height z-score than children who had not taken infliximab.

Infliximab Maintenance Versus Episodic Therapy

One RCT of 40 children,[195] comparing absolute weight gain, randomized patients who went into remission after induction infliximab to receive maintenance dosing of infliximab versus episodic dosing for patients who relapsed. Patients were followed for 50 weeks after randomization. Patients in the maintenance arm had an absolute mean weight gain of 4.3 +/- 5.4 kg, compared to -0.1 +/- 5.7 kg in the episodic therapy group ($P < 0.001$).

Methotrexate Versus Placebo

The above cohort study[199] also reported that children who had taken methotrexate had a significantly higher fat mass–height z-score than children who had not taken methotrexate.

Corticosteroids Versus Placebo

The above cohort study[199] also reported that children who had taken corticosteroids had a significantly higher fat mass–height z score than those who had not taken corticosteroids.

Budesonide Versus Prednisone

One retrospective cohort study of 120 children[198] looked at pediatric patients with mild-to-moderate Crohn's disease. This study looked at weight loss or gain in children who had received treatment with either prednisone or budesonide. After reviewing patient records, they found that those children who had received prednisone gained significantly more weight than those children who had received budesonide after 8 weeks.

Table 63. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of weight change

Comparison	Weight Measure	Type of Studies	Number of Studies	Results	Conclusions	Strength of Evidence
Infliximab vs. placebo	Lean mass – height z-score	Case-control study	1[199]	Beta-coefficient, 0.30; 95% CI, 0.02 to 0.58	$P < 0.05$	Low
Infliximab vs. placebo	Fat mass – height z-score	Case-control study	1[199]	Beta-coefficient, 0.29; 95% CI, 0.06 to 0.52	$P < 0.05$	Low
Infliximab (maintenance vs. episodic therapy)	Weight gain (kg)	RCT	1[195]	4.3 maintenance -0.1 episodic	*$P < 0.05$*	Low
Methotrexate vs. placebo	Fat mass – height z-score	Case-control study	1[199]	Beta-coefficient, 0.30; 95% CI, 0.04 to 0.56	$P < 0.05$	Low
Corticosteroids vs. placebo	Fat mass – height z-score	Case-control study	1[199]	Beta-coefficient, 0.69; 95% CI, 0.12 to 1.26	$P < 0.05$	Low
Budesonide vs. prednisone	Weight gain (kg)	Retrospective cohort study	1[198]	+2.54 kg budesonide +4.6 kg prednisone	$P < 0.05$	Low

CI = confidence interval; kg = kilogram; RCT = randomized controlled trial

Note: We defined the strength of the evidence as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Study Quality

For serious infections (intra-abdominal abscess), the quality of the one RCT[192] was good due to adequate allocation sequence and concealment, adequate blinding, and complete outcome data (Appendix D, Evidence Table 25). A pharmaceutical company supported this study.[192]

For other infections (herpetic infections), the quality of one RCT[191] was poor because the allocation sequence and concealment, blinding technique, and completeness of outcome data were unclear. The quality of the retrospective cohort study[198] was fair due to good descriptions of outcomes, interventions, and patient characteristics.

For other infections (pharyngitis), the quality of one study[202] was good due to adequate allocation sequence and concealment, adequate blinding, and complete outcome data.

For height change, seven studies[192,195-200] had variable quality. The quality of one RCT[192] was good due to adequate allocation sequence and concealment, adequate blinding, and complete outcome data. One RCT[195] had poor quality because of absence of blinding. Two cohort studies[198,199] had fair quality due to good descriptions of outcomes and patient characteristics. Two other cohort studies[196,200] had poor quality due to study population selection bias. A pharmaceutical company supported one study.[192]

For weight change, two cohort studies[198,199] had fair quality with good descriptions of outcomes and patient characteristics. The one RCT[195] had poor quality because of absence of blinding.

Discussion

Key Findings and Clinical Implications

The purpose of this review was to compare the effectiveness and safety of biologics, immunomodulators, corticosteroids, and aminosalicylates in the treatment of Crohn's disease.

This section provides a summary of the findings, compares the findings with related systematic reviews, lists limitations of the data and the approach, and suggests future directions.

Summary of Key Findings for Adults

Key Question 1. Induction of Remission Measured in Terms of Disease Activity

Of the 78 comparisons with evidence, four resulted in high strength of evidence and 20 resulted in moderate strength of evidence (see Table 6). Consistency of effect was based on a medication comparison having the same direction of effect for both disease activity (across evaluable time points) and for at least one other outcome.

Infliximab was found to have the greatest consistency across the outcomes of disease activity, mucosal healing, fistula healing, and IBDQ when compared with placebo (based on two trials). It was also the only comparison that included a high SOE for a given outcome (fistula healing).

Other consistent comparisons that included at least one outcome with a moderate SOE included: infliximab was favored over azathioprine for disease activity and mucosal healing (based on one trial), the combination of infliximab and azathioprine was favored over azathioprine alone for disease activity and mucosal healing (based on two trials), and the combination of infliximab and azathioprine was favored over infliximab alone for disease activity, mucosal healing (based on one trial). In all three of these comparisons, IBDQ was not different between treatment arms.

Several placebo-controlled trials were also found to be consistent across outcomes. However, all the individual outcomes were rated as low SOE. The following interventions were favored over placebo: prednisone/6-methylprednisolone for disease activity and fistula healing (based on two trials), sulfasalazine for disease activity and fistula healing (based on two trials), and thiopurine for disease activity and fistula healing (based on one trial). Thiopurines and placebo did not differ in corticosteroid reduction and IBDQ.

For head-to-head trails, the following comparisons were consistent across outcomes with all individual outcomes rated as low SOE: combination of infliximab and methotrexate favored over infliximab alone for disease activity, steroid reduction, and IBDQ (based on one trial), and corticosteroids favored over thiopurines for disease activity and fistula healing (based on one trial).

Key Question 2. Maintenance of Remission Measured in Terms of Disease Activity

Of the 55 comparisons with evidence, none resulted in high strength of evidence and 11 resulted in moderate strength of evidence (see Table 21). Consistency of effect was based on a medication comparison having the same direction of effect for both disease activity (across evaluable time points) and for at least one other outcome.

Infliximab was found to have the greatest consistency across outcomes when compared with placebo for disease activity, mucosal healing, hospitalization, surgery, corticosteroid reduction, fistula healing, and IBDQ (based on three trials). Adalimumab was also favored over placebo for the outcomes of disease activity, hospitalization, surgery, and corticosteroid reduction (based on two trials); however, adalimumab was not favored over placebo for IBDQ.

Other consistent comparisons with at least one outcome rated as moderate SOE included: natalizumab favored over placebo for disease activity, steroid reduction, and IBDQ (based on one trial), azathioprine over budesonide for disease activity and mucosal healing (based on one trial), and budesonide over aminosalicylates for disease activity and IBDQ (based on one trial). Thiopurines were consistently favored over placebo for disease activity and corticosteroid reduction (based on four trials); however, all the outcomes were rated as low SOE.

Key Question 3. Safety

The SOE for nearly every comparison was graded as insufficient or low for safety-related outcomes. Frequently, comparisons graded with low SOE did not favor either medication compared. We graded comparisons as high SOE for only two safety comparisons, both from a single RCT, and both for an outcome of infusion and injection-site reactions. One comparison favored oral azathioprine with placebo infusion over intravenous infliximab, and another favored placebo over intravenous azathioprine.

Key Question 4. Patient-Reported Outcomes After Intestinal Resection

We included one RCT that measured a patient-reported outcome (Inflammatory Bowel Disease Questionnaire [IBDQ]) after intestinal resection and no difference was found between azathioprine and mesalamine. Although the data were limited, patient-reported outcomes after intestinal resection had not been addressed in a previous systematic review.[19]

Summary of Key Findings for Pediatrics

Ten studies were identified that reported on pediatric outcomes. The SOE was graded as low or insufficient to support any medication to induce or maintain remission in pediatric Crohn's disease for KQ1 and KQ2. No pediatric study reported on a serious adverse event such as mortality, progressive multifocal leukoencephalopathy, lymphoma, or other cancers. No pediatric study reported on a patient-reported outcome.

Applicability of Remission Results for Adults

Populations

- The majority of trials enrolled only Caucasians. African Americans, Hispanics, and Asians were not well represented.
- The median age at enrollment in most trials ranged between 25 and 40 years of age. Older persons were not well represented.
- Mean duration of disease, with the exception of a few trials,[45,48] was often greater than 10 years. Understanding the effectiveness of medications on the natural history of disease, such as the proposed benefits of top-down compared with step-up therapy, requires trials with recently diagnosed patients.

Intervention

- The doses and delivery methods of medications used sometimes differed across trials.

Comparisons

- There were very few direct comparisons of medications.

Outcomes

- Improvement in CDAI score is non-specific for Crohn's disease. CDAI score also varies with irritable bowel-type symptoms.[203] This may explain why many of the studies had high placebo rates of response and remission.
- Few trials reported on outcomes other than the CDAI. Some outcomes such as mucosal healing and fistula response were frequently analyzed as subgroup analyses and not as primary endpoints.

Timing

- There were very few trials that evaluated endpoints beyond 1 year. For a lifelong disease, the amount of time represented by these trials is very short.

Setting

- Most trials took place in North America and Europe. Thus, results may not necessarily be transferred to other locales.

Other—Conflict of Interest

- In KQ1, of the 36 trials (82 percent) trials that reported on conflicts of interest, 86 percent received pharmaceutical support with 56 percent having pharmaceutical company employed co-authors. For the 25 trials (69 percent) reporting on conflicts of interest for KQ2, the figures were 80 percent and 44 percent, respectively.

Applicability of Safety Results for Adults

The non-RCTs that reported safety outcomes of interest did not have as many eligibility criteria as the RCTs. Very few non-RCTs had disease activity or disease location exclusions. Because observational studies made fewer restrictions on the patient populations, they likely apply to Crohn's disease patients of all disease severities. Despite the differences in eligibility criteria, the RCTs and observational studies did not have meaningful differences in safety signals. The studies that included all IBD patients had similar safety findings as studies that included only Crohn's disease patients or those studies that reported results for both Crohn's disease and IBD patients.

Pediatric Applicability

The applicability of these studies was limited because of the small number of studies, with few participants per study. Also, very few medications were compared. The longest RCT had only 18 months of followup and the longest prospective study had less than 4 years of followup.

Comparison With Existing Guidelines and Systematic Reviews

Several clinical guidelines have been developed based on comprehensive literature searches combined with expert opinion[8,204-206] and numerous systematic reviews comparing treatments for Crohn's disease have been performed.[11,17,207-216] Although the findings of our systematic review are consistent with most of the published guidelines and reviews, we note a few differences in the methodology, strength of evidence and the findings. Our methodologic approach:

- Searched publication databases without year of publication restrictions
- Considered a clinically meaningful threshold to identify differences in treatments outcomes rather than relying on statistical significance
- Abstracted information at multiple clinically relevant time points instead of focusing on the last time point reported
- Included multiple outcomes associated with treatment aimed at achieving remission, instead of using the Crohn's Disease Activity Index to measure response or remission and some safety events with occasional use of endoscopic healing and other outcomes
- Specifically included mortality, progressive multifocal leukoencephalopathy, hepatosplenic-T-cell lymphoma, other lymphomas and cancers, and serious infections and infusion reactions, whereas many reviews consider more generic categories as reported in trials such as overall adverse events, serious adverse events, and infections
- Required that all studies have a comparison group, allowed head-to-head trials, and allowed observational studies for safety outcomes
- Did not include antibiotics and enteral nutrition as comparators of interest
- Did not consider disease location in assessments in contrast with the clinical guidelines which often recommend different initial treatments depending on the location and extent of disease
- Reviewed and graded the strength of evidence separately for safety and efficacy compared with considering the balance between safety and efficacy in a single grade of the SOE.

The strength of evidence was generally graded the same or lower in our review compared with others. This difference might be due to the fact that the other studies pooled all comparisons regardless of study or statistical heterogeneity, whereas we only pooled studies when we felt studies were comparable and statistical heterogeneity was low, frequently leading to inconsistent and imprecise evidence.

The major difference in findings between this review and others pertains to infliximab. Other reviews found that all TNF-alpha inhibitors are efficacious at inducing and maintaining remission. We also would come to this conclusion if we based results on the meta-analysis of TNF-alpha inhibitors that we performed at week 2 after induction. However, when we consider the clinically meaningful threshold for a difference in treatment effects and examine the consistency of efficacy across the different outcomes of interest, infliximab is the only TNF-alpha inhibitor that is consistently favored over placebo at multiple time points and for multiple outcomes.

Limitations

Our review has a number of limitations, most of which are related to the limitations of the available data. The major limitations in the data were:

- Lack of head-to-head studies
- Study heterogeneity limited meta-analyses
- Inability to isolate patients with moderate-to-severe Crohn's disease from those with mild disease
- Potential measurement error as a result of abstracting data from figures
- Limited reporting of results for the subgroup populations of interest
- Short trial durations
- Difficulty interpreting studies that compared the same drug delivered at different time points (i.e., on-demand versus maintenance therapy for biologics).

The major limitations in our review methods were:

- No standard existed to select a threshold of 10 percent to define a clinically meaningful difference between comparison groups
- Trouble separating induction from maintenance studies (i.e., some studies that met criteria for induction had endpoints of 26 weeks or longer).

Limitations in the Data

Lack of Head-to-Head Studies

There was a paucity of head-to-head studies, particularly for maintenance trials. Practitioners deciding between two maintenance therapies in patients with Crohn's disease need to be aware that little evidence exists to make evidence-based treatment decisions. On initiation of this project, we knew that there were few head-to-head trials in the literature. However, we felt that it was important to systematically document the literature in order to better understand the gaps. Additionally, we had intended to perform a network meta-analysis in order to indirectly compare drug classes that have not been compared in the literature to help address the evidence gap resulting from direct comparisons of treatments. However, study heterogeneity and sparse data (few studies addressed each comparison of interest) prevented a network meta-analysis.

Study Heterogeneity Limited Meta-Analyses

One common source of heterogeneity was the variation in study designs, especially for the maintenance trials. For example, the studies of maintenance therapy varied in how they identified a patient's eligibility for randomization to the study arms. Some of the maintenance trials had a run-in period where all patients received the active study medication followed by randomization of patients with a response to the study drug. Other maintenance trials enrolled patients that had a response to the study medication of interest in a previous remission trial or who had long-term inactive disease based on clinic visits.

An additional source of heterogeneity was related to the baseline characteristics of the enrolled patients, particularly with use of previous and concurrent medication to treat Crohn's disease. For example, many TNF-alpha inhibitor studies included both TNF-alpha inhibitor exposed and naïve patients. Additionally, maintenance studies varied with regard to the use of corticosteroids and other medications at randomization and throughout the trial.

Another source of heterogeneity was the use of varied definitions of remission. Among the studies, there were different disease activity scales and different disease activity scale thresholds for remission. For example, some studies required a change in corticosteroid dose and a change in disease activity to define remission whereas other studies considered remission a change in disease activity regardless of a decrease in corticosteroid dose.

We also found heterogeneity in study duration, especially for the safety outcomes where results ranged from trial reports at 2 weeks to observational studies of over 5 years. Finally, we found it difficult to compare studies published prior to the 2000s and after as the study designs and reporting of the design details differed substantially. We often rated the newer studies as having lower risk of bias.

Inability To Isolate Patients With Moderate-to-Severe Crohn's Disease

Our original intention was to look at patients with moderate-to-severe Crohn's disease. However, we found that most induction of remission trials included patients with any active disease, including those with mild disease. Identifying patients with moderate-to-severe disease was even more of a challenge with maintenance of remission trials, where most studies randomized patients while in remission, so it was impossible to ascertain the original disease severity.

Potential for Measurement Error for Time Points Other Than the Primary Outcome of Interest

Because we included clinically meaningful time points of interest that may not have corresponded to the primary outcome of interest, we frequently abstracted data for these time points from figures. The article figures did not consistently display time points of assessment as reported in the study design and rarely included measures of variation for each time point. The lack of information on the variation of an outcome was especially pronounced for reporting of the IBDQ scores, and prevented us from performing statistical analyses of the difference in IBDQ scores between treatment groups.

Subgroup Analyses Were Limited

Most of the subgroup population analyses were limited by poor reporting of statistical interaction terms. This becomes particularly important as many studies allowed patients to use Crohn's medications at randomization and throughout the study as long as the medication dose remained stable.

Short Trial Durations

The maintenance of remission evidence was limited to 2 years (104 weeks), a very brief period of time for a chronic condition. For many comparisons, especially the newer trials of biologics, the maximum trial duration was 1 year. For instance, the azathioprine and 6-methylprednisolone were found to consistently outperform placebo at 1 and 2 years with azathioprine also reducing the need for corticosteroids at 6 months (the last reported time point available). However, the evidence for the other efficacious agents, natalizumab and infliximab, is limited to 1 year. The limited duration of trials for a relapsing and remitting chronic condition limits the information that health care providers can share with their patients regarding the efficacy of medications to treat Crohn's disease.

Inclusion of Studies That Evaluated the Same Drug at Different Points in Time

Per our methods, we excluded studies that compared different doses of the same medication unless a comparison to an additional medication was made. However, we came across TNF-alpha inhibitor maintenance trials[87,95,217] that were intended to compare episodic (on-demand) treatment with regularly scheduled treatment to mimic clinical practice. Additionally, the one study that directly addressed step-up versus top-down therapy examined different time points for introducing immune-based therapies such as thiopurines and infliximab.[48] As a result, patients in both study arms may have received both classes of medications. Although these studies presented challenges in interpretation compared with more traditional trial designs, they were included because they are very applicable to clinical practice.

Other Limitations of the Data

Other limitations included: (a) most trials were sponsored by the manufacturer of the medications, which has been associated with the reporting of results that are more favorable than studies not supported by industry;[218] (b) our analyses indicated the presence of publication bias as measured by Begg's and Egger's tests, especially for corticosteroids and aminosalicylates.

Limitations in Our Review Method

No Standard Existed To Define a Clinically Meaningful Difference Between Comparison Groups

When we assessed the efficacy and safety of the medications, we sought to consider whether differences were clinically meaningful, instead of focusing on statistical significance. In the absence of a standard for a clinically meaningful absolute difference in remission rate for Crohn's disease, we chose a relatively low absolute difference of 10 percent as the threshold for identifying a clinically meaningful difference in the induction and maintenance of remission outcomes. An example of this difference is that if 50 percent of placebo participants were in remission, 60 percent or more active medication participants had to be in remission to label the effect clinically meaningful. Although individual studies may have been designed to have only enough statistical power to detect larger differences in remission rates, we believed it was important to keep in mind that patients with the debilitating symptoms of Crohn's disease might want to know whether a treatment could provide a modest 10 percent absolute increase in their chance at remission. If we had used a higher threshold for identifying a clinically meaningful difference in remission rates, fewer differences would have been considered clinically meaningful in this report.

Because many of the adverse events are very rare, we did not assign a threshold for a clinically meaningful difference for safety. We relied on a statistically significant difference instead, which resulted in only two comparisons graded as high SOE, both with a greater than 10 percent absolute difference between the treatment groups for the outcome of infusion- and injection-site reactions.

Trouble Separating Induction From Maintenance Studies

Our inclusion criteria arbitrarily defined eligibility for induction if patients had active disease at randomization and eligibility for maintenance if participants had inactive disease at randomization. However, we acknowledge that time points for induction trials after 12-16 weeks

are more consistent with maintenance studies. The alternative was to present the later time points of the induction trials with the maintenance trials, although we thought this would lead to unnecessary repetition of study and population characteristics.

Other Limitations

Other limitations included:

- We excluded 223 non-English articles.
- We only included information from peer-reviewed journals (excluding information reported in abstract-only form which has been documented to differ from the subsequent peer-reviewed article).[219,220]
- We did not examine certain classes of medications including antibiotics or probiotics. We also did not examine other therapies such as enteral or parenteral feeding, as we felt this was out of the scope of this systematic review.

Future Research Needs

We found many gaps in the literature on medical therapy for Crohn's disease. Most studies evaluated white adults under 50 years of age who often had been diagnosed at least 10 years prior to the start of the study. Further attention needs to be given to non-white populations, pediatric patients, older adults (over 50 years of age), newly diagnosed patients or those who have been on few medications for Crohn's disease, and patients with severe Crohn's disease (including those with complications including abscess and fistula formation).

With regard to intervention and study design, we found few head-to-head trials involving TNF-alpha inhibitor agents and natalizumab. We also need further studies to evaluate the introduction of immunosuppressive therapy early in the disease course (top-down approach) versus more traditional step-up medication strategies as many physicians are beginning to use top-down treatment in the absence of strong evidence to support this treatment paradigm.

Researchers need to design safety studies so they have sufficient power to detect clinically meaningful differences between medications. Randomized trials should also be adequately powered to compare specific, important safety events if they intend to report on safety outcomes. Keeping in mind the practical limitations of acquiring investigator-initiated funding, more trials that are independent of industry input in the design, analysis, interpretation, and design to publish, but with industry sponsorship, combined with investigators who are not paid consultants of industry could help minimize conflicts of interest.

In terms of outcomes, more studies need to evaluate outcomes beyond disease activity, including mucosal healing, rates of hospitalization and surgery, fistula healing, and patient-reported outcomes (including post-surgical studies). Given that Crohn's disease may last many decades, we should extend outcomes for RCTs on maintenance therapy beyond 2 years. Observational studies for safety should be sufficiently long to observe safety outcomes, such as cancer, that may not manifest themselves for many years.

Conclusions

Infliximab was the only medication that was found to be consistently effective compared with placebo across a number of outcomes for both induction and maintenance of remission. For most medication comparisons, data was lacking on outcomes other than disease activity indices. In children, the evidence was insufficient to permit assessment of the consistency of medication

efficacy across outcomes. The quality of the safety evidence was poor due to poor reporting of the methods in trials and poor confounding control in observational studies. No strong or previously unidentified signals of harm were identified. Comparing Crohn's disease medications directly using pragmatic clinical trials will help to understand the effectiveness of medications in clinical practice using outcomes other than the Crohn's Disease Activity Index.

References

(list applies to full report and appendixes)

1. Loftus EV Jr, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. Aliment Pharmacol Ther 2002; 16(1):51-60. PMID: 11856078
2. Bousvaros A, Sylvester F, Kugathasan S, et al. Challenges in pediatric inflammatory bowel disease. Inflammatory Bowel Dis. 2006; 12(9):885-913. PMID: 16954808.
3. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med 2009; 361(21):2066-78. PMID: 19923578
4. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. SCAND. J. GASTROENTEROL. 1995; 30(7):699-706. PMID: 7481535.
5. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol 2010; 105(2):289-97. PMID: 19861953
6. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. 1932. Mt Sinai J Med 2000; 67(3):263-8. PMID: 10828911
7. Korelitz BI. A history of immunosuppressive drugs in the treatment of inflammatory bowel disease: origins at The Mount Sinai Hospital. Mt Sinai J Med 2000; 67(3):214-26. PMID: 10828907
8. Lichtenstein GR, Hanauer SB, Sandborn WJ et al. Management of Crohn's disease in adults. Am. J. Gastroenterol. 2009; 104(2):465-83. PMID: 19174807.
9. Institute of Medicine. Initial National Priorities for Comparative Effectiveness Research. Report Brief [Web Page]. June 2009; Available at www.hrsonline.org/Policy/LegislationTakeAction/upload/CER-report-brief-6-22-09.pdf. Accessed June 2011.
10. Shergill AK, Terdiman JP. Controversies in the treatment of Crohn's disease: the case for an accelerated step-up treatment approach. World J Gastroenterol 2008; 14(17):2670-7. PMID: 18461652
11. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut 2005; 54 (8):1121-5. PMID: 16009685
12. Vermeire S, van Assche G, Rutgeerts P. Review article: Altering the natural history of Crohn's disease--evidence for and against current therapies. Aliment Pharmacol Ther 2007; 25 (1):3-12. PMID: 17229216
13. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006; 130(3):935-9. PMID: 16530531
14. Lichtenstein GR, Sbreu MT, Cohen R, Tremaine W. [American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease]. Rev Gastroenterol Mex 2006; 71(3):351-401. PMID: 17140062
15. Strong SA, Koltun WA, Hyman NH et al. Practice parameters for the surgical management of Crohn's disease. Dis. Colon Rectum 2007; 50(11):1735-46. PMID: 17690937.
16. Rozin AP, Hasin T, Toledano K, Guralnik L, Balbir-Gurman A. Seronegative polyarthritis as severe systemic disease. Neth J Med 2010; 68(6):236-41. PMID: 20558853. PMID: 20558853.
17. Prefontaine E, Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2010; 6:CD000545. PMID: 20556747

18. Szwebel TA, Casadevall M, Chosidow O et al. [Atypical recurrent aseptic cutaneous abscesses as the presenting manifestation of Crohn's disease.]. Rev Med Interne 2010. PMID: 20541855

19. Doherty G, Bennett G, Patil S, Cheifetz A, Moss AC. Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst Rev 2009; (4):CD006873. PMID: 19821389

20. Higgins J. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2.The Cochrane Collaboration, 2008.

21. Guide for Conducting Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality, 2007.

22. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998; 52(6):377-84. PMID: 9764259

23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7(3):177-88. PMID: 3802833

24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414):557-60. PMID: 12958120

25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50(4):1088-101. PMID: 7786990

26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315(7109):629-34. PMID: 9310563

27. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut 1989; 30(7):983-9. PMID: 2668130

28. Irvine EJ. Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality-of-life instrument for adult patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1999; 28(4):S23-7. PMID: 10204520

29. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 2007; 26(1):53-77. PMID: 16596572

30. Hernandez AV, Walker E, Ioannidis JP, Kattan MW. Challenges in meta-analysis of randomized clinical trials for rare harmful cardiovascular events: the case of rosiglitazone. Am Heart J 2008; 156(1):23-30. PMID: 18585493

31. Owens DK, Lohr KN, Atkins D et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol 2010; 63(5):513-23. PMID: 19595577

32. Targan SR, Feagan BG, Fedorak RN et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. Gastroenterology 2007; 132(5):1672-83. PMID: 17484865

33. Sandborn WJ, Colombel JF, Enns R et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med 2005; 353(18):1912-25. PMID: 16267322

34. Gordon FH, Lai CW, Hamilton MI et al. A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 integrin in active Crohn's disease. Gastroenterology 2001; 121(2):268-74. PMID: 11487536

35. Sands BE, Kozarek R, Spainhour J et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. Inflamm Bowel Dis 2007; 13(1):2-11. PMID: 17206633

36. Guyatt G, Mitchell A, Irvine EJ et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989; 96(3):804-10. PMID: 2644154

37. Hanauer SB, Sandborn WJ, Rutgeerts P et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006; 130(2):323-33; quiz 591. PMID: 16472588

38. Sandborn WJ, Rutgeerts P, Enns R et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med 2007; 146(12):829-38. PMID: 17470824

39. Sandborn WJ, Feagan BG, Stoinov S et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007; 357(3):228-38. PMID: 17634458

40. Schreiber S, Rutgeerts P, Fedorak RN et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology 2005; 129(3):807-18. PMID: 16143120

41. Winter TA, Wright J, Ghosh S, Jahnsen J, Innes A, Round P. Intravenous CDP870, a PEGylated Fab' fragment of a humanized antitumour necrosis factor antibody, in patients with moderate-to-severe Crohn's disease: an exploratory study. Aliment Pharmacol Ther 2004; 20 (11-12):1337-46. PMID: 15606396

42. Sandborn WJ, Schreiber S, Feagan BG et al. Certolizumab Pegol for Active Crohn's Disease: A Placebo-Controlled, Randomized Trial. Clin Gastroenterol Hepatol 2011. PMID: 21642014

43. Targan SR, Hanauer SB, van Deventer SJ et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997; 337(15):1029-35. PMID: 9321530

44. Present DH, Rutgeerts P, Targan S et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999; 340(18):1398-405. PMID: 10228190.

45. Colombel JF, Sandborn WJ, Reinisch W et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010; 362(15):1383-95. PMID: 20393175

46. Lemann M, Mary JY, Duclos B et al. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. Gastroenterology 2006; 130(4):1054-61. PMID: 16618399

47. Schroder O, Blumenstein I, Stein J. Combining infliximab with methotrexate for the induction and maintenance of remission in refractory Crohn's disease: a controlled pilot study. Eur J Gastroenterol Hepatol 2006; 18(1):11-6. PMID: 16357613

48. D'Haens G, Baert F, van Assche G et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 2008; 371(9613):660-7. PMID: 18295023

49. D'haens G, Van Deventer S, Van Hogezand R et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology 1999; 116(5):1029-34. PMID: 10220494

50. Sandborn W, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. Cochrane Database Syst Rev 2000; (2):CD000545. PMID: 10796557

51. Reinisch W, Panes J, Lemann M et al. A multicenter, randomized, double-blind trial of everolimus versus azathioprine and placebo to maintain steroid-induced remission in patients with moderate-to-severe active Crohn's disease. Am J Gastroenterol 2008; 103(9):2284-92. PMID: 18671816

52. Mate-Jimenez J, Hermida C, Cantero-Perona J, Moreno-Otero R. 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. Eur J Gastroenterol Hepatol 2000; 12(11):1227-33. PMID: 11111780

53. Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. Gut 1995; 37(5):674-8. PMID: 8549944

54. Ewe K, Press AG, Singe CC et al. Azathioprine combined with prednisolone or monotherapy with prednisolone in active Crohn's disease. Gastroenterology 1993; 105(2):367-72. PMID: 8335191

55. Rankin GB, Watts HD, Melnyk CS, Kelley ML Jr. National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. Gastroenterology 1979; 77(4 Pt 2):914-20. PMID: 467943

56. Summers RW, Switz DM, Sessions JT Jr et al. National Cooperative Crohn's Disease Study: results of drug treatment. Gastroenterology 1979; 77 (4 Pt 2):847-69. PMID: 38176

57. Oren R, Moshkowitz M, Odes S et al. Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. Am J Gastroenterol 1997; 92(12):2203-9. PMID: 9399753

58. Ardizzone S, Bollani S, Manzionna G, Imbesi V, Colombo E, Bianchi Porro G. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. Dig Liver Dis 2003; 35(9):619-27. PMID: 14563183

59. Sandborn WJ, Tremaine WJ, Wolf DC et al. Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. North American Azathioprine Study Group. Gastroenterology 1999; 117(3):527-35. PMID: 10464128

60. Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med 1980; 302(18):981-7. PMID: 6102739

61. Rhodes J, Bainton D, Beck P, Campbell H. Controlled trial of azathioprine in Crohn's disease. Lancet 1971; 2(7737):1273-6. PMID: 4143532

62. Klein M, Binder HJ, Mitchell M, Aaronson R, Spiro H. Treatment of Crohn's disease with azathioprine: a controlled evaluation. Gastroenterology 1974; 66(5):916-22. PMID: 4597093

63. Feagan BG, Rochon J, Fedorak RN et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. N Engl J Med 1995; 332(5):292-7. PMID: 7816064

64. Malchow H, Ewe K, Brandes JW et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. Gastroenterology 1984; 86 (2):249-66. PMID: 6140202

65. Tremaine WJ, Hanauer SB, Katz S et al. Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. Am J Gastroenterol 2002; 97(7):1748-54. PMID: 12135030

66. Greenberg GR, Feagan BG, Martin F et al. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. N Engl J Med 1994; 331(13):836-41. PMID: 8078529

67. Bar-Meir S, Chowers Y, Lavy A et al. Budesonide versus prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. Gastroenterology 1998; 115(4):835-40. PMID: 9753485

68. Campieri M, Ferguson A, Doe W, Persson T, Nilsson LG. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. Gut 1997; 41(2):209-14. PMID: 9301500

69. Rutgeerts P, Lofberg R, Malchow H et al. A comparison of budesonide with prednisolone for active Crohn's disease. N Engl J Med 1994; 331(13):842-5. PMID: 8078530

70. Thomsen OO, Cortot A, Jewell D et al. A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. N Engl J Med 1998; 339(6):370-4. PMID: 9691103

71. Prantera C, Cottone M, Pallone F et al. Mesalamine in the treatment of mild to moderate active Crohn's ileitis: results of a randomized, multicenter trial. Gastroenterology 1999; 116(3):521-6. PMID: 10029609

72. Gross V, Andus T, Fischbach W et al. Comparison between high dose 5-aminosalicylic acid and 6-methylprednisolone in active Crohn's ileocolitis. A multicenter randomized double-blind study. German 5-ASA Study Group. Z Gastroenterol 1995; 33(10):581-4. PMID: 7502549

73. Martin F, Sutherland L, Beck IT et al. Oral 5-ASA versus prednisone in short term treatment of Crohn's disease: A multicentre controlled trial. Can J Gastroenterol 1990; 4(7):452-7.

74. Tromm A, Bunganic I, Tomsova E et al. Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. Gastroenterology 2011; 140(2):425-34.e1; quiz e13-4. PMID: 21070781

75. Singleton JW, Summers RW, Kern F Jr et al. A trial of sulfasalazine as adjunctive therapy in Crohn's disease. Gastroenterology 1979; 77(4 Pt 2):887-97. PMID: 38179

76. Rijk MC, van Hogezand RA, van Lier HJ, van Tongeren JH. Sulphasalazine and prednisone compared with sulphasalazine for treating active Crohn disease. A double-blind, randomized, multicenter trial. Ann Intern Med 1991; 114(6):445-50. PMID: 1671631

77. Tremaine WJ, Schroeder KW, Harrison JM, Zinsmeister AR. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. J Clin Gastroenterol 1994; 19(4):278-82. PMID: 7876505

78. Rasmussen SN, Lauritsen K, Tage-Jensen U et al. 5-Aminosalicylic acid in the treatment of Crohn's disease. A 16-week double-blind, placebo-controlled, multicentre study with Pentasa. Scand J Gastroenterol 1987; 22(7):877-83. PMID: 3313678

79. Singleton JW, Hanauer SB, Gitnick GL et al. Mesalamine capsules for the treatment of active Crohn's disease: Results of a 16-week trial. Gastroenterology 1993; 104(5):1293-301. PMID: 8482443.

80. Sandborn WJ, Feagan BG, Fedorak RN et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. Gastroenterology 2008; 135(4):1130-41. PMID: 18706417

81. Feagan BG, Sandborn WJ, Hass S, Niecko T, White J. Health-related quality of life during natalizumab maintenance therapy for Crohn's disease. Am J Gastroenterol 2007; 102(12):2737-46. PMID: 18042106

82. Colombel JF, Sandborn WJ, Rutgeerts P et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007; 132(1):52-65. PMID: 17241859

83. Sandborn WJ, Hanauer SB, Rutgeerts P et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007; 56(9):1232-9. PMID: 17299059

84. Schreiber S, Khaliq-Kareemi M, Lawrance IC et al. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med 2007; 357(3):239-50. PMID: 17634459

85. Rutgeerts P, D'Haens G, Targan S et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology 1999; 117(4):761-9. PMID: 10500056

86. Hanauer SB, Feagan BG, Lichtenstein GR et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002; 359(9317):1541-9. PMID: 12047962

87. Sands BE, Anderson FH, Bernstein CN et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004; 350(9):876-85. PMID: 14985485

88. Mantzaris GJ, Viazis N, Petraki K et al. A pilot study comparing hydrocortisone premedication to concomitant azathioprine treatment in preventing loss of response to infliximab. Eur J Gastroenterol Hepatol 2009; 21(9):1042-8. PMID: 20139856

89. Van Assche G, Magdelaine-Beuzelin C, D'Haens G et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology 2008; 134(7):1861-8. PMID: 18440315

90. Feagan BG, Panaccione R, Sandborn WJ et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. Gastroenterology 2008; 135(5):1493-9. PMID: 18848553

91. Rutgeerts P, Diamond RH, Bala M et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc 2006; 63 (3):433-42; quiz 464. PMID: 16500392

92. Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology 2005; 128(4):862-9. PMID: 15825070

93. Feagan BG, Yan S, Bala M, Bao W, Lichtenstein GR. The effects of infliximab maintenance therapy on health-related quality of life. Am J Gastroenterol 2003; 98(10):2232-8. PMID: 14572573

94. Rutgeerts P, Feagan BG, Lichtenstein GR et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004; 126(2):402-13. PMID: 14762776

95. Colombel JF, Sandborn WJ, Rutgeerts P et al. Comparison of two adalimumab treatment schedule strategies for moderate-to-severe Crohn's disease: results from the CHARM trial. Am J Gastroenterol 2009; 104(5):1170-9. PMID: 19352339

96. Loftus EV, Feagan BG, Colombel JF et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. Am J Gastroenterol 2008; 103(12):3132-41. PMID: 18853973

97. Sands BE, Blank MA, Patel K, van Deventer SJ. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. Clin Gastroenterol Hepatol 2004; 2(10):912-20. PMID: 15476155

98. Lemann M, Mary JY, Colombel JF et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. Gastroenterology 2005; 128(7):1812-8. PMID: 15940616

99. Willoughby JM, Beckett J, Kumar PJ, Dawson AM. Controlled trial of azathioprine in Crohn's disease. Lancet 1971; 2(7731):944-7. PMID: 4107900.

100. O'Donoghue DP, Dawson AM, Powell-Tuck J, Bown RL, Lennard-Jones JE. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. Lancet 1978; 2(8097):955-7. PMID: 81986

101. Vilien M, Dahlerup JF, Munck LK, Norregaard P, Gronbaek K, Fallingborg J. Randomized controlled azathioprine withdrawal after more than two years treatment in Crohn's disease: increased relapse rate the following year. Aliment Pharmacol Ther 2004; 19(11):1147-52. PMID: 15153167

102. Mantzaris GJ, Christidou A, Sfakianakis M et al. Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. Inflamm Bowel Dis 2009; 15(3):375-82. PMID: 19009634

103. Hirsh EH, Galambos JT, Armstrong H, Fincher M, Hersh T. Hepatic infarction in ulcerative colitis during pregnancy. Gastroenterology 1980; 78(3):571-5. PMID: 7351293

104. Rosenberg JL, Levin B, Wall AJ, Kirsner JB. A controlled trial of azathioprine in Crohn's disease. Am J Dig Dis 1975; 20(8):721-6. PMID: 1098449

105. Feagan BG, Fedorak RN, Irvine EJ et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. New Engl. J. Med. 2000; 342(22):1627-32. PMID: 10833208.

106. Hanauer S, Sandborn WJ, Persson A, Persson T. Budesonide as maintenance treatment in Crohn's disease: a placebo-controlled trial. Aliment Pharmacol Ther 2005; 21(4):363-71. PMID: 15709986

107. Cortot A, Colombel JF, Rutgeerts P et al. Switch from systemic steroids to budesonide in steroid dependent patients with inactive Crohn's disease. Gut 2001; 48(2):186-90. PMID: 11156638

108. Ferguson A, Campieri M, Doe W, Persson T, Nygard G. Oral budesonide as maintenance therapy in Crohn's disease--results of a 12-month study. Global Budesonide Study Group. Aliment Pharmacol Ther 1998; 12(2):175-83. PMID: 9692692

109. Gross V, Andus T, Ecker KW et al. Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. The Budesonide Study Group. Gut 1998; 42(4):493-6. PMID: 9616309

110. Lofberg R, Rutgeerts P, Malchow H et al. Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease. A placebo controlled one year study. Gut 1996; 39(1):82-6. PMID: 8881815

111. Greenberg GR, Feagan BG, Martin F et al. Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. Gastroenterology 1996; 110(1):45-51. PMID: 8536887

112. Brignola C, Campieri M, Farruggia P et al. The possible utility of steroids in the prevention of relapses of Crohn's disease in remission. A preliminary study. J Clin Gastroenterol 1988; 10(6):631-4. PMID: 3230278

113. Mantzaris GJ, Petraki K, Sfakianakis M et al. Budesonide versus mesalamine for maintaining remission in patients refusing other immunomodulators for steroid-dependent Crohn's disease. Clin Gastroenterol Hepatol 2003; 1(2):122-8. PMID: 15017504

114. van Dullemen HM, de Jong E, Slors F, Tytgat GN, van Deventer SJ. Treatment of therapy-resistant perineal metastatic Crohn's disease after proctectomy using anti-tumor necrosis factor chimeric monoclonal antibody, cA2: report of two cases. Dis Colon Rectum 1998; 41 (1):98-102. PMID: 9510318

115. Prantera C, Bellinvia S. The suspension of an announced trial on relapse prevention in Crohn's ileitis with a 5-ASA formulation in microgranular form. Dig Liver Dis 2005; 37(2):135-6 . PMID: 15733528

116. Mahmud N, Kamm MA, Dupas JL et al. Olsalazine is not superior to placebo in maintaining remission of inactive Crohn's colitis and ileocolitis: a double blind, parallel, randomised, multicentre study. Gut 2001; 49(4):552-6. PMID: 11559654

117. Sutherland LR, Martin F, Bailey RJ et al. A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. Gastroenterology 1997; 112(4):1069-77. PMID: 9097988

118. de Franchis R, Omodei P, Ranzi T et al. Controlled trial of oral 5-aminosalicylic acid for the prevention of early relapse in Crohn's disease. Aliment Pharmacol Ther 1997; 11(5):845-52. PMID: 9354191

119. Modigliani R, Colombel JF, Dupas JL et al. Mesalamine in Crohn's disease with steroid-induced remission: effect on steroid withdrawal and remission maintenance, Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gastroenterology 1996; 110(3):688-93. PMID: 8608877

120. Thomson AB, Wright JP, Vatn M et al. Mesalazine (Mesasal/Claversal) 1.5 g b.d. vs. placebo in the maintenance of remission of patients with Crohn's disease. Aliment Pharmacol Ther 1995; 9(6):673-83. PMID: 8824656

121. Arber N, Odes HS, Fireman Z et al. A controlled double blind multicenter study of the effectiveness of 5-aminosalicylic acid in patients with Crohn's disease in remission. J Clin Gastroenterol 1995; 20(3):203-6. PMID: 7797827

122. Gendre JP, Mary JY, Florent C et al. Oral mesalamine (Pentasa) as maintenance treatment in Crohn's disease: a multicenter placebo-controlled study. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). Gastroenterology 1993; 104(2):435-9. PMID: 8425685

123. Prantera C, Pallone F, Brunetti G, Cottone M, Miglioli M. Oral 5-aminosalicylic acid (Asacol) in the maintenance treatment of Crohn's disease. The Italian IBD Study Group. Gastroenterology 1992; 103(2):363-8. PMID: 1634054

124. Brignola C, Iannone P, Pasquali S et al. Placebo-controlled trial of oral 5-ASA in relapse prevention of Crohn's disease. Dig Dis Sci 1992; 37 (1):29-32. PMID: 1728527

125. Bresci G, Parisi G, Banti S. Long-term therapy with 5-aminosalicylic acid in Crohn's disease: Is it useful? Our four years experience. Int J Clin Pharmacol Res 1995; 14(4):133-8. PMID: 7607786.

126. Wellmann W, Schroder U. New oral preparations for maintenance therapy in Crohn's disease. CAN J GASTROENTEROL 1988; 2(SUPPL. A):71A-2A.

127. Siffledeen JS, Siminoski K, Jen H, Fedorak RN. Vertebral fractures and role of low bone mineral density in Crohn's disease. Clin Gastroenterol Hepatol 2007; 5(6):721-8. PMID: 17482522

128. Orlando A, Colombo E, Kohn A et al. Infliximab in the treatment of Crohn's disease: predictors of response in an Italian multicentric open study. Dig Liver Dis 2005; 37(8):577-83. PMID: 15886081

129. Sokol H, Seksik P, Carrat F et al. Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. Gut 2010; 59(10):1363-8. PMID: 20587545.

130. Beaugerie L, Brousse N, Bouvier AM et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet 2009; 374(9701):1617-25. PMID: 19837455

131. Lichtenstein GR, Feagan BG, Cohen RD et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006; 4(5):621-30. PMID: 16678077

132. Vavricka SR, Schoepfer AM, Bansky G et al. Efficacy and safety of certolizumab pegol in an unselected crohn's disease population: 26-week data of the FACTS II survey. Inflamm Bowel Dis 2010. PMID: 21182028

133. Armstrong RG, West J, Card TR. Risk of Cancer in Inflammatory Bowel Disease Treated With Azathioprine: A UK Population-Based Case-Control Study. Am J Gastroenterol 2010. PMID: 20104215

134. Lewis JD, Gelfand JM, Troxel AB et al. Immunosuppressant medications and mortality in inflammatory bowel disease. Am J Gastroenterol 2008; 103(6):1428-35; quiz 1436. PMID: 18494836

135. Gupta G, Lautenbach E, Lewis JD. Incidence and risk factors for herpes zoster among patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2006; 4(12):1483-90. PMID: 17162240

136. Lewis JD, Bilker WB, Brensinger C, Deren JJ, Vaughn DJ, Strom BL. Inflammatory bowel disease is not associated with an increased risk of lymphoma. Gastroenterology 2001; 121(5):1080-7. PMID: 11677199

137. Colombel JF, Loftus EV Jr, Tremaine WJ et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology 2004; 126(1):19-31. PMID: 14699483

138. Ricart E, Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. Am J Gastroenterol 2001; 96(3):722-9. PMID: 11280541

139. Toruner M, Loftus EV Jr, Harmsen WS et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 2008; 134(4):929-36. PMID: 18294633

140. Swoger JM, Loftus EV Jr, Tremaine WJ et al. Adalimumab for Crohn's disease in clinical practice at Mayo clinic: the first 118 patients. Inflamm Bowel Dis 2010; 16(11):1912-21. PMID: 20848486

141. Kane S, Khatibi B, Reddy D. Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. Am J Gastroenterol 2008; 103(3):631-6. PMID: 17941962

142. Goldstein MJ, Gelzayd EA, Kirsner JB. Some observations on the hazards of corticosteroid therapy in patients with inflammatory bowel disease. Trans Am Acad Ophthalmol Otolaryngol 1967; 71(2):254-61. PMID: 4292814

143. Lashner BA. Risk factors for small bowel cancer in Crohn's disease. Dig Dis Sci 1992; 37(8):1179-84. PMID: 1499440

144. Lees CW, Critchley J, Chee N et al. Lack of association between cervical dysplasia and IBD: a large case-control study. Inflamm Bowel Dis 2009; 15(11):1621-9. PMID: 19618462

145. Lees CW, Ali AI, Thompson AI et al. The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. Aliment Pharmacol Ther 2009; 29(3):286-97. PMID: 19132970

146. Campbell S, Ghosh S. Effective maintenance of inflammatory bowel disease remission by azathioprine does not require concurrent 5-aminosalicylate therapy. Eur J Gastroenterol Hepatol 2001; 13(11):1297-301. PMID: 11692054

147. Moss AC, Kim KJ, Fernandez-Becker N, Cury D, Cheifetz AS. Impact of concomitant immunomodulator use on long-term outcomes in patients receiving scheduled maintenance infliximab. Dig Dis Sci 2010; 55(5):1413-20. PMID: 19533357

148. Moss AC, Fernandez-Becker N, Jo Kim K, Cury D, Cheifetz AS. The impact of infliximab infusion reactions on long-term outcomes in patients with Crohn's disease. Aliment Pharmacol Ther 2008; 28(2):221-7. PMID: 18485127

149. Biancone L, Orlando A, Kohn A et al. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. Gut 2006; 55(2):228-33. PMID: 16120759

150. Cottone M, Kohn A, Daperno M et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol 2011; 9(1):30-5. PMID: 20951835

151. Hutfless SM, Weng X, Liu L, Allison J, Herrinton LJ. Mortality by medication use among patients with inflammatory bowel disease, 1996-2003. Gastroenterology 2007; 133(6):1779-86. PMID: 18054550

152. Hutfless S, Fireman B, Kane S, Herrinton LJ. Screening differences and risk of cervical cancer in inflammatory bowel disease. Aliment Pharmacol Ther 2008; 28(5):598-605. PMID: 18549465

153. Fidder H, Schnitzler F, Ferrante M et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. Gut 2009; 58(4):501-8. PMID: 18832524

154. Vermeire S, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut 2007; 56(9):1226-31. PMID: 17229796

155. Seksik P, Cosnes J, Sokol H, Nion-Larmurier I, Gendre JP, Beaugerie L. Incidence of benign upper respiratory tract infections, HSV and HPV cutaneous infections in inflammatory bowel disease patients treated with azathioprine. Aliment Pharmacol Ther 2009; 29(10):1106-13. PMID: 19222411

156. Shah JA, Edwards CM, Probert CS. Should azathioprine and 5-aminosalicylates be coprescribed in inflammatory bowel disease?: an audit of adverse events and outcome. Eur J Gastroenterol Hepatol 2008; 20(3):169-73. PMID: 18301295

157. Govani SM, Higgins PD. Combination of thiopurines and allopurinol: adverse events and clinical benefit in IBD. J Crohns Colitis 2010; 4(4):444-9. PMID: 21122542

158. Lofberg R, Louis EV, Reinisch W et al. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: Results from CARE. Inflammatory Bowel Dis. 2012; 18(1):1-9. PMID: 21351211.

159. Sprakes MB, Hamlin PJ, Warren L, Greer D, Ford AC. Adalimumab as second line anti-tumour necrosis factor alpha therapy for Crohn's disease: A single centre experience. J. Crohn's Colitis 2011; 5(4):324-31. PMID: 21683302.

160. Chaparro M, Panes J, Garcia V et al. Long-term durability of response to adalimumab in Crohn's disease. Inflamm Bowel Dis 2011. PMID: 21618353

161. Lichtiger S, Binion DG, Wolf DC et al. The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. Aliment Pharmacol Ther 2010; 32(10):1228-39. PMID: 20955442

162. Kinney T, Rawlins M, Kozarek R, France R, Patterson D. Immunomodulators and "on demand" therapy with infliximab in Crohn's disease: clinical experience with 400 infusions. Am J Gastroenterol 2003; 98(3):608-12. PMID: 12650795

163. af Bjorkesten CG, Nieminen U, Turunen U, Arkkila PE, Sipponen T, Farkkila MA. Endoscopic monitoring of infliximab therapy in Crohn's disease. Inflamm Bowel Dis 2011; 17(4):947-53. PMID: 20860048

164. Hamzaoglu H, Cooper J, Alsahli M, Falchuk KR, Peppercorn MA, Farrell RJ. Safety of infliximab in Crohn's disease: A large single-center experience. Inflammatory Bowel Dis. 2010; 16(12):2109-16. PMID: 20848473.

165. Lawrance IC, Radford-Smith GL, Bampton PA et al. Serious infections in patients with inflammatory bowel disease receiving anti-tumor-necrosis-factor-alpha therapy: an Australian and New Zealand experience. J Gastroenterol Hepatol 2010; 25(11):1732-8. PMID: 21039834

166. Lennard-Jones JE. Sulphasalazine in asymptomatic Crohn's disease. A multicentre trial. Gut 1977; 18(1):69-72. PMID: 14057

167. Van Assche G, Van Ranst M, Sciot R et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med 2005; 353(4):362-8. PMID: 15947080

168. Marehbian J, Arrighi HM, Hass S, Tian H, Sandborn WJ. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease . Am J Gastroenterol 2009; 104(10):2524-33. PMID: 19532125

169. Cooke CB, Krenacs L, Stetler-Stevenson M et al. Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic gamma delta T-cell origin. Blood 1996; 88(11):4265-74. PMID: 8943863

170. Long MD, Herfarth HH, Pipkin CA, Porter CQ, Sandler RS, Kappelman MD. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2010; 8(3):268-74. PMID: 20005977

171. Terdiman JP, Steinbuch M, Blumentals WA, Ullman TA, Rubin DT. 5-Aminosalicylic acid therapy and the risk of colorectal cancer among patients with inflammatory bowel disease. Inflamm Bowel Dis 2007; 13(4):367-71. PMID: 17206695

172. Tang J, Sharif O, Pai C, Silverman AL. Mesalamine protects against colorectal cancer in inflammatory bowel disease. Dig Dis Sci 2010; 55(6):1696-703. PMID: 19705280

173. Seiderer J, Goke B, Ochsenkuhn T. Safety aspects of infliximab in inflammatory bowel disease patients. A retrospective cohort study in 100 patients of a German University Hospital. Digestion 2004; 70(1):3-9. PMID: 15297773

174. Mortimore M, Gibson PR, Selby WS, Radford-Smith GL, Florin TH. Early Australian experience with infliximab, a chimeric antibody against tumour necrosis factor-alpha, in the treatment of Crohn's disease: is its efficacy augmented by steroid-sparing immunosuppressive therapy? The Infliximab User Group. Intern Med J 2001; 31(3):146-50. PMID: 11478343

175. Rudolph SJ, Weinberg DI, McCabe RP. Long-term durability of Crohn's disease treatment with infliximab. Dig Dis Sci 2008; 53(4):1033-41. PMID: 17934827

176. Maher MM, Nassar MI. Acute cytomegalovirus infection is a risk factor in refractory and complicated inflammatory bowel disease. Dig Dis Sci 2009; 54(11):2456-62. PMID: 19093204

177. Singleton JW, Law DH, Kelley ML Jr, Mekhjian HS, Sturdevant RA. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. Gastroenterology 1979; 77(4 Pt 2):870-82 . PMID: 38177

178. Food and Drug Administration. Remicade (infliximab) - Black Box Warning [Web Page]. 23 October 2001; Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm172751.htm. Accessed 7 July 2011.

179. Food and Drug Administration. Humira (adalimumab) [Web Page]. 20 December 2002; Available at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm092762.pdf. Accessed 7 July 2011.

180. Food and Drug Administration. Cimzia (certolizumab pegol) [Web Page]. April 2012; Available at www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory. Accessed 26 April 2012.

181. Clare DF, Alexander FC, Mike S et al. Accelerated infliximab infusions are safe and well tolerated in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol 2009; 21(1):71-5. PMID: 19060632

182. Keshavarzian A, Mayer L, Salzberg B et al. A multicenter retrospective experience of infliximab in Crohn's disease patients: Infusion reaction rates and treatment persistency. Gastroenterol. Hepatol. 2007; 3(5):381-90. PMID: 21960854.

183. Baert F, Noman M, Vermeire S et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003; 348(7):601-8. PMID: 12584368

184. Lee TW, Singh R, Fedorak RN. A one-hour infusion of infliximab during maintenance therapy is safe and well tolerated: A prospective cohort study. Aliment. Pharmacol. Ther. 2011; 34(2):181-7. PMID: 21615434.

185. Schoon EJ, Bollani S, Mills PR et al. Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn's disease. Clin Gastroenterol Hepatol 2005; 3(2):113-21. PMID: 15704045

186. Bernstein CN, Blanchard JF, Metge C, Yogendran M. The association between corticosteroid use and development of fractures among IBD patients in a population-based database. Am J Gastroenterol 2003; 98(8):1797-801. PMID: 12907335

187. Ullom-Minnich P. Prevention of osteoporosis and fractures. Am Fam Physician 1999; 60(1):194-202. PMID: 10414638

188. Reinisch W, Angelberger S, Petritsch W et al. Azathioprine versus mesalazine for prevention of postoperative clinical recurrence in patients with Crohn's disease with endoscopic recurrence: efficacy and safety results of a randomised, double-blind, double-dummy, multicentre trial. Gut 2010; 59(6):752-9. PMID: 20551460

189. Myrelid P, Svarm S, Andersson P, Almer S, Bodemar G, Olaison G. Azathioprine as a postoperative prophylaxis reduces symptoms in aggressive Crohn's disease. Scand J Gastroenterol 2006; 41(10):1190-5. PMID: 16990204

190. Escher JC. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multicentre trial. Eur J Gastroenterol Hepatol 2004; 16(1):47-54. PMID: 15095852

191. Levine A, Weizman Z, Broide E et al. A comparison of budesonide and prednisone for the treatment of active pediatric Crohn disease. J Pediatr Gastroenterol Nutr 2003; 36(2):248-52. PMID: 12548062

192. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. Gastroenterology 2000; 119(4):895-902. PMID: 11040176

193. Turner D, Griffiths AM, Walters TD et al. Appraisal of the Pediatric Crohn's Disease Activity Index on Four Prospectively Collected Datasets: Recommended Cutoff Values and Clinimetric Properties. Am J Gastroenterol 2010. PMID: 20372111

194. Cezard JP, Munck A, Mouterde O et al. Prevention of relapse by mesalazine (Pentasa) in pediatric Crohn's disease: a multicenter, double-blind, randomized, placebo-controlled trial. Gastroenterol Clin Biol 2009; 33(1 Pt 1):31-40. PMID: 19118966

195. Ruemmele FM, Lachaux A, Cezard JP et al. Efficacy of infliximab in pediatric Crohn's disease: a randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. Inflamm Bowel Dis 2009; 15(3):388-94. PMID: 19023899

196. Issenman RM, Atkinson SA, Radoja C, Fraher L. Longitudinal assessment of growth, mineral metabolism, and bone mass in pediatric Crohn's disease. J Pediatr Gastroenterol Nutr 1993; 17 (4):401-6. PMID: 8145096

197. Saha MT, Ruuska T, Laippala P, Lenko HL. Growth of prepubertal children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1998; 26(3):310-4. PMID: 9523867

198. Levine A, Broide E, Stein M et al. Evaluation of oral budesonide for treatment of mild and moderate exacerbations of Crohn's disease in children. J Pediatr 2002; 140(1):75-80. PMID: 11815767

199. Thayu M, Denson LA, Shults J et al. Determinants of Changes in Linear Growth and Body Composition in Incident Pediatric Crohn Disease. Gastroenterology 2010. PMID: 20417635

200. Alemzadeh N, Rekers-Mombarg LT, Mearin ML, Wit JM, Lamers CB, van Hogezand RA. Adult height in patients with early onset of Crohn's disease. Gut 2002; 51(1):26-9. PMID: 12077087

201. Bell SJ, Halligan S, Windsor AC, Williams AB, Wiesel P, Kamm MA. Response of fistulating Crohn's disease to infliximab treatment assessed by magnetic resonance imaging. Aliment Pharmacol Ther 2003; 17(3):387-93. PMID: 12562451

202. Bremner AR, Beattie RM. Therapy of Crohn's disease in childhood. Expert Opin Pharmacother 2002; 3(7):809-25. PMID: 12083982

203. Lahiff C, Safaie P, Awais A, Akbari M, Gashin L, Sheth S, Lembo A et al. The Crohn's disease activity index (CDAI) is similarly elevated in patients with Crohn's disease and in patients with irritable bowel syndrome. Aliment Pharmacol Ther 2013; 37(8):786-94. PMID: 23432394

204. Sadowski DC, Bernstein CN, Bitton A, Croitoru K, Fedorak RN, Griffiths A. Canadian Association of Gastroenterology Clinical Practice Guidelines: The use of tumour necrosis factor-alpha antagonist therapy in Crohn's disease. Can J Gastroenterol 2009; 23(3):185-202. PMID: 19319383

205. Mayberry JF, Lobo A, Ford AC, Thomas A. NICE clinical guideline (CG152): the management of Crohn's disease in adults, children, and young people. Aliment Pharmacol Ther 2013; 37(2):195-203. PMID: 23151246

206. Dignass A, Van Assche G, Lindsay JO et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis 2010; 4(1):28-62. PMID: 21122489

207. MacDonald JK, McDonald JW. Natalizumab for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2007; (1):CD006097. PMID: 17253580

208. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2008; (1):CD006893. PMID: 18254120

209. Lim WC, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev 2010; (12):CD008870. PMID: 21154400

210. Patel V, Macdonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009; (4):CD006884. PMID: 19821390

211. Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst. Rev. 2009; (4). PMID: 18646064.

212. Benchimol EI, Seow CH, Otley AR, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009; (1):CD002913. PMID: 19160212

213. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2008; (2):CD006792. PMID: 18425970

214. Talley NJ, Abreu MT, Achkar J-P et al. An Evidence-Based Systematic Review on Medical Therapies for Inflammatory Bowel Disease. 2011; 106(S1):S2-S25. PMID: 21472012.

215. Masunaga Y, Ohno K, Ogawa R, Hashiguchi M, Echizen H, Ogata H. Meta-analysis of risk of malignancy with immunosuppressive drugs in inflammatory bowel disease. Ann Pharmacother 2007; 41 (1):21-8. PMID: 17200426

216. Talley NJ, Abreu MT, Achkar JP et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. Am J Gastroenterol 2011; 106 Suppl 1:S2-25; quiz S26. PMID: 21472012

217. Chen QK, Yuan SZ, Wen ZF et al. Characteristics and therapeutic efficacy of sulfasalazine in patients with mildly and moderately active ulcerative colitis. World J Gastroenterol 2005; 11(16):2462-6. PMID: 15832418

218. Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. Ann Intern Med 2010; 153(3):158-66. PMID: 20679560

219. Toma M, McAlister FA, Bialy L, Adams D, Vandermeer B, Armstrong PW. Transition from meeting abstract to full-length journal article for randomized controlled trials. JAMA 2006; 295(11):1281-7. PMID: 16537738

220. Scherer RW, Langenberg P, von Elm E. Full publication of results initially presented in abstracts. Cochrane Database Syst Rev 2007; (2):MR000005. PMID: 17443628

221. Griffiths A, Koletzko S, Sylvester F, Marcon M, Sherman P. Slow-release 5-aminosalicylic acid therapy in children with small intestinal Crohn's disease. J Pediatr Gastroenterol Nutr 1993; 17(2):186-92. PMID: 8229546

222. Singleton JW, Hanauer S, Robinson M. Quality-of-life results of double-blind, placebo-controlled trial of mesalamine in patients with Crohn's disease. Dig Dis Sci 1995; 40 (5):931-5. PMID: 7729281

223. Bergman L, Krause U. Postoperative treatment with corticosteroids and salazosulphapyridine (Salazopyrin) after radical resection for Crohn's disease. Scand J Gastroenterol 1976; 11 (7):651-6. PMID: 11545

224. Thomson ABR. Coated oral 5-aminosalicylic acid versus placebo in maintaining remission of inactive Crohn's disease. ALIMENT. PHARMACOL. THER. 1990; 4(1):55-64. PMID; 2104074.

225. Caspersen S, Elkjaer M, Riis L et al. Infliximab for inflammatory bowel disease in Denmark 1999-2005: clinical outcome and follow-up evaluation of malignancy and mortality. Clin Gastroenterol Hepatol 2008; 6(11):1212-7; quiz 1176. PMID: 18848503

226. Crombe V, Salleron J, Savoye G et al. Long-term outcome of treatment with infliximab in pediatric-onset Crohn's disease: A population-based study. Inflamm Bowel Dis 2011. PMID: 21287665

227. de Vries HS, van Oijen MG, de Jong DJ. Serious events with infliximab in patients with inflammatory bowel disease: a 9-year cohort study in the Netherlands. Drug Saf 2008; 31(12):1135-44. PMID: 19026030

228. Domenech E, Zabana Y, Manosa M, Garcia-Planella E, Cabre E, Gassull MA. Infliximab reintroduction is not associated to a higher rate of immune-related adverse effects in patients with inflammatory bowel disease initially treated with a three-infusion induction regimen. J Clin Gastroenterol 2010; 44(1):34-7. PMID: 19417683

229. Malik S, Wong SC, Bishop J et al. Improvement in growth of children with Crohn disease following anti-TNF-alpha therapy can be independent of pubertal progress and glucocorticoid reduction. J Pediatr Gastroenterol Nutr 2011; 52(1):31-7. PMID: 21150651

230. Schneeweiss S, Korzenik J, Solomon DH, Canning C, Lee J, Bressler B. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. Aliment Pharmacol Ther 2009; 30(3):253-64. PMID: 19438424

231. Farrell RJ, Ang Y, Kileen P et al. Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. Gut 2000 ; 47(4):514-9. PMID: 10986211

232. Fraser AG, Orchard TR, Robinson EM, Jewell DP. Long-term risk of malignancy after treatment of inflammatory bowel disease with azathioprine. Aliment Pharmacol Ther 2002; 16(7):1225-32. PMID: 12144571

233. Tay GS, Binion DG, Eastwood D, et al. Multivariate analysis suggests improved perioperative outcome in Crohn's disease patients receiving immunomodulator therapy after segmental resection and/or strictureplasty. Surgery 2003; 134(4):565-72; discussion 572-3. PMID: 14605616

234. van Schaik FD, van Oijen MG, Smeets HM, et al. Thiopurines prevent advanced colorectal neoplasia in patients with inflammatory bowel disease. Gut 2011. PMID: 21602529

235. Bernstein CN, Nugent Z, Blanchard JF. 5-aminosalicylate is not chemoprophylactic for colorectal cancer in IBD: a population based study. Am J Gastroenterol 2011; 106(4):731-6. PMID: 21407180

236. Russell RK, Wilson ML, Loganathan S et al. A british society of paediatric gastroenterology, hepatology and nutrition survey of the effectiveness and safety of Adalimumab in children with inflammatory bowel disease. Aliment. Pharmacol. Ther. 2011; 33(8):946-53. PMID: 21342211.

237. Thayu M, Denson LA, Shults J et al. Determinants of changes in linear growth and body composition in incident pediatric Crohn's disease. Gastroenterology 2010; 139(2):430-8. PMID: 20417635.

238. Lewis JD. Immortal time bias in estimates of mortality among infliximab-treated patients with Crohn's disease. Gut 2010; 59(11):1586-7. PMID: 20732919

239. Sofos S, Savoye G, Ramirez S, Bauer F, Lerebours E. Transient type III atrioventricular block after infliximab infusion in a fistulizing perianal Crohn's disease patient. Am J Gastroenterol 2007; 102(1):217-9. PMID: 17278277

240. Mahida YR, Jewell DP. Slow-release 5-amino-salicylic acid (Pentasa) for the treatment of active Crohn's disease. Digestion 1990; 45(2):88-92. PMID: 2190851

241. Colombel JF, Schwartz DA, Sandborn WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut 2009; 58(7):940-8 . PMID: 19201775

242. Hanauer SB, Panes J, Colombel J-F, et al. Clinical trial: Impact of prior infliximab therapy on the clinical response to certolizumab pegol maintenance therapy for Crohn's disease. Aliment. Pharmacol. Ther. 2010; 32(3):384-93. PMID: 20491747.

Appendix A. Detailed Electronic Database Search Strategies

PubMed Strategy

Terms	Returns
("Crohn Disease"[mh] OR "Crohn's Disease"[tiab] OR "Crohn Disease"[tiab] OR "Crohns Disease"[tiab] OR (Crohn*[tiab] AND (ileitis[tiab] OR enteritis[tiab] OR ileocolitis[tiab] OR colitis[tiab])) OR "inflammatory bowel diseases"[mh] OR "inflammatory bowel disease"[tiab] OR "inflammatory bowel diseases"[tiab] OR IBD[tiab]) AND ("Aminosalicylic acids"[mh] OR "Anti-inflammatory agents, non-steroidal"[mh] OR mesalamine[mh] OR sulfasalazine[mh] OR "5-aminosalicylic acid"[tiab] OR "5-aminosalicylic acids"[tiab] OR "5-aminosalicylate"[tiab] OR "5-aminosalicylates"[tiab] OR "5-ASA"[tiab] OR aminosalicyl*[tiab] OR mesalamine*[tiab] OR mesalazine*[tiab] OR sulfasalazine*[tiab] OR sulphasalazine*[tiab] OR balsalazide[tiab] OR olsalazine[tiab] OR "immunosuppressive agents"[mh] OR azathioprine[mh] OR methotrexate[mh] OR "6-mercaptopurine"[mh] OR immunosuppression[tiab] OR immunosuppressive[tiab] OR immunosuppressives[tiab] OR immunomodulator*[tiab] OR immunomodulating[tiab] OR "anti-metabolite"[tiab] OR "anti-metabolites"[tiab] OR antimetabolit*[tiab] OR azathioprine[tiab] OR methotrexate[tiab] OR "6-mercaptopurine"[tiab] OR "antibodies, monoclonal/therapeutic use"[mh] OR "antibodies, monoclonal/administration and dosage"[mh] OR "antibodies, monoclonal/adverse effects"[mh] OR "anti-inflammatory agents"[mh] OR (("tumour necrosis factor"[tiab] OR "tumour necrosis factor-alpha"[tiab] OR "tumor necrosis factor"[tiab] OR "tumor necrosis factor-alpha"[tiab] OR TNF[tiab] OR TNF-alpha[tiab]) AND (antibod*[tiab] OR antagonist[tiab] OR antagonists[tiab] OR inhibitor*[tiab]) AND (agent*[tiab] OR treatment*[tiab] OR treated[tiab] OR therap*[tiab] OR drug[tiab] OR drugs[tiab] OR medication*[tiab])) OR "anti-tumour necrosis"[tiab] OR "anti-tumor necrosis"[tiab] OR anti-TNF*[tiab] OR biologic[tiab] OR biologics[tiab] OR adalimumab[tiab] OR infliximab[tiab] OR certolizumab[tiab] OR natalizumab[tiab] OR ustekinumab[tiab] OR budesonide[mh] OR glucocorticoids[mh] OR hydrocortisone[mh] OR methylprednisolone[mh] OR prednisolone[mh] OR prednisone[mh] OR "6-methylprednisolone"[tiab] OR budesonide[tiab] OR corticosteroid*[tiab] OR glucocorticosteroid*[tiab] OR prednisolone[tiab] OR prednisone[tiab]) NOT (animal[mh] NOT human [mh]) NOT (comment[pt] or editorial[pt])	11717

EMBASE Strategy

'crohn disease'/exp OR 'crohn disease' OR (crohn* NEXT/2 (disease OR ileitis OR enteritis OR ileocolitis OR colitis)):ab,ti OR 'inflammatory bowel disease':ab,ti OR 'inflammatory bowel diseases':ab,ti OR ibd:ab,ti AND ('mesalazine'/exp OR 'mesalazine' OR 'salazosulfapyridine'/exp OR 'salazosulfapyridine' OR '5-aminosalicylic acid':ab,ti OR '5-aminosalicylic acids':ab,ti OR '5-aminosalicylate':ab,ti OR '5-aminosalicylates':ab,ti OR '5-asa':ab,ti OR aminosalicyl*:ab,ti OR mesalamine*:ab,ti OR mesalazine*:ab,ti OR salazosulfapyridine*:ab,ti OR sulfasalazine*:ab,ti OR sulphasalazine*:ab,ti OR balsalazide:ab,ti OR olsalazine:ab,ti OR 'azathioprine'/exp OR 'azathioprine' OR 'methotrexate'/exp OR 'methotrexate' OR 'mercaptopurine'/exp OR 'mercaptopurine' OR immunosuppression:ab,ti OR immunosuppressive:ab,ti OR immunosuppressives:ab,ti OR immunomodulator*:ab,ti OR immunomodulating:ab,ti OR 'anti-metabolite':ab,ti OR 'anti-metabolites':ab,ti OR antimetabolit*:ab,ti OR azathioprine:ab,ti OR methotrexate:ab,ti OR '6-mercaptopurine':ab,ti OR 'adalimumab'/exp OR 'adalimumab' OR 'infliximab'/exp OR 'infliximab' OR 'certolizumab pegol'/exp OR 'certolizumab pegol' OR 'natalizumab'/exp OR 'natalizumab' OR 'ustekinumab'/exp OR 'ustekinumab' OR ((('tumour necrosis factor' OR 'tumor necrosis factor' OR tnf) NEXT/2 (antibod* OR antagonist OR antagonists OR inhibitor*)):ab,ti AND (agent*:ab,ti OR treatment*:ab,ti OR treated:ab,ti OR therap*:ab,ti OR drug:ab,ti OR drugs:ab,ti OR medication*:ab,ti)) OR 'anti-tumour necrosis':ab,ti OR 'anti-tumor necrosis':ab,ti OR 'anti tnf':ab,ti OR 'anti tnfalpha':ab,ti OR 'anti tnf alpha':ab,ti OR biologic:ab,ti OR biologics:ab,ti OR adalimumab:ab,ti OR infliximab:ab,ti OR certolizumab:ab,ti OR natalizumab:ab,ti OR ustekinumab:ab,ti OR 'budesonide'/exp OR 'budesonide' OR 'methylprednisolone'/exp OR 'methylprednisolone' OR 'prednisolone'/exp OR 'prednisolone' OR 'prednisone'/exp OR 'prednisone' OR '6-methylprednisolone':ab,ti OR budesonide:ab,ti OR corticosteroid*:ab,ti OR glucocorticosteroid*:ab,ti OR prednisolone:ab,ti OR prednisone:ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT (letter:it OR comment:it OR editorial:it) AND ('article'/it OR 'review'/it OR 'article in press'/it)	12653

The Cochrane Central Register of Controlled Trials (CENTRAL)

((crohn* NEAR/2 (disease OR ileitis OR enteritis OR ileocolitis OR colitis)):ti,ab,kw OR "inflammatory bowel disease":ti,ab,kw OR "inflammatory bowel diseases":ti,ab,kw OR ibd:ti,ab,kw) AND ("5-aminosalicylic acid":ti,ab,kw OR "5-aminosalicylic acids":ti,ab,kw OR "5-aminosalicylate":ti,ab,kw OR "5-aminosalicylates":ti,ab,kw OR "5-asa":ti,ab,kw OR aminosalicyl*:ti,ab,kw OR mesalamine*:ti,ab,kw OR mesalazine*:ti,ab,kw OR salazosulfapyridine*:ti,ab,kw OR sulfasalazine*:ti,ab,kw OR sulphasalazine*:ti,ab,kw OR balsalazide:ti,ab,kw OR olsalazine:ti,ab,kw OR immunosuppression:ti,ab,kw OR immunosuppressive:ti,ab,kw OR immunosuppressives:ti,ab,kw OR immunomodulator*:ti,ab,kw OR immunomodulating:ti,ab,kw OR "anti-metabolite":ti,ab,kw OR "anti-metabolites":ti,ab,kw OR antimetabolit*:ti,ab,kw OR azathioprine:ti,ab,kw OR methotrexate:ti,ab,kw OR "6-mercaptopurine":ti,ab,kw OR ((("tumour necrosis factor" OR "tumor necrosis factor" OR tnf) NEAR/2 (antibod* OR antagonist OR antagonists OR inhibitor*)):ti,ab,kw AND (agent*:ti,ab,kw OR treatment*:ti,ab,kw OR treated:ti,ab,kw OR therap*:ti,ab,kw OR drug:ti,ab,kw OR drugs:ti,ab,kw OR medication*:ti,ab,kw)) OR "anti-tumour necrosis":ti,ab,kw OR "anti-tumor necrosis":ti,ab,kw OR "anti tnf":ti,ab,kw OR "anti tnfalpha":ti,ab,kw OR "anti tnf alpha":ti,ab,kw OR biologic:ti,ab,kw OR biologics:ti,ab,kw OR adalimumab:ti,ab,kw OR infliximab:ti,ab,kw OR certolizumab:ti,ab,kw OR natalizumab:ti,ab,kw OR ustekinumab:ti,ab,kw OR "6-methylprednisolone":ti,ab,kw OR budesonide:ti,ab,kw OR corticosteroid*:ti,ab,kw OR glucocorticosteroid*:ti,ab,kw OR prednisolone:ti,ab,kw OR prednisone:ti,ab,kw)	577

Appendix B. Forms

https://systematic-review.ca/Submit/RenderForm.php?id=1&hide_abstract=1 1/1

DistillerSR

Reviewer10

Project Crohn's Disease (Switch) User Lilly.Haberl (My Settings)
Messages Nothing new
Live Support | User Guide

Review | Datarama | Reports | References | Forms | Manage Levels | Users | Project | Logout

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

BACKGROUND: Skateboarding has been a popular sport among teenagers even with its attendant associated risks. The literature is packed with articles regarding the perils of skateboards. Is the skateboard as dangerous as has been portrayed?

METHODS: This was a retrospective study conducted over a 5 year period. All skateboard related injuries seen in the Orthopaedic unit were identified and data collated on patient demographics, mechanism & location of injury, annual incidence, type of injury, treatment needed including hospitalisation.

RESULTS: We encountered 50 patients with skateboard related injuries. Most patients were males and under the age of 15. The annual incidence has remained low at about 10. The upper limb was predominantly involved with most injuries being fractures. Most injuries occurred during summer. The commonest treatment modality was plaster immobilisation. The distal radius was the commonest bone to be fractured. There were no head & neck injuries, open fractures or injuries requiring surgical intervention.

CONCLUSION: Despite its negative image among the medical fraternity, the skateboard does not appear to be a dangerous sport with a low incidence and injuries encountered being not severe. Skateboarding should be restricted to supervised skateboard parks and skateboarders should wear protective gear. These measures would reduce the number of skateboarders injured in motor vehicle collisions, reduce the personal injuries among skateboarders, and reduce the number of pedestrians injured in collisions with skateboarders.

Submit Form and go to [ ] or Skip to Next

Comparative Effectiveness and Safety of Pharmacologic Therapies for the Management of Crohn's Disease
Abstract Review Form

WE SHOULD INCLUDE BOTH RCTs AND OBSERVATIONAL STUDIES FOR THE ABSTRACT REVIEW

Drugs of interest: ASA: sulfasalazine, mesalamine
Anti-metabolite: azathioprine, methotrexate, 6-mercaptopurine
Biologic: adalimumab, infliximab, certolizumab pegol, natalizumab, ustekinumab
Corticosteroids: prednisone, prednisolone, 6-methylpredisolone, hydrocortisone, budesonide

Click here to view KQs and exclusion/inclusion criteria

1. Exclude article because... **(check the first reason why study should be excluded)**

- [ ] No original data (e.g., review article, commentary, or editorial)
- [ ] No subjects with Crohn's disease
- [ ] Does not evaluate a drug of interest
- [ ] Does not apply to any of the key questions (specify):
- [ ] Case report or case series unless hepatosplenic t-cell lymphoma or progressive multifocal leukoencephalopathy
- [ ] Other observational study or open label trial without a comparison group unless hepatosplenic t-cell lymphoma or progressive multifocal leukoencephalopathy
- [ ] No human data reported
- [ ] Not written in English
- [ ] Abstract only
- [ ] Other reason for exclusion

2. Unclear

- [ ] Unclear - pull article for review

3. Include article for review

- [ ] Include

4. Exclude from review, but pull for handsearching

- [ ] Pull for handsearching (e.g., systematic review that applies to the key question and published since 2005)

5. Comments (limit 250 characters)

Submit Form and go to [ ] or Skip to Next

DistillerSR

Reviewer10

Project Crohn's Disease (Switch) User Lilly.Haberl (My Settings)
Messages Nothing new
Live Support User Guide

Review | Datarama | Reports | References | Forms | Manage Levels | Users | Project | Logout

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Comparative Effectiveness and Safety of Pharmacologic Therapies for the Management of Crohn's Disease
Article Review Form

1. Exclude article because.... (check the first reason why study should be excluded)

- [ ] No **original data** (e.g., review article, commentary, or editorial)
- [ ] No subjects with **Crohn's Disease**
- [ ] Does not evaluate a **comparison** of interest (e.g., drug of interest compared to either placebo or another drug of interest)
- [ ] Does not apply to any of the **key questions**
- [ ] **Case report or case series** unless hepatosplenic t-cell lymphoma or progressive multifocal leukoencephalopathy
- [ ] **Other observational study or open-label trial without a comparison group** unless hepatosplenic t-cell lymphoma or progressive multifocal leukoencephalopathy
- [ ] Cohort or observational study AND does not report **side effects by medication class** or there's no clear comparison group specified in aims or methods
- [ ] No **human** data reported
- [ ] Not written in **English**
- [ ] **Abstract** only
- [ ] Other reason for exclusion (specify):

2. Include article for review. Please mark if (check all that apply):

- [ ] Pediatrics
- [ ] Adults
- [ ] RCT - KQ1 (induction)
- [ ] RCT - KQ2 (maintenance)
- [ ] Cohort or other observational study
- [ ] KQ4 (post-resection quality of life/patient-reported outcomes, either RCT or observational)
- [ ] Case report or case series on hepatosplenic t-cell lymphoma or progressive multifocal leukoencephalopathy

3. Exclude from review, but pull for handsearching

- [ ] Pull for handsearching (e.g., systematic review that applies to the key question and published since 2005)

4. Comments (limit 250 characters)

Submit Form and go to or Skip to Next

DistillerSR

Reviewer10

Project Crohn's Disease (Switch) User Lilly.Haberl (My Settings)
Messages Nothing new
Live Support | User Guide

Review | Datarama | Reports | References | Forms | Manage Levels | Users | Project | Logout

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Comparative Effectiveness and Safety of Pharmacologic Therapies for the Management of Crohn's Disease
Study Design Form

Please complete this form for each included study.

1. Name of trial or study cohort **(Select one response)**

Select an Answer

2. On what continent(s) did the study occur? **(Select all that apply)**

- [ ] United States
- [ ] North America (outside US)
- [ ] South America
- [ ] Europe
- [ ] Asia
- [ ] Australia
- [ ] Africa
- [ ] Other (specify):
- [ ] Not reported

3. Did the study occur at more than one study center? **(Select one response)**

Select an Answer

4. Study period **(Enter 4-digit year between 1900-2010)**

- ( ) Start year of enrollment

Clear Response

5. What study design was used? **(Select one response)**

Select an Answer

If "Randomized Controlled Trial" in Q5, skip to Q8.

If a **NON-RANDOMIZED** study, what was the average follow-up period? **(Enter mean or median number and then select units; If RCT, skip to next question.)**

(Enter number between 0 and 100 for either mean or median)	(Select Units)
[ ] Mean	Select an Answer
[ ] Median	
[ ] Not reported	

If "Randomized Controlled Trial" in Q5, answer Q8-Q17. Otherwise, skip to Q18.

8. If a **randomized controlled trial**, select type. **(Select all that apply)**

- [ ] Parallel arms
- [ ] Factorial design
- [ ] Crossover design
- [ ] Other (specify):

9. If a **randomized controlled trial**, was there a period of follow-up before patients were randomized aka "run-in period"? **(Select one response)**

Select an Answer

If "Yes" in Q9, answer Q10-11. Otherwise, skip to Q12.
If **there was a run-in period**, what was the duration of the run-in period? **(Enter number and then select units)**

10. (Enter number between 0 and 100)	11. (Select units)
( ) Duration	Select an Answer

○ Not reported Clear Response	

If a **randomized controlled study**, what was the duration of assigned treatment from randomization? **(Enter number and then select units)**

12. **(Enter number between 0 and 100)**	13. **(Select units)**
○ Duration ○ Not reported Clear Response	Select an Answer

For studies that apply to **KQ2 only**, what was the duration of response or remission prior to randomization? **(Enter number and then select units)**

14. **(Enter number between 0 and 100)**	15. **(Select units)**
○ Duration ○ Not reported Clear Response	Select an Answer

16. If a **randomized controlled trial**, was adherence reported? **(Select one response)**

Select an Answer

If adherence was reported in Q16, answer Q17. Otherwise, skip to Q18.

17. If adherence was reported, was adherence >= 80% in all study arms? **(Select one response)**

Select an Answer

18. Which subgroups analyses were conducted? **(Select all that apply)**

- ☐ Age at diagnosis
- ☐ Age at study start
- ☐ Duration of disease
- ☐ Baseline CRP
- ☐ Baseline CDAI
- ☐ Comorbid conditions
- ☐ Gender
- ☐ Race/ethnicity
- ☐ Prior treatment
- ☐ Prior surgery
- ☐ Family history of IBD
- ☐ Smoking status
- ☐ Concurrent use of aminosalicylates
- ☐ Concurrent use of anti-TNFs
- ☐ Concurrent use of corticosteroids
- ☐ Concurrent use of thiopurines
- ☐ Concurrent use of methotrexate
- ☐ Concurrent use of other medication (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ No subgroup analyses were conducted

Please select and specify the **INCLUSION** criteria. **Please mark exclusion criteria as inclusion criteria (e.g., If a study excluded patients who had a previous CD surgery, then the inclusion criteria would be "No previous CD surgery.")**

☐ Pediatrics ☐ Adults	
☐ Crohn's disease only ☐ IBD	
☐ Males only ☐ Females only	
☐ Previous CD surgery (specify): ☐ No previous CD surgery	**(Specify type of surgery)**
☐ CDAI score (specify criteria): ☐ Pediatric CDAI score (specify criteria): ☐ Harvey-Bradshaw Index (specify criteria): ☐ Other index (specify name and criteria):	**(If other index, specify name and criteria. If CDAI, PCDAI, or HBI, specify criteria.)** ☐ Other index (specify): ☐ >

	☐ <
☐ Duration of remission (specify):	**(Specify number of weeks, months, or years)** ☐ Weeks ☐ Months ☐ Years
☐ Previous use of medications (specify):	☐ Antibiotics ☐ Aminosalicylates ☐ Anti-TNFs ☐ Corticosteroids ☐ Thiopurines ☐ Methotrexate ☐ Infliximab ☐ Adalimumab ☐ Certolizumab pegol ☐ Other (specify): ☐ Other (specify): ☐ Other (specify):
☐ No previous use of medications (specify):	☐ Antibiotics ☐ Aminosalicylates ☐ Anti-TNFs ☐ Corticosteroids ☐ Thiopurines ☐ Methotrexate ☐ Infliximab ☐ Adalimumab ☐ Certolizumab pegol ☐ Other (specify): ☐ Other (specify): ☐ Other (specify):
☐ Disease activity (specify source/metric):	**(Specify source/metric and then indicate disease activity)** ☐ Source/metric (specify): ☐ Active disease ☐ Inactive disease ☐ Mild disease ☐ Moderate disease ☐ Severe disease
☐ Perianal fistulizing ☐ Not pregnant ☐ Not nursing ☐ Using adequate contraception ☐ No short bowel syndrome ☐ No ostomy ☐ No abscess ☐ No obstructive symptoms with strictures ☐ No history of tuberculosis, positive chest radiograph, or positive PPD ☐ No demyelinating disease ☐ No cancer	
☐ Smoking status (specify):	**(Specify smoking status)**
☐ Other (specify):	
☐ Other (specify):	
☐ Other (specify):	

Other (specify):	
Other (specify):	
Other (specify):	
Other (specify):	
Other (specify):	
Other (specify):	

55. Comments **(Limit 250 characters)**

56. Comments **(Limit 250 characters)**

57. Comments **(Limit 250 characters)**

Submit Form and go to or Skip to Next

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Comparative Effectiveness of Pharmacologic Therapies for the Management of Crohn's Disease
Intervention/Population Characteristics Form

Please complete this form for RCTs and cohort studies. Submit one form per intervention group.

PLEASE IDENTIFY DRUG COMPARISONS IN THE ORDER PRESENTED HERE. For instance, if a study compares infliximab vs. infliximab + azathioprine vs. placebo, then submit 3 intervention/population forms:
1) Group 1 = placebo
2) Group 2 = infliximab
3) Group 3 = azathioprine (in first row) + infliximab (in second row)

1. Indicate the group number. **(MANDATORY QUESTION. Select one response.)**
Select an Answer

For monotherapy comparisons, please complete the first row.
For combination comparisons, please use the first row for the first drug and the second row for the second drug.

2. Intervention **(Select one response)** Select an Answer	3. Brand name for mesalamine only **(Select one response)** Select an Answer	4. Route **(Select one response)** Select an Answer	5. Dosing **(If prospective, randomized trial, choose dose started at randomization. Select unit and then enter a number for dose.)** Select an Answer 6. every **(Specify frequency of dosing in Q5.)** Select an Answer 7. Other dosing aspects **(Select all that apply)** ☐ Steroid taper used ☐ Dose increase permitted ☐ Dose decrease permitted ☐ Change in route during study (e.g., IV converted to oral) ☐ Induction dosing only (biologics) ☐ Induction followed by maintenance dosing (biologics) ☐ Crossover study design 8. Average cumulative dose across study **(if available)**
9. Intervention **(Select one response)** Select an Answer	10. Brand name for mesalamine only **(Select one response)** Select an Answer	11. Route **(Select one response)** Select an Answer	12. Dosing **(If prospective, randomized trial, choose dose started at randomization. Select unit and then enter a number for dose.)** Select an Answer 13. every **(Specify frequency of dosing in Q12.)** Select an Answer 14. Other dosing aspects **(Select all that apply)** ☐ Steroid taper used ☐ Dose increase permitted ☐ Dose decrease permitted ☐ Change in route during study (e.g., IV converted to oral) ☐ Induction dosing only (biologics) ☐ Induction followed by maintenance dosing (biologics) ☐ Crossover study design 15. Average cumulative dose across study **(if available)**

16. Comments on intervention. **(Limit 250 characters)**

17. Comments on intervention. **(Limit 250 characters)**

Population Characteristics

Please complete the baseline characteristics for this study group.

If a randomized trial, answer Q18 and skip Q19.
If a non-randomized study, skip Q18 and answer Q19.

18. If a **randomized trial,** what was the total number randomized to treatment arm? **(Enter in number from 0 to 9999999).**

19. If a **non-randomized study,** what was the total number of patients who received this treatment? **(Enter in a number from 0 to 9999999).**

For the population characteristics below, you can report either n or %.

20. **Male**

☐ n ☐ % ☐ Gender not reported

Race

White ☐ n ☐ %

Hispanic ☐ n ☐ %

Black, African American ☐ n ☐ %

Asian ☐ n ☐ %

Other race/ethnicity ☐ n ☐ % ☐ (Specify):

Other race/ethnicity ☐ n ☐ % ☐ (Specify):

Other race/ethnicity ☐ n ☐ % ☐ (Specify):

Other race/ethnicity ☐ n ☐ % ☐ (Specify):

☐ Race not reported

Smokers ☐ n ☐ % ☐ Definition ☐ Smoking status not reported

Age at Crohn's diagnosis **(Enter number of years. If only age categories presented, enter minimum and maximum.)**

☐ Mean ☐ Median ☐ Minimum ☐ Maximum ☐ Age at diagnosis not reported

Duration of disease **(Enter number of years. If only age categories presented, enter minimum and maximum.)**

☐ Mean ☐ Median ☐ Minimum ☐ Maximum ☐ Duration of disease not reported

Age at start of study **(Enter number of years. If only age categories presented, enter minimum and maximum.)**

☐ Mean ☐ Median ☐ Minimum ☐ Maximum ☐ Age at study start not reported

Disease severity ☐ Metric/source used

Mild ☐ n ☐ %

Moderate ☐ n ☐ %

Mild-moderate ☐ n ☐ %

Moderate-severe ☐ n ☐ %

Severe ☐ n ☐ %

Remission/Inactive ☐ n ☐ %

Unknown/missing ☐ n ☐ %

☐ Disease severity not reported

Disease location ☐ Metric/source used

Ileal ☐ n ☐ %

Ileo-colonic ☐ n ☐ %

Colonic ☐ n ☐ %

Perianal ☐ n ☐ % ☐ Disease location not reported

Disease behavior

Inflammatory ☐ n ☐ %

Stricturing ☐ n ☐ %

Penetrating ☐ n ☐ %

☐ Disease behavior not reported

Disease activity index

CDAI at randomization (RCTs) or study start (cohorts) ☐ Mean ☐ Median ☐ Minimum ☐ Maximum

Pediatric CDAI at randomization (RCTs) or study start (cohorts) ☐ Mean ☐ Median ☐ Minimum ☐ Maximum

Harvey-Bradshaw Index at randomization (RCTs) or study start (cohorts) ☐ Mean ☐ Median ☐ Minimum ☐ Maximum

Other disease activity index at randomization (RCTs) or study start (cohorts) ☐ Mean ☐ Median ☐ Minimum ☐ Maximum ☐ Other index (specify):

☐ Disease activity index not reported

IBDQ at randomization or study start ☐ Mean ☐ Median ☐ Minimum ☐ Maximum

☐ IBDQ not reported

CRP at randomization or study start ☐ Mean ☐ Median ☐ Minimum ☐ Maximum

☐ CRP not reported

Diagnosed with Crohn's Disease (for observational studies with an IBD population) ☐ n ☐ % ☐ Not reported

Medications taken by patients <u>DURING</u> the study period (Indicate which medications then record N, % of patients, if available)		
☐ Aminosalicylates	☐ n	☐ %
☐ Antibiotics	☐ n	☐ %
☐ Anti-TNFs	☐ n	☐ %
☐ Corticosteroids	☐ n	☐ %
☐ Methotrexate	☐ n	☐ %
☐ Thiopurines	☐ n	☐ %
☐ Immunomodulators	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %

Medications taken by patients <u>BEFORE</u> the study period (Indicate which medications then record N, % of patients, if available)		
☐ Aminosalicylates	☐ n	☐ %
☐ Antibiotics	☐ n	☐ %
☐ Anti-TNFs	☐ n	☐ %
☐ Corticosteroids	☐ n	☐ %
☐ Methotrexate	☐ n	☐ %
☐ Thiopurines	☐ n	☐ %
☐ Immunomodulators	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %

Medications taken by patients <u>BEFORE</u> the study period or during the run-in period to <u>INDUCE REMISSION</u> (Indicate which medications then record N, % of patients, if

available)

Aminosalicylates	n	%
Antibiotics	n	%
Anti-TNFs	n	%
Corticosteroids	n	%
Methotrexate	n	%
Thiopurines	n	%
Immunomodulators	n	%
Other medication (specify):	n	%
Other medication (specify):	n	%
Other medication (specify):	n	%
Other medication (specify):	n	%

127. Comments on population characteristics. **(Limit 250 characters)**

128. Comments on population characteristics. **(Limit 250 characters)**

Submit Form and go to or Skip to Next

DistillerSR lisa.wilson Reviewer10

Project Crohn's Disease (Switch) User Lilly.Haberl (My Settings)
Messages Nothing new
Live Support | User Guide

Review | Datarama | Reports | References | Forms | Manage Levels | Users | Project | Logout

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to ▾ or Skip to Next

Comparative Effectiveness of Pharmacologic Therapies for the Management of Crohn's Disease
Case-Control Population Form

Only complete this form for case-control studies.

1. Indicate the group. **(Mandatory question. Select one response.)**

Select an Answer ▾

2. How were these controls selected? **(Select all that apply.)**

- ☐ Nested
- ☐ Neighborhood
- ☐ Friend/family controls
- ☐ Random digit dialing
- ☐ Hospital/clinic-based (specify diseases included):
- ☐ Other control selection (specify):
- ☐ N/A (i.e., cases)

3. What was the total number of cases/controls? **(Enter a number between 0 and 999999.)**

For the population characteristics below, you can report either n or %.

Male

☐ n ☐ % ☐ Gender not reported

Race

White ☐ n ☐ %
Hispanic ☐ n ☐ %
Black, African American ☐ n ☐ %
Asian ☐ n ☐ %
Other race/ethnicity ☐ n ☐ % ☐ (Specify):
Other race/ethnicity ☐ n ☐ % ☐ (Specify):
Other race/ethnicity ☐ n ☐ % ☐ (Specify):
Other race/ethnicity ☐ n ☐ % ☐ (Specify):

☐ Race not reported

Smokers ☐ n ☐ % ☐ (Definition) ☐ Smoking status not reported

Age at Crohn's diagnosis **(Enter number of years. If only age categories presented, enter minimum and maximum.)**

☐ Mean ☐ Median ☐ Minimum ☐ Maximum

☐ Age at diagnosis not reported

Duration of disease **(Enter number of years. If only age categories presented, enter minimum and maximum.)**

☐ Mean ☐ Median ☐ Minimum ☐ Maximum

☐ Duration of disease not reported

Age at study start (Enter number of years. If only age categories presented, enter minimum and maximum.)

☐ Mean ☐ Median ☐ Minimum ☐ Maximum

☐ Age at study start not reported

Disease severity ☐ Metric/source used (specify):

Mild ☐ n ☐ %

Moderate ☐ n ☐ %

Mild-moderate ☐ n ☐ %

Moderate-severe ☐ n ☐ %

Severe ☐ n ☐ %

Remission/Inactive ☐ n ☐ %

Unknown/missing ☐ n ☐ %

☐ Disease severity not reported

Disease location ☐ Metric/source used (specify):

Ileal ☐ n ☐ %

Ileo-colonic ☐ n ☐ %

Colonic ☐ n ☐ %

Perianal ☐ n ☐ %

☐ Disease location not reported

Disease behavior

Inflammatory ☐ n ☐ %

Stricturing ☐ n ☐ %

Penetrating ☐ n ☐ %

☐ Disease behavior not reported

Disease activity index

CDAI at randomization (RCTs) or study start (cohorts)

☐ Mean ☐ Median ☐ Minimum ☐ Maximum

Pediatric CDAI at randomization (RCTs) or study start (cohorts)

☐ Mean ☐ Median ☐ Minimum ☐ Maximum

Harvey Bradshaw Index at randomization (RCTs) or study start (cohorts)

☐ Mean ☐ Median ☐ Minimum ☐ Maximum

Other disease activity index at randomization (RCTs) or study start (cohorts)

☐ Mean ☐ Median ☐ Minimum ☐ Maximum ☐ Other index (specify):

☐ Disease activity index not reported

IBDQ at randomization (RCTs) or study start (cohorts)

☐ Mean ☐ Median ☐ Minimum ☐ Maximum ☐ IBDQ not reported

CRP at randomization (RCTs) or study start (cohorts)

☐ Mean ☐ Median ☐ Minimum ☐ Maximum ☐ CRP not reported

Diagnosed with Crohn's disease (for observational studies with an IBD population) ☐ n ☐ % ☐ Not reported

Medications taken by patients <u>DURING</u> the study period (Indicate which medications then record N, % of patients, if available)		
☐ Aminosalicylates	☐ n	☐ %
☐ Antibiotics	☐ n	☐ %

☐ Anti-TNF	☐ n	☐ %
☐ Corticosteroids	☐ n	☐ %
☐ Methotrexate	☐ n	☐ %
☐ Thiopurines	☐ n	☐ %
☐ Immunomodulators	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %

Medications taken by patients BEFORE the study period (Indicate which medications then record N, % of patients, if available)

☐ Aminosalicylates	☐ n	☐ %
☐ Antibiotics	☐ n	☐ %
☐ Anti-TNF	☐ n	☐ %
☐ Corticosteroids	☐ n	☐ %
☐ Methotrexate	☐ n	☐ %
☐ Thiopurines	☐ n	☐ %
☐ Immunomodulators	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %

Medications taken by patients BEFORE the study period or during the run-in period to INDUCE REMISSION (Indicate which medications then record N, % of patients, if available)

☐ Aminosalicylates	☐ n	☐ %
☐ Antibiotics	☐ n	☐ %
☐ Anti-TNF	☐ n	☐ %
☐ Corticosteroids	☐ n	☐ %
☐ Methotrexate	☐ n	☐ %
☐ Thiopurines	☐ n	☐ %
☐ Immunomodulators	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %
☐ Other medication (specify):	☐ n	☐ %

111. Comments **(Limit to 250 characters)**

112. Comments **(Limit to 250 characters)**

113. Comments **(Limit to 250 characters)**

Submit Form and go to or Skip to Next

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Comparative Effectiveness of Pharmacologic Therapies for the Management of Crohn's Disease
Outcomes Form

Please complete this form for RCTs and cohort studies. Submit one form per relevant outcome.

1. If reporting on an efficacy outcome, then choose one category:

Select an Answer

KQ1, KQ2, KQ4

Outcome of interest **(Select one response)**	Definition **(Select one response)**	Timing **(Select one response and then specify time in weeks. If more than 1 time point in each group, select the last time point. Be sure to subtract the run-in period.)**
○ CDAI ○ PCDAI ○ HBI ○ Other index (specify): Clear Response	Select an Answer	Select an Answer
○ Perianal disease Clear Response	Select an Answer	Select an Answer
○ Health-related quality of life Clear Response	Select an Answer	Select an Answer
○ Endoscopic healing Clear Response	Select an Answer	Select an Answer
○ Reduction of steroids ○ Steroid free ○ Number of hospitalizations ○ Need for surgery Clear Response	Define (for reduction of steroids):	Select an Answer

KQ3

Outcome of interest **(Select one response)**	Definition **(Select one response)**	Timing **(Select one response and then specify time in weeks. If more than 1 time point in each group, select the last time point.)**	Indicate the population for this analysis **(Select one response)**
○ Mortality ○ Lymphoma ○ Cervical cancer ○ Other cancers (including colon cancer) ○ Serious infections ○ TB ○ Other infections ○ Infusion and injection-site reactions ○ Bone fracture ○ Height ○ Weight Clear Response	○ Define: ○ Not specified Clear Response	Select an Answer	Select an Answer

Answer Q23-25 for adverse events (KQ3) only. Otherwise, skip to Tables.

21. Was the mode of adverse event collection active or passive? **(Select one response)**
Active ascertainment of harms indicates
a) that participants are asked about the occurrence of specific harms in structured questionnaires or interviews or pre-defined laboratory or diagnostic tests, usually performed at pre-specified time intervals.
b) that the potential occurrence of harmful events are collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery.
These events are potentially expected harms as a result of the intervention.

Select an Answer

22. Did the study specify frequency and timing of adverse event collection? **(Select one response)**

Select an Answer

23. **If RCT, answer Q25. Otherwise, skip to Tables.**

Was the analysis for this outcome "intention-to-treat?" **(Select one response)**

Select an Answer

Table 1. Incidence of outcome

Intervention	N for analysis	Outcome measure	Denominator	P-value	Reference group
Intervention Group1		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group2		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group3		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group4		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group5		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group6		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group7		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group8		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer

Table 2. Measure of Association

Intervention	N for analysis	Point estimate (Select one response)	Measure of variability (Select one response)	95% CI	P-value	Reference group
		Select an Answer	Select an Answer			
Intervention Group1				☐ LL ☐ UL		Select an Answer
Intervention Group2				☐ LL ☐ UL		Select an Answer

Intervention Group3				☐ LL ☐ UL		Select an Answer
Intervention Group4				☐ LL ☐ UL		Select an Answer
Intervention Group5				☐ LL ☐ UL		Select an Answer
Intervention Group6				☐ LL ☐ UL		Select an Answer
Intervention Group7				☐ LL ☐ UL		Select an Answer
Intervention Group8				☐ LL ☐ UL		Select an Answer

114. What variables, if any, were adjusted for in the model? **(Select all that apply)**

- ☐ Matching factors
- ☐ Age
- ☐ Sex
- ☐ Race/ethnicity
- ☐ Duration of disease
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Results not adjusted

Table 3. Mean difference from other group (G1-G2)

Intervention	N for analysis	Point estimate (Select one response) Select an Answer	Measure of variability (Select one response) Select an Answer	CI or IQR (Select one response) Select an Answer	P-value	Reference group
Intervention Group1				☐ LL ☐ UL		Select an Answer
Intervention Group2				☐ LL ☐ UL		Select an Answer
Intervention Group3				☐ LL ☐ UL		Select an Answer
Intervention Group4				☐ LL ☐ UL		Select an Answer
Intervention Group5				☐ LL ☐ UL		Select an Answer
Intervention Group6				☐ LL ☐ UL		Select an Answer
Intervention Group7				☐ LL ☐ UL		Select an Answer

Intervention Group8				☐ LL ☐ UL		Select an Answer

Table 4. Mean difference from baseline. **(This should be recorded as Final - Baseline. If the values decrease from baseline, then value should be negative. If the values increase from baseline, then the value should be positive. Note: Reference group should always be baseline.)**

Intervention	N for analysis	Point estimate (Select one response) Select an Answer	Measure of variability (Select one response) Select an Answer	CI or IQR (Select one response) Select an Answer	P-value
Intervention Group1				☐ LL ☐ UL	
Intervention Group2				☐ LL ☐ UL	
Intervention Group3				☐ LL ☐ UL	
Intervention Group4				☐ LL ☐ UL	
Intervention Group5				☐ LL ☐ UL	
Intervention Group6				☐ LL ☐ UL	
Intervention Group7				☐ LL ☐ UL	
Intervention Group8				☐ LL ☐ UL	

Table 5. Baseline measures.

Intervention	N for analysis	Point estimate (Select one response) Select an Answer	Measure of variability (Select one response) Select an Answer	CI or IQR (Select one response) Select an Answer
Intervention Group1				☐ LL ☐ UL
Intervention Group2				☐ LL ☐ UL
Intervention Group3				☐ LL ☐ UL
Intervention Group4				☐ LL ☐ UL
Intervention Group5				☐ LL ☐ UL

Intervention Group6				☐ LL ☐ UL
Intervention Group7				☐ LL ☐ UL
Intervention Group8				☐ LL ☐ UL

Table 6. Final measures

Intervention	**N for analysis**	**Point estimate (Select one response)** Select an Answer	**Measure of variability (Select one response)** Select an Answer	**CI or IQR (Select one response)** Select an Answer	**P-value**	**Reference group**
Intervention Group1				☐ LL ☐ UL		Select an Answer
Intervention Group2				☐ LL ☐ UL		Select an Answer
Intervention Group3				☐ LL ☐ UL		Select an Answer
Intervention Group4				☐ LL ☐ UL		Select an Answer
Intervention Group5				☐ LL ☐ UL		Select an Answer
Intervention Group6				☐ LL ☐ UL		Select an Answer
Intervention Group7				☐ LL ☐ UL		Select an Answer
Intervention Group8				☐ LL ☐ UL		Select an Answer

Comments **(Limit 250 characters)**

Comments **(Limit 250 characters)**

297. Comments **(Limit 250 characters)**

Submit Form and go to or Skip to Next

DistillerSR

lisa.wilson Reviewer10

Project Crohn's Disease (Switch) User Lilly.Haberl (My Settings)
Messages Nothing new
Live Support | User Guide

Review | Datarama | Reports | References | Forms | Manage Levels | Users | Project | Logout

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Comparative Effectiveness of Pharmacologic Therapies for the Management of Crohn's Disease
Case-Control Outcomes Form

Please complete this form only for case-control studies.

Outcome of interest **(Select one response)**	Definition **(Select one response)**	Indicate the population for this analysis **(Select one response)**
Select an Answer	Select an Answer	Select an Answer

4. Did the study include an analysis using dose of medication or duration of use? **(Select one response)**

Select an Answer

Select the medication **(Select one response)**	Duration of use	Cases **(Select case group being reported here)** Select an Answer	Control **(Select control group being reported here)** Select an Answer	Point estimate **(Select one)** Select an Answer	Measure of variability **(Select one response)** Select an Answer	95% CI	P-v
Select an Answer	Select an Answer	n / %	n / %			LL / UL	
Select an Answer	Select an Answer	n / %	n / %			LL / UL	
Select an Answer	Select an Answer	n / %	n / %			LL / UL	
Select an Answer	Select an Answer	n / %	n / %			LL / UL	
Select an Answer	Select an Answer	n / %	n / %			LL / UL	
Select an Answer	Select an Answer	n / %	n / %			LL / UL	

63. Where the results adjusted for ...? **(Select all that apply)**

- Matching factors
- Age
- Sex
- Race/ethnicity
- Duration of disease
- Other (specify):
- Other (specify):
- Other (specify):
- Results were not adjusted

64. Comments **(Limit 250 characters)**

65. Comments **(Limit 250 characters)**

66. Comments **(Limit 250 characters)**

Submit Form and go to or Skip to Next

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Comparative Effectiveness of Pharmacologic Therapies for the Management of Crohn's Disease
Quality form for RCTs

Sequence Generation

1. Was the allocation sequence adequately generated?

Select an Answer

Criteria for a judgment of "YES" (i.e., low risk of bias)

- *The investigators describe a random component in the sequence generation process such as:*
  - *Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization. Minimization may be implemented without a random element, and this is considered to be equivalent to being random.*

Criteria for a judgment of "NO" (i.e., high risk of bias)

- *The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:*
  - *Sequence generated by odd or even date of birth;*
  - *Sequence generated by some rule based on date (or day) of admission;*
  - *Sequence generated by some rule based on hospital or clinic record number.*
- *Other non-random approached happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgment or some method of non-random categorization of participants, for example:*
  - *Allocation by judgment of the clinician;*
  - *Allocation by preference of the participant;*
  - *Allocation based on the results of a laboratory test or a series of tests.*

Criteria for a judgment of "UNCLEAR" (i.e., uncertain risk of bias)

- *Insufficient information about the sequence generation process to permit judgement of "YES" or "NO."*

Allocation Concealment

2. Was allocation adequately concealed?

Select an Answer

Criteria for a judgment of "YES" (i.e. low risk of bias)

- *Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:*
  - *Central allocation (including telephone, web-based, and pharmacy-controlled, randomization);*
  - *Sequentially numbered drug containers of identical appearance;*
  - *Sequentially numbered, opaque, sealed envelopes.*

Criteria for a judgment of "NO" (i.e. high risk of bias)

- *Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:*
  - *Using an open random allocation schedule (e.g. a list of random numbers);*
  - *Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);*
  - *Alternation or rotation;*
  - *Date of birth;*
  - *Case record number;*
  - *Any other explicitly unconcealed procedure*

Criteria for the judgment of "UNCLEAR" (i.e. uncertain risk of bias)

- *Insufficient information about the sequence generation process to permit judgment of "YES" or "NO".*

- *This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.*

Blinding of Participants, Personnel, and Outcome Assessors

3. Was knowledge of the allocated interventions adequately prevented during the study?
Select an Answer

Criteria for a judgment of "YES" (i.e. low risk of bias)

- *Any one of the following:*
  - *No blinding, but the review authors judge that the outcome and the outcome*
  - *Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;*
  - *Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the nonblinding of others unlikely to introduce bias.*

Criteria for a judgment of "NO" (i.e. high risk of bias)

- *Any one of the following:*
  - *No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding;*
  - *Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;*
  - *Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.*

Criteria for the judgment of "UNCLEAR" (i.e. uncertain risk of bias)

- *Any one of the following:*
  - *Insufficient information to permit judgment of 'Yes' or 'No';*
  - *The study did not address this outcome.*

Incomplete Outcome Data

4. Were incomplete outcome data adequately addressed?
Select an Answer

Criteria for a judgment of "YES" (i.e. low risk of bias)

- *Any one of the following:*
  - *No missing outcome data;*
  - *Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);*
  - *Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;*
  - *For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;*
  - *For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;*
  - *Missing data have been imputed using appropriate methods.*

Criteria for a judgment of "NO" (i.e. high risk of bias)

- *Any one of the following:*
  - *Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;*
  - *For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;*
  - *For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;*
  - *'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;*
  - *Potentially inappropriate application of simple imputation*

Criteria for the judgment of "UNCLEAR" (i.e. uncertain risk of bias)

- *Any one of the following:*
  - *Insufficient reporting of attrition/exclusions to permit judgment of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided);*
  - *The study did not address this outcome.*

Other Potential Threats to Validity

5. Was the study apparently free of other problems that could put it at a risk of bias?
Select an Answer

Criteria for a judgment of "YES" (i.e. low risk of bias)

- *The study appears to be free of other sources of bias.*

Criteria for a judgment of "NO" (i.e. high risk of bias)

- *There is at least one important risk of bias. For example, the study:*
  - *Had a potential source of bias related to the specific study design used; or*
  - *Stopped early due to some data-dependent process (including a formal-stopping rule); or*
  - *Had extreme baseline imbalance; or*
  - *Has been claimed to have been fraudulent; or*
  - *Had some other problem.*

Criteria for the judgment of "UNCLEAR" (i.e. uncertain risk of bias)

- *There may be a risk of bias, but there is either:*
  - *Insufficient information to assess whether an important risk of bias exists; or*
  - *Insufficient rationale or evidence that an identified problem will introduce bias.*

Pharmaceutical Support

6. Did this study receive support (research funds, medications provided, writing services, author or staff was employee) from a company having a financial interest in any of the medications studied?

Select an Answer

7. If "Yes," did the company have any involvement in the design, conduct, or reporting of the study?
For "NO," the authors are not employees of the company and the authors had complete access to the data, and the company was not involved in the design, conduct, analysis, or reporting of the study.

Select an Answer

Overall Quality of Study

8. Please rate the overall quality of the study:

Select an Answer

Criteria for a judgment of "GOOD" (i.e. low risk of bias)

- *These studies have the least bias and results are considered valid*
- *A study that adheres mostly to the commonly held concepts of high quality including the following:*
  - *A formal randomized controlled study;*
  - *Clear description of the population, setting, interventions, and comparison groups;*
  - *Appropriate measurements of outcomes;*
  - *Appropriate statistical and analytic methods and reporting;*
  - *No reporting errors;*
  - *Low dropout rate; and*
  - *Clear reporting of dropouts*

Criteria for a judgment of "FAIR"

- *These studies are susceptible to some bias, but it is not sufficient to invalidate the results.*
- *Do not meet all the criteria required for a rating of good qualities because they have some deficiencies, but no flaw is likely to cause major bias.*
- *The study may be missing information, making it difficult to assess limitations and potential problems*

Criteria for a judgment of "POOR" (i.e. high risk of bias)

- *These studies have significant flaws that imply biases of various types that may invalidate the results.*
- *Have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.*

9. Were >20% of the study participants lost to followup at any of the following time points?

Select an Answer

10. Please add comments below.

Submit Form and go to or Skip to Next

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Comparative Effectiveness of Pharmacologic Therapies for the Management of Crohn's Disease
Quality Form for Observational Studies

Reporting

1. Are the main outcomes to be measured clearly described in the Introduction or Methods section?

   If the main outcomes are both identified and defined, then the answer is "YES". If the main outcomes are first mentioned in the Results section, the question should be answered "NO".

   YES
   NO
   UNABLE TO DETERMINE
   Clear Response

2. Are the characteristics of the patients included in the study clearly described?

   In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

   YES
   NO
   UNABLE TO DETERMINE
   Clear Response

3. Are the interventions of interest clearly described?

   Treatments and placebo (where relevant) that are to be compared should be identified and defined.

   YES
   NO
   UNABLE TO DETERMINE
   Clear Response

4. Are the distributions of principal confounders in each group of subjects to be compared clearly described?

   The confounders should be 1) identified and 2)defined along with 3) distribution in each group. A list of principal confounders is provided in text (identification) with definitions of each confounder. Table 1 and/or the first paragraph of the Results usually provide the distribution of potential confounders by treatment/case status.

   YES
   NO
   UNABLE TO DETERMINE
   Clear Response

Selection Bias

5. Were the patients in different intervention groups (cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

   The patients in each group should be 1) from the same source population, 2) with the same inclusion/exclusion criteria applied (other than exposure/case status), 3) recruited over the same period of time.
   For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

   YES
   NO
   UNABLE TO DETERMINE
   Clear Response

6. Were losses of patients to follow-up taken into account?

Methods to account for losses to follow-up include calculating the incidence rate directly or using a survival/life table method.
If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was less than 20% in each arm at the end of the study, the question should be answered "YES".

- YES
- NO
- UNABLE TO DETERMINE

Clear Response

Confounding

7. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

If the authors report their results using a fully-adjusted model, multivariate/multivariable model, model resulting from step-wise regression or results stratified by the demonstrated confounders of interest, the answer is "YES".
If the effect of the main confounders was not investigated or confounding was demonstrated (different distribution of potential confounders by exposure/case group) but no adjustment was made in the final analyses the question should be answered as "NO".
If the study was a matched case-control study and the method of analysis was not conditional logistic regression, the answer is "NO".

- YES
- NO
- UNABLE TO DETERMINE

Clear Response

Overall Quality of Study

8. Please rate the overall quality of the study using the reporting, selection bias and confounding domains:

Good indicates all "YES" responses
Fair indicates mostly "YES" for Reporting and all "YES" for Selection Bias and Confounding bias.
Poor indicates at least 1 "NO" or "Unable to determine" for selection or confounding bias.

- GOOD
- FAIR
- POOR

Clear Response

Conflict of Interest

9. Did this study receive support (research funds, medications provided, writing services, author or staff was employee) from a company having a financial interest in any of the medications studied?

- YES
- NO
- UNABLE TO DETERMINE

Clear Response

10. If above question is answered yes: did the company have any involvement in the design, conduct, or reporting of the study?

For "NO," the authors are not employees of the company and the authors had complete access to the data, and the company was not involved in the design, conduct, analysis, or reporting of the study.

- YES
- NO
- UNABLE TO DETERMINE

Clear Response

11. Please add any comments below:

Submit Form and go to or Skip to Next

Appendix C. Excluded Articles

Aberra, F. N., Lewis, J. D., Hass, D., Rombeau, J. L., Osborne, B., and Lichtenstein, G. R. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology. 2003; 125 (2): 320-7. **Does not apply to key questions**

Aberra, F. N., Stettler, N., Brensinger, C., Lichtenstein, G. R., and Lewis, J. D. Risk for active tuberculosis in inflammatory bowel disease patients. Clin Gastroenterol Hepatol. 2007; 5 (9): 1070-5. **Does not report side effects by medication class**

Abitbol, V., Roux, C., Chaussade, S., Guillemant, S., Kolta, S., Dougados, M., Couturier, D., and Amor, B. Metabolic bone assessment in patients with inflammatory bowel disease. Gastroenterology. 95; 108 (2): 417-22. **Does not evaluate a drug of interest**

Achkar, J. P., Stevens, T., Easley, K., Brzezinski, A., Seidner, D., and Lashner, B. Indicators of clinical response to treatment with six-mercaptopurine or azathioprine in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2004; 10 (4): 339-45. **Does not report side effects by medication class**

Acosta-Ramirez, D., Pagan-Ocasio, V., Torres, E. A., Rodriguez, M., and Caro, O. Profile of the inflammatory bowel disease patient with depressive disorders. P R Health Sci J. 2001; 20 (3): 215-20. **Does not report side effects by medication class**

Actis, G. C. and Rosina, F. Outpatient care for inflammatory bowel disease at a primary referral hospital in Turin. Minerva Gastroenterol Dietol. 2010; 56 (1): 27-34. **Does not apply to key questions; other observational study without a comparison group**

Adamiak, T., Stephens, M., and Werlin, S. L. Angioedema Occurring in Pediatric Patients With Crohn Disease Treated With Adalimumab. J Pediatr Gastroenterol Nutr. 2010. **Does not apply to key questions**

Agnholt, J., Dahlerup, J. F., Buntzen, S., Tottrup, A., Nielsen, S. L., and Lundorf, E. Response, relapse and mucosal immune regulation after infliximab treatment in fistulating Crohn's disease. Aliment Pharmacol Ther. 2003; 17 (5): 703-10. **Does not evaluate a drug of interestOther observational study without a comparison group**

Agrawal, A., Durrani, S., Leiper, K., Ellis, A., Morris, A. I., and Rhodes, J. M. Effect of systemic corticosteroid therapy on risk for intra-abdominal or pelvic abscess in non-operated Crohn's disease. Clin Gastroenterol Hepatol. 2005; 3 (12): 1215-20. **Does not evaluate a drug of interest**

Ainsworth, M. A., Bendtzen, K., and Brynskov, J. Tumor necrosis factor-alpha binding capacity and anti-infliximab antibodies measured by fluid-phase radioimmunoassays as predictors of clinical efficacy of infliximab in Crohn's disease. Am J Gastroenterol. 2008; 103 (4): 944-8. **Does not apply to key questions; does not report side effects by medication class**

Al Rifai, A., Prasad, N., Shuttleworth, E., McBurney, H., Pushpakom, S., Robinson, A., Newman, W., and Campbell, S. Natural history of azathioprine-associated lymphopenia in inflammatory bowel disease patients: a prospective observational study. Eur J Gastroenterol Hepatol. 2011; 23 (2): 153-8. **Other observational study without a comparison groupOther reason**

Alcain, G., Andrade, R. J., Queipo de Llano, M. P., Moreno, M. J., Garcia-Cortes, M., and Franquelo, E. Acute leukemia after infliximab therapy. Am J Gastroenterol. 2003; 98 (11): 2577. **Case report or case series**

Allez, M., Lemann, M., Bonnet, J., Cattan, P., Jian, R., and Modigliani, R. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. Am J Gastroenterol. 2002; 97 (4): 947-53. **Does not apply to key questions; does not report side effects by medication class**

Allez, M., Vermeire, S., Mozziconacci, N., Michetti, P., Laharie, D., Louis, E., Bigard, M. A., Hebuterne, X., Treton, X., Kohn, A., Marteau, P., Cortot, A., Nichita, C., van Assche, G., Rutgeerts, P., Lemann, M., and Colombel, J. F. The efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF antibodies. Aliment Pharmacol Ther. 2010; 31 (1): 92-101. **Does not evaluate a drug of interest; does not report side effects by medication class**

Allsop, J. R. and Lee, E. C. Factors which influenced postoperative complications in patients with ulcerative colitis or Crohn's disease of the colon on corticosteroids. Gut. 78; 19 (8): 729-34. **Does not apply to key questions; other observational study without a comparison group**

Ally, M. R., Veerappan, G. R., and Koff, J. M. Treatment of recurrent Crohn's uveitis with infliximab. Am J Gastroenterol. 2008; 103 (8): 2150-1. **Case report or case series**

Almer, S. H., Hjortswang, H., and Hindorf, U. 6-Thioguanine therapy in Crohn's disease--observational data in Swedish patients. Dig Liver Dis. 2009; 41 (3): 194-200. **Does not report side effects by medication class**

Alvarez Beltran, M., Infante Pina, D., Tormo Carnice, R., Segarra Canton, O., and Redecillas Ferreiro, S. [Optimising azathioprine treatment: determination of thiopurine methyltransferase activity and thiopurine metabolites]. An Pediatr (Barc). 2009; 70 (2): 126-31. **Not written in English**

Alzafiri, R., Holcroft, C. A., Malolepszy, P., Cohen, A., and Szilagyi, A. Infliximab therapy for moderately severe Crohn's disease and ulcerative colitis: A retrospective comparison over 6 years. Clin. Exp. Gastroenterol. 2011; 4 (1): 9-17. **Does not evaluate a drug of interest**

Alzahrani, M. Crohn's colitis in infancy. Ann. Saudi Med. 2003; 23 (3-4): 198-200. **Case report or case series**

Amiot, A., Gornet, J. M., Baudry, C., Munoz-Bongrand, N., Auger, M., Simon, M., Allez, M., Cattan, P., Sarfati, E., and Lemann, M. Crohn's disease recurrence after total proctocolectomy with definitive ileostomy. Dig Liver Dis. 2011. **Does not evaluate a drug of interest**

Ananthakrishnan, A. N., McGinley, E. L., and Binion, D. G. Inflammatory bowel disease in the elderly is associated with worse outcomes: a national study of hospitalizations. Inflamm Bowel Dis. 2009; 15 (2): 182-9. **Does not evaluate a drug of interest**

Andersson, P., Olaison, G., Bodemar, G., Nystrom, P. O., and Sjodahl, R. Surgery for Crohn colitis over a twenty-eight-year period: fewer stomas and the replacement of total colectomy by segmental resection. Scand J Gastroenterol. 2002; 37 (1): 68-73. **Does not apply to key questions; does not report side effects by medication class**

Andoh, A., Tsujikawa, T., Ban, H., Hashimoto, T., Bamba, S., Ogawa, A., Sasaki, M., Saito, Y., and Fujiyama, Y. Monitoring 6-thioguanine nucleotide concentrations in Japanese patients with inflammatory bowel disease. J Gastroenterol Hepatol. 2008; 23 (9): 1373-7. **Does not apply to key questions; other observational study without a comparison group**

Andus, T., Gross, V., Caesar, I., Schulz, H. J., Lochs, H., Strohm, W. D., Gierend, M., Weber, A., Ewe, K., and Scholmerich, J. Replacement of conventional glucocorticoids by oral pH-modified release budesonide in active and inactive Crohn's disease: results of an open, prospective, multicenter trial. Dig Dis Sci. 2003; 48 (2): 373-8. **Does not evaluate a drug of interest; pther observational study without a comparison group**

Annunziata, M. L., Bossa, F., Bozzi, R., Caprioli, F., Cassinotti, A., Costantino, G., Fiorino, G., Onali, S., Principi, M., Renna, S., and Tambasco, R. The Italian clinical experience with adalimumab in Crohn's disease: Eleven clinical cases. Dig. Liver Dis. Suppl. 2010; 4 (1): 1-3. **Other observational study without a comparison group**

Ansari, A., Arenas, M., Greenfield, S. M., Morris, D., Lindsay, J., Gilshenan, K., Smith, M., Lewis, C., Marinaki, A., Duley, J., and Sanderson, J. Prospective evaluation of the pharmacogenetics of azathioprine in the treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2008; 28 (8): 973-83. **Does not report side effects by medication class**

Ansari, A., Elliott, T., Fong, F., Arenas-Hernandez, M., Rottenberg, G., Portmann, B., Lucas, S., Marinaki, A., and Sanderson, J. Further experience with the use of 6-thioguanine in patients with Crohn's disease. Inflamm Bowel Dis. 2008; 14 (10): 1399-405. **Does not evaluate a drug of interest**

Ansari, A., Patel, N., Sanderson, J., O'Donohue, J., Duley, J. A., and Florin, T. H. Low-dose azathioprine or mercaptopurine in combination with allopurinol can bypass many adverse drug reactions in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2010; 31 (6): 640-7. **Other observational study without a comparison group**

Anthonisen, P., Barany, F., Folkenborg, O., Holtz, A., Jarnum, S., Kristensen, M., Riis, P., Walan, A., and Worning, H. The clinical effect of salazosulphapyridine (Salazopyrin r) in Crohn's disease. A controlled double-blind study. Scand J Gastroenterol. 74; 9 (6): 549-54. **Other observational study without a comparison group**

Antonija, B., Babic, Z., Marija, G., and Matek, P. The role of sulfasalazine in the treatment of patients with inflammatory bowel disease with spondyloarthropathies. Croat. J. Gastroenterol. Hepatol. 96; 5 (2-3): 31-34. **Does not evaluate a drug of interest; does not report side effects by medication class**

Arden, N. K. and Cooper, C. Osteoporosis in patients with inflammatory bowel disease. Gut. 2002; 50 (1): 9-10. **No original data; does not report side effects by medication class**

Ardizzone, S., Colombo, E., Maconi, G., Bollani, S., Manzionna, G., Petrone, M. C., and Bianchi Porro, G. Infliximab in treatment of Crohn's disease: the Milan experience. Dig Liver Dis. 2002; 34 (6): 411-8. **Other observational study without a comparison group**

Ardizzone, S., Maconi, G., Colombo, E., Manzionna, G., Bollani, S., and Bianchi Porro, G. Perianal fistulae following infliximab treatment: clinical and endosonographic outcome. Inflamm Bowel Dis. 2004; 10 (2): 91-6. **Other observational study without a comparison group; does not report side effects by medication class**

Ardizzone, S., Maconi, G., Sampietro, G. M., Russo, A., Radice, E., Colombo, E., Imbesi, V., Molteni, M., Danelli, P. G., Taschieri, A. M., and Bianchi Porro, G. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease. Gastroenterology. 2004; 127 (3): 730-40. **Does not apply to key questions**

Arnott, I. D., McDonald, D., Williams, A., and Ghosh, S. Clinical use of Infliximab in Crohn's disease: the Edinburgh experience. Aliment Pharmacol Ther. 2001; 15 (10): 1639-46. **Other observational study without a comparison group; does not report side effects by medication class**

Arnott, I. D., McNeill, G., and Satsangi, J. An analysis of factors influencing short-term and sustained response to infliximab treatment for Crohn's disease. Aliment Pharmacol Ther. 2003; 17 (12): 1451-7. **Does not apply to key questionsOther observational study without a comparison group**

Arslan, S., Kav, T., Besisik, F., Kaymakoglu, S., Pinarbasi, B., Tozun, N., Hamzaoglu, H. O., Duman, D., Ulker, A., Parlak, E., Palabiyikoglu, M., and Dokmeci, A. Clinical outcome of Crohn's disease treated with infliximab. Hepatogastroenterology. 2003; 50 (52): 952-6. **Other observational study without a comparison group**

Asakura, H., Yao, T., Matsui, T., Koganei, K., Fukushima, T., Takazoe, M., Hobara, R., Nakano, H., Okamura, S., Matsueda, K., Kashida, H., Makiyama, K., Hiwatashi, N., Kashiwagi, K., and Hibi, T. Efficacy of treatment with chimeric monoclonal antibody (Infliximab) to tumor necrosis factor-alpha for Crohn's disease in Japan: evaluation by rapid turnover proteins, and radiologic and endoscopic findings. J Gastroenterol Hepatol. 2001; 16 (7): 763-9. **Does not evaluate a drug of interest; other observational study without a comparison group**

Askling, J., Brandt, L., Lapidus, A., Karlen, P., Bjorkholm, M., Lofberg, R., et al. Risk of haematopoietic cancer in patients with inflammatory bowel disease. Gut. 2005; 54 (5): 617-22. **Does not evaluate a drug of interest; other observational study without a comparison group**

Asteria, C. R., Ficari, F., Bagnoli, S., Milla, M., and Tonelli, F. Treatment of perianal fistulas in Crohn's disease by local injection of antibody to TNF-alpha accounts for a favourable clinical response in selected cases: a pilot study. Scand J Gastroenterol. 2006; 41 (9): 1064-72. **Other observational study without a comparison group**

Atienza Amores, M. R., Martin-Garrido, I., Garcia-Contreras, R., and Varela Aguilar, J. M. [Alopecia as adverse reaction of mesalazine]. Rev Clin Esp. 2009; 209 (3): 153-4. **Case report or case seriesNot written in English**

Avila Alvarez, A., Solar Boga, A., and Garcia-Alonso, L. Anti-TNF agents for the treatment of Crohn's disease: Agentes anti-TNF en el tratamiento de la enfermedad de Crohn. Acta Pediatr. Esp. 2010; 68 (1): 19-24. **Not written in English**

Azad Khan, A. K., Piris, J., and Truelove, S. C. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet. 77; 2 (8044): 892-5. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; does not apply to key questions**

Baars, J. E., Vogelaar, L., Wolfhagen, F. H., Biermann, K., Kuipers, E. J., et al. A short course of corticosteroids prior to surveillance colonoscopy to decrease mucosal inflammation in inflammatory bowel disease patients: results from a randomized controlled trial. J Crohns Colitis. 2010; 4 (6): 661-8. **Does not apply to key questions**

Baert, F. J., D'Haens, G. R., Peeters, M., Hiele, M. I., Schaible, T. F., Shealy, D., et al. Tumor necrosis factor alpha antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. Gastroenterology. 99; 116 (1): 22-8. **Does not apply to key questions**

Baert, F., Moortgat, L., Van Assche, G., Caenepeel, P., Vergauwe, P., De Vos, M., et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010; 138 (2): 463-8; quiz e10-1. **Does not apply to key questions; other reason**

Baldassano, R. N. Infliximab in pediatric Crohn's disease patients. Gastroenterol. Hepatol. 2006; 2 (7): 467. **No original data**

Baldassano, R., Braegger, C. P., Escher, J. C., DeWoody, K., Hendricks, D. F., Keenan, G. F., et al. Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. Am J Gastroenterol. 2003; 98 (4): 833-8. **Other observational study without a comparison group**

Ban, H., Andoh, A., Tanaka, A., Tsujikawa, T., Sasaki, M., Saito, Y., et al. Analysis of thiopurine S-methyltransferase genotypes in Japanese patients with inflammatory bowel disease. Intern Med. 2008; 47 (19): 1645-8. **Other observational study without a comparison group; does not report side effects by medication class**

Banovic, I., Gilibert, D., and Cosnes, J. Perception of improved state of health and subjective quality of life in Crohn's disease patients treated with Infliximab. J. Crohn's Colitis. 2009; 3 (1): 25-31. **Does not apply to key questions; other observational study without a comparison group**

Barabino, A., Torrente, F., Ventura, A., Cucchiara, S., Castro, M., and Barbera, C. Azathioprine in paediatric inflammatory bowel disease: an Italian multicentre survey. Aliment Pharmacol Ther. 2002; 16 (6): 1125-30. **Does not evaluate a drug of interest; other observational study without a comparison group**

Baron, T. H., Truss, C. D., and Elson, C. O. Low-dose oral methotrexate in refractory inflammatory bowel disease. Dig Dis Sci. 93; 38 (10): 1851-6. O**ther observational study without a comparison group**

Baryshnikov, E. N., Lazebnik, L. B., and Parfenov, A. I. [Adalimumab therapy in Crohn's disdease]. Eksp Klin Gastroenterol. 2009; (5): 92-8. **Not written in English**

Bastida Paz, G., Nos Mateu, P., Aguas Peris, M., Beltran Niclos, B., Rodriguez Soler, M., and Ponce Garcia, J. [Optimization of immunomodulatory treatment with azathioprine or 6-mercaptopurine in inflammatory bowel disease]. Gastroenterol Hepatol. 2007; 30 (9): 511-6. **Not written in English**

Bastida, G. and Munoz, F. [Systemic corticosteroids in inflammatory bowel disease: are they really effective. What is their real toxicity?]. Gastroenterol Hepatol. 2008; 31 Suppl 3 3-9. **Not written in English**

Bastida, G., Nos, P., Aguas, M., Beltran, B., Iborra, M., et al. The effects of thiopurine therapy on health-related quality of life in Inflammatory Bowel Disease patients. BMC Gastroenterol. 2010; 10 26. **Does not report side effects by medication class**

Bastida, G., Nos, P., Aguas, M., Beltran, B., Rubin, A., et al. Incidence, risk factors and clinical course of thiopurine-induced liver injury in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2005; 22 (9): 775-82. **Does not evaluate a drug of interest; other observational study without a comparison group**

Bauditz, J., Lochs, H., and Schreiber, S. Chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. N Engl J Med. 98; 338 (5): 334. **No original data**

Baumgart, D. C., Grittner, U., Steingraber, A., Azzaro, M., and Philipp, S. Frequency, phenotype, outcome, and therapeutic impact of skin reactions following initiation of adalimumab therapy: Experience from a consecutive cohort of inflammatory bowel disease patients. Inflamm Bowel Dis. 2011. **Other observational study without a comparison group; does not report side effects by medication class**

Beattie, R. M. and Walker-Smith, J. A. Use of enteric coated prednisolone in Crohn's disease. Arch Dis Child. 94; 71 (3): 282. **Case report or case series**

Belaiche, J., Desager, J. P., Horsmans, Y., and Louis, E. Therapeutic drug monitoring of azathioprine and 6-mercaptopurine metabolites in Crohn disease. Scand J Gastroenterol. 2001; 36 (1): 71-6. **Other observational study without a comparison group; does not report side effects by medication class**

Bell, S. J., Halligan, S., Windsor, A. C., Williams, A. B., Wiesel, P., and Kamm, M. A. Response of fistulating Crohn's disease to infliximab treatment assessed by magnetic resonance imaging. Aliment Pharmacol Ther. 2003; 17 (3): 387-93. **Does not evaluate a drug of interest; other observational study without a comparison group**

Bellizzi, A., Anzivino, E., Ferrari, F., Di Nardo, G., Colosimo, M. T., Fioriti, D., et al. Polyomavirus JC reactivation and noncoding control region sequence analysis in pediatric Crohn's disease patients treated with infliximab. J Neurovirol. 2011. **Does not evaluate a drug of interest; does not apply to key questions**

Benavente, L. and Moris, G. Neurologic disorders associated with inflammatory bowel disease. Eur. J. Neurol. 2011; 18 (1): 138-143. **Does not apply to key questions**

Bendano, T. and Frisancho, O. Clinical and evolutive profile of Crohn's disease in Hospital Rebagliati (Lima-Peru): Perfil Clinico y Evolutivo de la Enfermedad de Crohn en el Hospital Rebagliati (Lima-Peru). Rev Gastroenterol Peru. 2010; 30 (1): 17-24. **Not written in English**

Berger, J. R. and Houff, S. A. Neurological infections: the year of PML and influenza. Lancet Neurol. 2010; 9 (1): 14-17. **No original data**

Bermejo, F., Lopez San Roman, A., Algaba, A., van Domselaar, M., Carneros, J. A., Rivero, M., Piqueras, B., et al. [Efficacy of premedication with intravenous corticosteroids and antihistaminics in preventing infusion reactions to infliximab]. Gastroenterol Hepatol. 2008; 31 (10): 629-32. **Not written in English**

Bermejo, F., Lopez-Sanroman, A., Algaba, A., Van-Domselaar, M., Gisbert, J. P., Garcia-Garzon, S., et al. Mercaptopurine rescue after azathioprine-induced liver injury in inflammatory bowel disease. Aliment Pharmacol Ther. 2010; 31 (1): 120-4. **Other observational study without a comparison group**

Bermejo, F., Lopez-Sanroman, A., Taxonera, C., Gisbert, J. P., Perez-Calle, J. L., Vera, I., et al. Acute pancreatitis in inflammatory bowel disease, with special reference to azathioprine-induced pancreatitis. Aliment Pharmacol Ther. 2008; 28 (5): 623-8. **Does not report side effects by medication class**

Bernklev, T., Jahnsen, J., Schulz, T., Sauar, J., Lygren, I., Henriksen, M., et al. Course of disease, drug treatment and health-related quality of life in patients with inflammatory bowel disease 5 years after initial diagnosis. Eur J Gastroenterol Hepatol. 2005; 17 (10): 1037-45. **Does not apply to key questions; does not report side effects by medication class**

Bernstein, C. N., Artinian, L., Anton, P. A., and Shanahan, F. Low-dose 6-mercaptopurine in inflammatory bowel disease is associated with minimal hematologic toxicity. Dig Dis Sci. 94; 39 (8): 1638-41. **Other observational study without a comparison group; does not report side effects by medication class**

Bernstein, C. N., Blanchard, J. F., Kliewer, E., and Wajda, A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer. 2001; 91 (4): 854-62. **Does not report side effects by medication class**

Bernstein, C. N., Seeger, L. L., Sayre, J. W., Anton, P. A., Artinian, L., and Shanahan, F. Decreased bone density in inflammatory bowel disease is related to corticosteroid use and not disease diagnosis. J Bone Miner Res. 95; 10 (2): 250-6. **Other reason**

Besnard, M., Jaby, O., Mougenot, J. F., Ferkdadji, L., Debrun, A., Faure, C., et al. Postoperative outcome of Crohn's disease in 30 children. Gut. 98; 43 (5): 634-8. **Does not apply to key questions**

Biancone, L., Cretella, M., Tosti, C., Palmieri, G., Petruzziello, C., Geremia, A., et al. Local injection of infliximab in the postoperative recurrence of Crohn's disease. Gastrointest Endosc. 2006; 63 (3): 486-92. **Other observational study without a comparison group**

Biancone, L., Pavia, M., Del Vecchio Blanco, G., D'Inca, R., Castiglione, F., De Nigris, F., et al. Hepatitis B and C virus infection in Crohn's disease. Inflamm Bowel Dis. 2001; 7 (4): 287-94. **Does not apply to key questions; does not report side effects by medication class**

Binion, D. G. Biologic Therapies for Crohn's Disease: Update from the 2009 ACG Meeting. Gastroenterol Hepatol (N Y). 2010; 6 (1 Suppl 1): 4-16. **No original data**

Birnie, G. G., McLeod, T. I., and Watkinson, G. Incidence of sulphasalazine-induced male infertility. Gut. 81; 22 (6): 452-5. **Does not evaluate a drug of interest; other observational study without a comparison group**

Bischoff, A. [Drug therapy of Crohn's disease: slowly increase or start aggressively right away?]. MMW Fortschr Med. 2010; 152 (1-2): 20. **No original data; not written in English**

Blomqvist, P., Feltelius, N., Lofberg, R., and Ekbom, A. A 10-year survey of inflammatory bowel diseases-drug therapy, costs and adverse reactions. Aliment Pharmacol Ther. 2001; 15 (4): 475-81. **Does not report side effects by medication class**

Blumenstein, I., Herrmann, E., Filmann, N., Zosel, C., Tacke, W., Bock, H., et al. Female patients suffering from inflammatory bowel diseases are treated less frequently with immunosuppressive medication and have a higher disease activity A subgroup analysis of a large multi-centre, prospective, internet-based study. J Crohns Colitis. 2011; 5 (3): 203-210. **Does not evaluate a drug of interest; does not apply to key questions**

Bokemeyer, B. Infiximab in an outpatient gastroenterological practice: Tolerance, prognostic parameters and cost-effectiveness: Infliximab in der gastroenterologischen fachpraxis: Vertraglichkeit, prognoseparameter und kosteneffektivitat. Verdauungskrankheiten. 2002; 20 (3): 107-113. **Not written in English**

Bonaz, B., Boitard, J., Marteau, P., Lemann, M., Coffin, B., Flourie, B., et al. Tioguanine in patients with Crohn's disease intolerant or resistant to azathioprine/mercaptopurine. Aliment Pharmacol Ther. 2003; 18 (4): 401-8. **Does not evaluate a drug of interest**

Bondesen, S., Rasmussen, S. N., Rask-Madsen, J., Nielsen, O. H., Lauritsen, K., Binder, V., et al. F. 5-Aminosalicylic acid in the treatment of inflammatory bowel disease. Acta Med Scand. 87; 221 (3): 227-42. **No original data**

Bonnet, N., Guis, S., Koeppel, M.-C., Roudier, J., Grimaud, J.-C., Jean-Pastor, M.-J., et al. Cutaneous events during anti-TNF alpha therapy: A prospective observational study of 41 cases: Evenements cutaneomuqueux au cours des traitements par anti-TNF alpha : etude observationnelle prospective de 41 cas. Ann. Dermatol. Venereol. 2010; 137 (1): 12-20. **Not written in English**

Boot, A. M., Bouquet, J., Krenning, E. P., and de Muinck Keizer-Schrama, S. M. Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. Gut. 98; 42 (2): 188-94. **Does not evaluate a drug of interest; does not apply to key questions**

Bordeianou, L., Stein, S. L., Ho, V. P., Dursun, A., Sands, B. E., Korzenik, J. R., and Hodin, R. A. Immediate versus tailored prophylaxis to prevent symptomatic recurrences after surgery for ileocecal Crohn's disease?. Surgery (USA). 2011; 149 (1): 72-78. **Does not report side effects by medication class**

Borrelli, O., Bascietto, C., Viola, F., Bueno de Mesquita, M., Barbato, M., Mancini, V., Bosco, S., and Cucchiara, S. Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. Dig Liver Dis. 2004; 36 (5): 342-7. **Does not report side effects by medication class**

Borrelli, O., Cordischi, L., Cirulli, M., Paganelli, M., Labalestra, V., Uccini, S., Russo, P. M., and Cucchiara, S. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. Clin Gastroenterol Hepatol. 2006; 4 (6): 744-53. **Does not evaluate a drug of interest**

Boruchowicz, A., Gallon, P., Foissey, D., Gower, P., Gamblin, C., Cuingnet, P., Maunoury, V., Cortot, A., and Colombel Frederic, J. F. Acute pancreatitis associated with corticosteroids in Crohn's disease: Pancreatite aigue associee a un traitement corticoide au cours de la maladie de Crohn. Gastroenterol. Clin. Biol. 2003; 27 (5): 560-561. **Not written in English**

Bossa, F., Biscaglia, G., Merla, A., and Terracciano, F. Long-term remission with adalimumab in steroid-dependent Crohn's disease patients with multiple drug intolerances. Dig. Liver Dis. Suppl. 2010; 4 (1): 7-9. **Case report or case series**

Bossi, A., Giuliani, G. E., Del Poggio, P., Fenili, D., and Ragaini, S. Uncoated versus coated 5-aminosalicylic acid in Crohn's disease. Lancet. 89; 1 (8632): 276. **Case report or case series**

Bouguen, G., Trouilloud, I., Siproudhis, L., Oussalah, A., Bigard, M. A., Bretagne, J. F., and Peyrin-Biroulet, L. Long-term outcome of non-fistulizing (ulcers, stricture) perianal Crohn's disease in patients treated with infliximab. Aliment Pharmacol Ther. 2009; 30 (7): 749-56. **Does not report side effects by medication class**

Bouhnik, Y., Lemann, M., Mary, J. Y., Scemama, G., Tai, R., Matuchansky, C., Modigliani, R., and Rambaud, J. C. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. Lancet. 96; 347 (8996): 215-9. **Does not evaluate a drug of interest**

Boyle, B., Mackner, L., Ross, C., Moses, J., Kumar, S., and Crandall, W. A single-center experience with methotrexate after thiopurine therapy in pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2010; 51 (6): 714-7. **Does not report side effects by medication class**

Bresci, G., Parisi, G., Bertoni, M., Masolino, P., Scatena, F., and Capria, A. Does the initial location of Crohn's disease have an influence on the time-to-relapse in patients under maintenance treatment with oral mesalamine?. J Clin Gastroenterol. 2000; 31 (2): 147-51. **Does not apply to key questions**

Bresci, G., Petrucci, A., and Banti, S. 5-aminosalicylic acid in the prevention of relapses of Crohn's disease in remission: a long-term study. Int J Clin Pharmacol Res. 91; 11 (4): 200-2. **Does not report side effects by medication class**

Breynaert, C., Ferrante, M., Fidder, H., Van Steen, K., Noman, M., Ballet, V., et al. Tolerability of shortened infliximab infusion times in patients with inflammatory bowel diseases: a single-center cohort study. Am J Gastroenterol. 2011; 106 (4): 778-85. **Does not evaluate a drug of interest; other observational study without a comparison group**

Briggs, R. C. Jr. Five year follow-up study of sixty cases of inflammatory diseases treated with alternate day corticosteroid therapy. Ariz Med. 72; 29 (2): 120-8. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; does not evaluate a drug of interest**

Brignola, C., De Simone, G., Belloli, C., Iannone, P., Belluzzi, A., Gionchetti, P., et al. Steroid treatment in active Crohn's disease: a comparison between two regimens of different duration. Aliment Pharmacol Ther. 94; 8 (4): 465-8. **Does not evaluate a drug of interest**

Brignola, C., De Simone, G., Iannone, P., Belloli, C., Evangelisti, A., Campieri, M., et al. Influence of steroid treatment's duration in patients with active Crohn's disease. Agents Actions. 92; Spec No C90-2. **Does not evaluate a drug of interest**

Brooke, B. N., Cave, D. R., and King, D. W. Place of azathioprine for Crohn's disease. Lancet. 76; 1 (7968): 1041-2. **Does not report side effects by medication class**

Brooke, B. N., Javett, S. L., and Davison, O. W. Further experience with azathioprine for Crohn's disease. Lancet. 70; 2 (7682): 1050-3. **Case report or case series; other observational study without a comparison group**

Brown, C. H. and Achkar, E. Azathioprine therapy for inflammatory bowel disease. A preliminary report. Am J Gastroenterol. 70; 54 (4): 363-77. **Does not evaluate a drug of interest; other observational study without a comparison group**

Brown, S. L., Greene, M. H., Gershon, S. K., Edwards, E. T., and Braun, M. M. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum. 2002; 46 (12): 3151-8. **Case report or case series**

Brunasso, A. M., Laimer, M., and Massone, C. Paradoxical reactions to targeted biological treatments: A way to treat and trigger?. Acta Derm Venereol. 2010; 90 (2): 183-5. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; case report or case series**

Bujanover, Y. and Weiss, B. Anti-tumor necrosis factor therapy for pediatric inflammatory bowel diseases. Isr Med Assoc J. 2008; 10 (8-9): 634-9. **No original data**

Buller, H. A. Objectives and outcomes in the conventional treatment of pediatric Crohn's disease. J Pediatr Gastroenterol Nutr. 2001; 33 Suppl 1 S11-8. **No original data**

Burakoff, R., Barish, C. F., Riff, D., Pruitt, R., Chey, W. Y., Farraye, F. A., et al. A phase 1/2A trial of STA 5326, an oral interleukin-12/23 inhibitor, in patients with active moderate to severe Crohn's disease. Inflamm Bowel Dis. 2006; 12 (7): 558-65. **Does not evaluate a drug of interest**

Burger, D. C. and Florin, T. H. Peripheral neuropathy with infliximab therapy in inflammatory bowel disease. Inflamm Bowel Dis. 2009; 15 (12): 1772. **Case report or case series**

Burmester, G. R., Mease, P., Dijkmans, B. A., Gordon, K., Lovell, D., Panaccione, R., et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis. 2009; 68 (12): 1863-9. **No original data; other observational study without a comparison group**

Busam, J., Berghaus, D., and Garbe, W. E. [Oral high dose mesalazine treatment in Crohn's disease and ulcerative colitis]. Verdauungskrankheiten. 96; 14 (2): 60-67. **Not written in English**

Cadahia, V., Garcia-Carbonero, A., Vivas, S., Fuentes, D., Nino, P., Rebollo, P., et al. Infliximab improves quality of life in the short-term in patients with fistulizing Crohn's disease in clinical practice. Rev Esp Enferm Dig. 2004; 96 (6): 369-74; 374-8. **Does not evaluate a drug of interest; other observational study without a comparison group**

Caesar, I., Gross, V., Roth, M., Andus, T., Schmidt, C., Raedsch, R., et al. Treatment of active and postactive ileal and colonic Crohn's disease with oral pH-modified-release budesonide. German Budesonide Study Group. Hepatogastroenterology. 97; 44 (14): 445-51. **Does not evaluate a drug of interestOther observational study without a comparison group**

Caesar, I., Gross, V., Roth, M., Andus, T., Schmidt, C., Raedsch, R., et al. Treatment of active Crohn's ileocolitis with oral pH-modified budesonide. Germany Budesonide Study Group. Z Gastroenterol. 95; 33 (5): 247-50. **Other observational study without a comparison group; does not report side effects by medication class**

Cagnard, B., Tosoni-Verlingue, D., Tribut, O., Moizard, C., Bridoux-Henno, L., Delaperriere, N., et al. [Advantages of different dosages of active metabolites in the follow-up of azathioprine treatment for Crohn disease]. Arch Pediatr. 2006; 13 Suppl 1 S67-8. **Not written in English**

Campbell, S. and Ghosh, S. Is neutropenia required for effective maintenance of remission during azathioprine therapy in inflammatory bowel disease?. Eur J Gastroenterol Hepatol. 2001; 13 (9): 1073-6. **Other observational study without a comparison group; does not report side effects by medication class**

Campieri, M., Lanfranchi, G. A., Brignola, C., Bazzochi, G., Gionchetti, P., Minguzzi, M. R., et al. 5-aminosalicylic acid for the treatment of inflammatory bowel diseases. Gastroenterology. 85; 89 (3): 701-3. **No original data**

Cao, Q., Zhu, Q., Shang, Y., Gao, M., and Si, J. Thiopurine methyltransferase gene polymorphisms in Chinese patients with inflammatory bowel disease. Digestion. 2009; 79 (1): 58-63. **Does not report side effects by medication class**

Caprilli, R., Andreoli, A., Capurso, L., Corrao, G., D'Albasio, G., Gioieni, A., et al. Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of post-operative recurrence of Crohn's disease. Gruppo Italiano per lo Studio del Colon e del Retto (GISC). Aliment Pharmacol Ther. 94; 8 (1): 35-43. **Does not apply to key questions; other reason**

Caprilli, R., Andreoli, A., Capurso, L., Corrao, G., D'Albasio, G., Gioieni, A., et al. Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of post-operative recurrence of Crohn's disease. ALIMENT. PHARMACOL. THER. 94; 8 (1): 35-43. **Other reason**

Carbone, J., Gonzalez-Lara, V., Sarmiento, E., Chean, C., Perez, J. L., Marin, I., et al. Humoral and cellular monitoring to predict the development of infection in Crohn's disease patients beginning treatment with infliximab. Ann N Y Acad Sci. 2007; 1107 346-55. **Does not evaluate a drug of interest; does not report side effects by medication class**

Card, T., West, J., Hubbard, R., and Logan, R. F. Hip fractures in patients with inflammatory bowel disease and their relationship to corticosteroid use: a population based cohort study. Gut. 2004; 53 (2): 251-5. **Other reason**

Carter, M. J. and Lobo, A. J. Lack of effect of intravenous azathioprine on time to respond for steroid treated Crohn's disease. Gut. 2001; 48 (3): 295-6. **No original data**

Casellas, F., Rodrigo, L., Nino, P., Pantiga, C., Riestra, S., and Malagelada, J. R. Sustained improvement of health-related quality of life in Crohn's disease patients treated with infliximab and azathioprine for 4 years. Inflamm Bowel Dis. 2007; 13 (11): 1395-400. **Other observational study without a comparison group**

Casellas, F., Vallano, A., and Malagelada, J. R. Leukopenia and thrombocytopenia as adverse effects of treatment with 5-aminosalicylic suppositories. J Clin Gastroenterol. 96; 22 (2): 160-1. **Case report or case series**

Cassinotti, A., Fichera, M., Ardizzone, S., and Porro, G. B. Is mucosal healing a predictor of decreased risk of Crohn's disease relapse after withdrawal of 1-year, successful adalimumab?. Dig. Liver Dis. Suppl. 2010; 4 (1): 18-21. **Case report or case series**

Castro, M., Rossi, L., Papadatou, B., Bracci, F., Knafelz, D., Ambrosini, M. I., et al. Long-term treatment with autologous red blood cells loaded with dexamethasone 21-phosphate in pediatric patients affected by steroid-dependent Crohn disease. J Pediatr Gastroenterol Nutr. 2007; 44 (4): 423-6. **Does not evaluate a drug of interest**

Cattan, P., Bonhomme, N., Panis, Y., Lemann, M., Coffin, B., Bouhnik, Y., et al. Fate of the rectum in patients undergoing total colectomy for Crohn's disease. Br J Surg. 2002; 89 (4): 454-9. **Does not apply to key questions; does not report side effects by medication class**

Cattan, S., Lemann, M., Thuillier, F., Bengoufa, D., Rabian, C., Ngo, Y., et al. [6-mercaptopurine levels and study of blood lymphocyte subsets during azathioprine treatment of Crohn's disease]. Gastroenterol Clin Biol. 98; 22 (2): 160-7. **Not written in English**

Caviglia, R., Ribolsi, M., Rizzi, M., Emerenziani, S., Annunziata, M. L., and Cicala, M. Maintenance of remission with infliximab in inflammatory bowel disease: efficacy and safety long-term follow-up. World J Gastroenterol. 2007; 13 (39): 5238-44. **Does not evaluate a drug of interest; does not report side effects by medication class**

Cezard JP, Munck A, Mouterde O, Morali A, Lenaerts C, Lachaux A, et al. Prevention of recurrence by mesalamine (PENTASA) in pediatric Crohn's disease. A multicentric double blind trial. Journal of Pediatric Gastroenterology and Nutrition. 2003; 36 (4): 542. **Abstract only**

Cezard, J. P., Nouaili, N., Talbotec, C., Hugot, J. P., Gobert, J. G., Schmitz, J., et al. A prospective study of the efficacy and tolerance of a chimeric antibody to tumor necrosis factors (remicade) in severe pediatric crohn disease. J Pediatr Gastroenterol Nutr. 2003; 36 (5): 632-6. **Does not evaluate a drug of interest; other observational study without a comparison group**

Chalupna, P., Lukas, M., Kumsta, M., and Sebesta, I. [Effect of the activity of thiopurine methyltransfrase on the results of long-term immunosuppressive therapy with azathioprin (6-mercaptopurine) in patients with inflammatory bowel diseases]. Ceska Slov. Gastroenterol. Hepatol. 2002; 56 (6): 208-213. **Not written in English**

Chande, N., Abdelgadir, I., and Gregor, J. The Safety and Tolerability of Methotrexate for Treating Patients With Crohn's Disease. J Clin Gastroenterol. 2011. **Other observational study without a comparison group; does not report side effects by medication class**

Chaparro, M., Panes, J., Garcia, V., Manosa, M., Esteve, M., Merino, O., et al. Long-term durability of infliximab treatment in Crohn's disease and efficacy of dose “escalation” in patients losing response. J Clin Gastroenterol. 2011; 45 (2): 113-8. **Does not apply to key questions; does not report side effects by medication class**

Chapman, P. Sulphasalazine and inflammatory bowel disease. N Z Med J. 87; 100 (822): 257. **No original data**

Chaudhary, R. and Ghosh, S. Prediction of response to infliximab in Crohn's disease. Dig. Liver Dis. 2005; 37 (8): 559-563. **No original data**

Chebli, J. M., Gaburri, P. D., De Souza, A. F., Pinto, A. L., Chebli, L. A., Felga, G. E., et al. Long-term results with azathioprine therapy in patients with corticosteroid-dependent Crohn's disease: open-label prospective study. J Gastroenterol Hepatol. 2007; 22 (2): 268-74. **Other observational study without a comparison group; does not report side effects by medication class**

Chehade, M. and Benkov, K. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn disease. J Pediatr Gastroenterol Nutr. 2001; 32 (2): 120-1. **No original data; other reason**

Cheikh, I., Ben Ammar, A., Essid, M., Azzouz, M., Ettahri, N., Krichene, M., et al. Treatment and outcomes of Crohn's disease. Results of a multicentric and retrospectif Tunisian's study: Traitement et evolution de la maladie de crohn initialement non compliquee. Resultats d'une etude retrospective et multicentrique tunisienne. Tunis. Med. 2002; 80 (4): 193-198. **Not written in English**

Chen, M., Xia, B., Chen, B., Guo, Q., Li, J., Ye, M., and Hu, Z. N-acetyltransferase 2 slow acetylator genotype associated with adverse effects of sulphasalazine in the treatment of inflammatory bowel disease. Can J Gastroenterol. 2007; 21 (3): 155-8. **Does not apply to key questions; other reason**

Chevrel, B. Acute and maintenance therapy of intestinal inflammatory disease with pentasa: LE PENTASA. TRAITEMENT D'ATTAQUE ET D'ENTRETIEN DES MALADIES INFLAMMATOIRES INTESTINALES. MED. CHIR. DIG. 89; 18 (7): 431-436. **Not written in English**

Chevrel, B. Treatment of mild to moderate Crohn's disease by budesonide: Traitement des formes legeres a moderees de la maladie de Crohn par le budesonide. Med. Chir. Dig. 99; 28 (7-8): 265-269. **Not written in English**

Chong, R. Y., Hanauer, S. B., and Cohen, R. D. Efficacy of parenteral methotrexate in refractory Crohn's disease. Aliment Pharmacol Ther. 2001; 15 (1): 35-44. **Other observational study without a comparison group; does not report side effects by medication class**

Chopra, A., Pardi, D. S., Loftus, E. V. Jr, Tremaine, W. J., Egan, L. J., Faubion, W. A., et al. Budesonide in the treatment of inflammatory bowel disease: the first year of experience in clinical practice. Inflamm Bowel Dis. 2006; 12 (1): 29-32. **Other observational study without a comparison group; does not report side effects by medication class**

Chouliaras, G., Panayiotou, J., Dimakou, C., Pachoula, J., Orfanou, I., Chrousos, G. P., et al. Biological agents in paediatric inflammatory bowel disease: a clinical observation study from Greece. Acta Gastroenterol Belg. 2010; 73 (3): 342-8. **Does not report side effects by medication class**

Christodoulou, D., Katsanos, K., Baltayannis, G., Tzabouras, N., and Tsianos, E. V. A report on efficacy and safety of azathioprine in a group of inflammatory bowel disease patients in northwest Greece. Hepatogastroenterology. 2003; 50 (52): 1021-4. **Other observational study without a comparison group; does not report side effects by medication class**

Cino, M. and Greenberg, G. R. Bone mineral density in Crohn's disease: a longitudinal study of budesonide, prednisone, and nonsteroid therapy. Am J Gastroenterol. 2002; 97 (4): 915-21. **Other observational study without a comparison group; does not report side effects by medication class**

Cocco, A. E. and Pavlides, G. P. Fever due to azathioprine in the treatment of patients with an inflammatory bowel disease. Md State Med J. 77; 26 (6): 61-2. **Case report or case series**

Cohen, A. D., Dreiher, J., and Birkenfeld, S. Psoriasis associated with ulcerative colitis and Crohn's disease. J Eur Acad Dermatol Venereol. 2009; 23 (5): 561-5. **Does not apply to key questions**

Cohen, R. D. Efficacy and safety of repeated infliximab infusions for Crohn's disease: 1-year clinical experience. Inflamm Bowel Dis. 2001; 7 Suppl 1 S17-22. **Other observational study without a comparison group; does not report side effects by medication class**

Cohen, R. D., Lewis, J. R., Turner, H., Harrell, L. E., Hanauer, S. B., and Rubin, D. T. Predictors of adalimumab dose escalation in patients with crohn's disease at a tertiary referral center. Inflamm Bowel Dis. 2011. **Does not apply to key questions; case report or case series**

Cohen, R. D., Tsang, J. F., and Hanauer, S. B. Infliximab in Crohn's disease: first anniversary clinical experience. Am J Gastroenterol. 2000; 95 (12): 3469-77. **Other observational study without a comparison group**

Colbert, C., Chavarria, A., and Berkelhammer, C. Fulminant hepatic failure in chronic hepatitis B on withdrawal of corticosteroids, azathioprine and infliximab for Crohn's disease. Inflamm Bowel Dis. 2007; 13 (11): 1453-4. **Case report or case series**

Colli, M. V., Amaro, T. A., Pinto, A. L., Gaburri, P. D., and Chebli, J. M. [Azathioprine toxicity in Crohn's disease: incidence, approach and course]. Rev Assoc Med Bras. 2008; 54 (5): 415-21. **Not written in English**

Colombel JF, Lomann M, Cassagnou M, Bouhnik Y, Duclos B, Dupas JL, et al. Ciprofloxacin Vs Mesalazine in the Treatment of Active Crohn's Disease [abstract]. Gut. 96; 39 Suppl 3 A188. **Abstract only**

Colombel, J. F., Loftus, E. V. Jr, Tremaine, W. J., Pemberton, J. H., Wolff, B. G., Young-Fadok, T., et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am J Gastroenterol. 2004; 99 (5): 878-83. **Does not apply to key questions**

Colombel, J. F., Ricart, E., Loftus, E. V. Jr, Tremaine, W. J., Young-Fadok, T., Dozois, E. J., et al. Management of Crohn's disease of the ileoanal pouch with infliximab. Am J Gastroenterol. 2003; 98 (10): 2239-44. **Other observational study without a comparison group**

Colombel, J. F., Sandborn, W. J., Panaccione, R., Robinson, A. M., Lau, W., Li, J., and Cardoso, A. T. Adalimumab safety in global clinical trials of patients with Crohn's disease. Inflamm Bowel Dis. 2009; 15 (9): 1308-19. **No original data**

Colonna, T. and Korelitz, B. I. The role of leukopenia in the 6-mercaptopurine-induced remission of refractory Crohn's disease. Am J Gastroenterol. 94; 89 (3): 362-6. **Other observational study without a comparison group; does not report side effects by medication class**

Condino, A. A., Fidanza, S., and Hoffenberg, E. J. A home infliximab infusion program. J Pediatr Gastroenterol Nutr. 2005; 40 (1): 67-9. **Does not report side effects by medication class**

Connell, W. R., Kamm, M. A., Dickson, M., Balkwill, A. M., Ritchie, J. K., and Lennard-Jones, J. E. Long-term neoplasia risk after azathioprine treatment in inflammatory bowel disease. Lancet. 94; 343 (8908): 1249-52. **Does not evaluate a drug of interest**

Connell, W. R., Kamm, M. A., Ritchie, J. K., and Lennard-Jones, J. E. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. Gut. 93; 34 (8): 1081-5. **Other observational study without a comparison group; does not report side effects by medication class**

Cortot A, Colombel J-F, Rutgeerts P, Lauritsen K, Malchow H, Haming J, et al. Safety of switching systemic steroids to budesonide controlled ileal release capsules in steroid-dependent patients with inactive crohns disease [abstract]. GUT. 2000; 47 (Suppl III A243): 939. **Abstract only**

Cortot A, Colombel JF, Rutgeerts P, Lauritsen K, Malchow H, Hamling J, et al. Switch from systemic steroids to budesonide controlled ileal release (CIR) capsules in steroid-dependent patients with Crohn`s disease (CD)[abstract]. GUT. 99; 45 (Suppl V): A22. **Abstract only**

Cosnes, J., Nion-Larmurier, I., Beaugerie, L., Afchain, P., Tiret, E., and Gendre, J. P. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. Gut. 2005; 54 (2): 237-41. **Does not apply to key questions**

Costantino, G., Navarra, G., Familiari, L., and Fries, W. Prevention of post-surgical recurrence with adalimumab in a patient with complicated Crohn's disease. Dig. Liver Dis. Suppl. 2010; 4 (1): 22-24. **Case report or case series**

Cottone M, Mocciaro F, and Scimeca D Adalimumab induction for Crohn's disease. Gastroenterology. 2006; 130 (6): 1929. **No original data**

Cottone, M. and Renna, S. IBD: incidence of HSV and HPV with azathioprine. Nat Rev Gastroenterol Hepatol. 2009; 6 (8): 444-5. **No original data**

Cottone, M., Orlando, A., and Mocciaro, F. Improving patients' QoL: how the success of treatment can improve workability. Dig. Liver Dis. Suppl. 2008; 2 (1): 17-18. **No original data**

Crandall, W. V. and Mackner, L. M. Infusion reactions to infliximab in children and adolescents: frequency, outcome and a predictive model. Aliment Pharmacol Ther. 2003; 17 (1): 75-84. **Does not evaluate a drug of interest; other observational study without a comparison group**

Crandall, W., Hyams, J., Kugathasan, S., Griffiths, A., Zrubek, J., et al. Infliximab therapy in children with concurrent perianal Crohn disease: observations from REACH. J Pediatr Gastroenterol Nutr. 2009; 49 (2): 183-90. **Does not evaluate a drug of interest**

Cravo, M., Guerreiro, C. S., Dos Santos, P. M., Brito, M., Ferreira, P., Fidalgo, C., et al. Risk factors for metabolic bone disease in Crohn's disease patients. Inflammatory Bowel Dis. 2010; 16 (12): 2117-2124. **Does not apply to key questions**

Cross, R. K., Lapshin, O., and Finkelstein, J. Patient subjective assessment of drug side effects in inflammatory bowel disease. J. Clin. Gastroenterol. 2008; 42 (3): 244-251. **Does not apply to key questions; does not report side effects by medication class**

Cuffari, C., Dassopoulos, T., Turnbough, L., Thompson, R. E., and Bayless, T. M. Thiopurine methyltransferase activity influences clinical response to azathioprine in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2004; 2 (5): 410-7. **Does not report side effects by medication class**

Cummings, J. R., Keshav, S., and Travis, S. P. Medical management of Crohn's disease. BMJ. 2008; 336 (7652): 1062-6. **No original data**

Curtis, J. R., Kramer, J. M., Martin, C., Saag, K. G., Patkar, N., Shatin, D., et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology (Oxford). 2007; 46 (11): 1688-93. **Does not report side effects by medication class**

Curtis, J. R., Martin, C., Saag, K. G., Patkar, N. M., Kramer, J., Shatin, D., et al. Confirmation of administrative claims-identified opportunistic infections and other serious potential adverse events associated with tumor necrosis factor alpha antagonists and disease-modifying antirheumatic drugs. Arthritis Rheum. 2007; 57 (2): 343-6. **Does not evaluate a drug of interest; does not report side effects by medication class**

Cury, D. B. and Moss, A. C. Ocular manifestations in a community-based cohort of patients with inflammatory bowel disease. Inflamm Bowel Dis. 2009. **Does not report side effects by medication class**

Cury, D. B., Moss, A. C., Elias, G., and Nakao, A. Adalimumab for cutaneous metastatic Crohn's disease. Inflamm Bowel Dis. 2010; 16 (5): 723-4. **Case report or case series**

Czaja-Bulsa, G., Gebala, A., and Korlatowicz-Bilar, A. [The impact of infliximab treatment on mucosal healing and clinical remission in pediatric patients with severe crohn's disease in the own observation]. Pediatr. Wspolczesna. 2010; 12 (2): 104-107. **Not written in English**

Dacute, Haens GR, Van deventer SJH, Van Hogezand R, Chalmers DM, Braakman TAJ, Bijl H, and Rutgeerts PJ Endoscopic Healing with cA2 Anti-TNF Antibodies in Crohn`s Disease: A European Multicenter Trial.(abstrac). Endoscopy. 96; 28 S31. **Abstract only**

Danese, S., Mocciaro, F., Guidi, L., Scribano, M. L., Comberlato, M., Annese, V., et al. Successful induction of clinical response and remission with certolizumab pegol in Crohn's disease patients refractory or intolerant to infliximab: a real-life multicenter experience of compassionate use. Inflamm Bowel Dis. 2008; 14 (8): 1168-70. **Other observational study without a comparison group; does not report side effects by medication class**

Daperno, M., Sostegni, R., Canaparo, R., Serpe, L., Lavagna, A., Crocella, L., et al. Prospective study of the effects of concomitant medications on thiopurine metabolism in inflammatory bowel disease. Aliment Pharmacol Ther. 2009; 30 (8): 843-53. **Does not report side effects by medication class**

Dayharsh, G. A., Loftus, E. V. Jr, Sandborn, W. J., Tremaine, W. J., Zinsmeister, A. R., Witzig, T. E., et al. Epstein-Barr virus-positive lymphoma in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. Gastroenterology. 2002; 122 (1): 72-7. **Case report or case series; other observational study without a comparison group**

De Bie, C. I., Hummel, T. Z., Kindermann, A., Kokke, F. T., Damen, G. M., Kneepkens, C. M., et al. The duration of effect of infliximab maintenance treatment in paediatric Crohn's disease is limited. Aliment Pharmacol Ther. 2011; 33 (2): 243-50. **Other observational study without a comparison group; does not report side effects by medication class**

de Boer, N. K., Zondervan, P. E., Gilissen, L. P., den Hartog, G., Westerveld, B. D., Derijks, L. J., et al. Absence of nodular regenerative hyperplasia after low-dose 6-thioguanine maintenance therapy in inflammatory bowel disease patients. Dig Liver Dis. 2008; 40 (2): 108-13. **Does not evaluate a drug of interestDoes not apply to key questions**

De Iudicibus, S., Stocco, G., Martelossi, S., Drigo, I., Norbedo, S., Lionetti, P., et al. Association of BclI polymorphism of the glucocorticoid receptor gene locus with response to glucocorticoids in inflammatory bowel disease. Gut. 2007; 56 (9): 1319-20. **Does not evaluate a drug of interest**

de Jong, D. J., Bac, D. J., Tan, G., de Boer, S. Y., Grabowsky, I. L., Jansen, J. B., et al. Maintenance treatment with budesonide 6 mg versus 9 mg once daily in patients with Crohn's disease in remission. Neth J Med. 2007; 65 (9): 339-45. **Does not report side effects by medication class; other reason**

de Jong, D. J., Goullet, M., and Naber, T. H. Side effects of azathioprine in patients with Crohn's disease. Eur J Gastroenterol Hepatol. 2004; 16 (2): 207-12. **Does not evaluate a drug of interest; does not report side effects by medication class**

de Jong, D. J., Mannaerts, L., van Rossum, L. G., Corstens, F. H., and Naber, A. H. Longitudinal study of bone mineral density in patients with Crohn's disease. Dig Dis Sci. 2003; 48 (7): 1355-9. **Does not apply to key questions; other observational study without a comparison group**

de Jong, D. J., Tielen, J., Habraken, C. M., Wetzels, J. F., and Naber, A. H. 5-Aminosalicylates and effects on renal function in patients with Crohn's disease. Inflamm Bowel Dis. 2005; 11 (11): 972-6. **Does not report side effects by medication class**

De La Morena, E. J., Abreu, L., Garcia, P., Pineda, J. R., Leal, J. C., Blasco, M., et al. [Treatment with 6-mercaptopurine in Crohn's disease]. GASTROENTEROL. HEPATOL. 94; 17 (7): 361-366. **Not written in English**

de Ridder, L., Escher, J. C., and Taminiau, J. A. [Infliximab therapy in children and adolescents with refractory Crohn's disease in the Netherlands; experience with 23 patients]. Ned Tijdschr Geneeskd. 2002; 146 (40): 1879-83. **Not written in English**

de Ridder, L., Escher, J. C., Bouquet, J., Schweizer, J. J., Rings, E. H., Tolboom, J. J., et al. Infliximab therapy in 30 patients with refractory pediatric crohn disease with and without fistulas in The Netherlands. J Pediatr Gastroenterol Nutr. 2004; 39 (1): 46-52. **Does not evaluate a drug of interest**

de Ridder, L., Rings, E. H., Damen, G. M., Kneepkens, C. M., Schweizer, J. J., Kokke, F. T., et al. Infliximab dependency in pediatric Crohn's disease: long-term follow-up of an unselected cohort. Inflamm Bowel Dis. 2008; 14 (3): 353-8. **Does not report side effects by medication class**

de Saussure, P., Lavergne-Slove, A., Mazeron, M. C., Alain, S., Matuchansky, C., and Bouhnik, Y. A prospective assessment of cytomegalovirus infection in active inflammatory bowel disease. Aliment Pharmacol Ther. 2004; 20 (11-12): 1323-7. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; does not report side effects by medication class**

Dejaco, C., Mittermaier, C., Reinisch, W., Gasche, C., Waldhoer, T., Strohmer, H., et al. Azathioprine treatment and male fertility in inflammatory bowel disease. Gastroenterology. 2001; 121 (5): 1048-53. **Other observational study without a comparison group; does not report side effects by medication class**

Del Corso, L., Moruzzo, D., Romanelli, A. M., Norpoth, M., Pentimone, F., and Bresci, G. [5-Aminosalicylic acid in the prevention of recurrences of Crohn's disease]. Dtsch Med Wochenschr. 95; 120 (50): 1723-7. **Not written in English**

Demetriou, A. A. Comparison of enteral nutrition and drug treatment in active Crohn's disease: results of the European Cooperative Crohn's Disease Study IV. J Parenter Enteral Nutr. 92; 16 (1): 84-5. **Does not evaluate a drug of interest**

Denson, L. A., Kim, M. O., Bezold, R., Carey, R., Osuntokun, B., Nylund, C., et al. A Randomized Controlled Trial of Growth Hormone in Active Pediatric Crohn Disease. J Pediatr Gastroenterol Nutr. 2010. **Does not evaluate a drug of interest**

Derijks, L. J., Gilissen, L. P., Engels, L. G., Bos, L. P., Bus, P. J., Lohman, J. J., et al. Pharmacokinetics of 6-mercaptopurine in patients with inflammatory bowel disease: implications for therapy. Ther Drug Monit. 2004; 26 (3): 311-8. **Other observational study without a comparison group**

Derkx, B., Taminiau, J., Radema, S., Stronkhorst, A., Wortel, C., Tytgat, G., et al. Tumour-necrosis-factor antibody treatment in Crohn's disease. Lancet. 93; 342 (8864): 173-4. **Case report or case series**

Desmond, A. N., O'Regan, K., Curran, C., McWilliams, S., Fitzgerald, T., Maher, M. M., et al. Crohn's disease: factors associated with exposure to high levels of diagnostic radiation. Gut. 2008; 57 (11): 1524-9. **Does not apply to key questions; does not report side effects by medication class**

Deter, H. C., Keller, W., von Wietersheim, J., Jantschek, G., Duchmann, R., and Zeitz, M. Psychological treatment may reduce the need for healthcare in patients with Crohn's disease. Inflamm Bowel Dis. 2007; 13 (6): 745-52. **Does not evaluate a drug of interest; does not apply to key questions**

Dew, M. J., Evans, B. K., and Rhodes, J. 5-Aminosalicylic acid for the treatment of inflammatory bowel disease. Gastroenterology. 84; 87 (2): 480-1. **No original data**

D'Haens G, Rutgeerts P, and Braakman T. Anti-tumor necrosis factor-alpha (cA2) induces remission and endoscopic healing in active Crohn's disease: A double-blind, placebo-controlled study. (ABSTRACT). Acta Gastroenterologica Belgica. 97; 60 (1). **Abstract only**

D'Haens G, Verstraete A, Bouillon R, and Rutgeerts P. Suppression of bone formation by short-term methylprednisolone but not by budesonide cir treatment in active ileocolonic Crohn's disease. (ABSTRACT). Acta Gastroenterologica Belgica. 97; 60 (1): C 34. **Abstract only**

D'Haens, G. and Rutgeerts, P. Immunosuppression-associated lymphoma in IBD. Lancet. 2009; 374 (9701): 1572-1573. **No original data**

D'Haens, G., Geboes, K., and Rutgeerts, P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. Gastrointest Endosc. 99; 50 (5): 667-71. **Other observational study without a comparison group; does not report side effects by medication class**

D'Haens, G., Geboes, K., Ponette, E., Penninckx, F., and Rutgeerts, P. Healing of severe recurrent ileitis with azathioprine therapy in patients with Crohn's disease. Gastroenterology. 97; 112 (5): 1475-81. **Does not apply to key questions; does not report side effects by medication class**

D'Haens, G., Verstraete, A., Cheyns, K., Aerden, I., Bouillon, R., and Rutgeerts, P. Bone turnover during short-term therapy with methylprednisolone or budesonide in Crohn's disease. Aliment Pharmacol Ther. 98; 12 (5): 419-24. **Does not apply to key questions**

Dhawan, S. S., Finks, A. L., and Wang, B. W. Mycobacterial coxitis masked by concomitant staphylococcal infection after infliximab for Crohn's disease. Joint Bone Spine. 2009; 76 (1): 107-8. **Case report or case series**

Dideberg, V., Theatre, E., Farnir, F., Vermeire, S., Rutgeerts, P., De Vos, M., et al. The TNF/ADAM 17 system: implication of an ADAM 17 haplotype in the clinical response to infliximab in Crohn's disease. Pharmacogenet Genomics. 2006; 16 (10): 727-34. **Does not evaluate a drug of interest; does not apply to key questions**

Din, S., Cochrane, C. J., Noble, C. L., Satsangi, J., and Arnott, I. D. Combination therapy of infliximab and azathioprine reduces disease progression in Crohn's disease. Inflamm Bowel Dis. 2008; 14 (1): 143-5. **Other observational study without a comparison group; does not report side effects by medication class**

Din, S., Dahele, A., Fennel, J., Aitken, S., Shand, A. G., Arnott, I. D., et al. Use of methotrexate in refractory Crohn's disease: the Edinburgh experience. Inflamm Bowel Dis. 2008; 14 (6): 756-62. **Does not report side effects by medication class**

Dinca, M., Fries, W., Luisetto, G., Peccolo, F., Bottega, F., Leone, L., et al. Evolution of osteopenia in inflammatory bowel disease. Am J Gastroenterol. 99; 94 (5): 1292-7. **Does not report side effects by medication class**

Domenech, E., Lopez San Roman, A., and Garcia-Planella, E. [How long should combined therapy with biological and immunomodulatory agents be maintained in inflammatory bowel disease?]. Gastroenterol Hepatol. 2010. **No original data; not written in English**

Domenech, E., Manosa, M., Navarro, M., Masnou, H., Garcia-Planella, E., Zabana, Y., et al. Long-term methotrexate for Crohn's disease: safety and efficacy in clinical practice. J Clin Gastroenterol. 2008; 42 (4): 395-9. **Other observational study without a comparison group; does not report side effects by medication class**

Domenech, E., Nos, P., Papo, M., Lopez-San Roman, A., Garcia-Planella, E., and Gassull, M. A. 6-mercaptopurine in patients with inflammatory bowel disease and previous digestive intolerance of azathioprine. Scand J Gastroenterol. 2005; 40 (1): 52-5. **Does not evaluate a drug of interest; case report or case series**

Domenech, E., Scala, L., Bernal, I., Garcia-Planella, E., Casalots, A., Pinol, M., et al. [Azathioprine and mesalazine in the prevention of postsurgical recurrence of Crohn's disease: a retrospective study.]. Gastroenterol Hepatol. 2004; 27 (10): 563-7. **Not written in English**

Donald, I. P. and Wilkinson, S. P. The value of 5-aminosalicylic acid in inflammatory bowel disease for patients intolerant or allergic to sulphasalazine. Postgrad Med J. 85; 61 (722): 1047-8. **Other reason**

D'Ovidio, V., Aratari, A., Viscido, A., Pimpo, M. T., Caprilli, R., and Torchio, P. Infliximab and quality of life in steroid-dependent Crohn's disease. Dig Liver Dis. 2004; 36 (8): 557-8. **Other observational study without a comparison group; does not report side effects by medication class**

D'Ovidio, V., Vernia, P., Gentile, G., Capobianchi, A., Marcheggiano, A., Viscido, A., et al. Cytomegalovirus infection in inflammatory bowel disease patients undergoing anti-TNFalpha therapy. J Clin Virol. 2008; 43 (2): 180-3. **Does not evaluate a drug of interest; other observational study without a comparison group**

Dreyling, K. W., Hoppe, U., Peskar, B. A., Schaarschmidt, K., and Peskar, B. M. Leukotrienes in Crohn's disease: effect of sulfasalazine and 5-aminosalicylic acid. Adv Prostaglandin Thromboxane Leukot Res. 87; 17A 339-43. **Does not apply to key questions; does not report side effects by medication class**

Drucker, W. R. and Jeejeebhoy, K. N. Azathioprine: an adjunct to surgical therapy of granulomatous enteritis. Ann Surg. 70; 172 (4): 618-26. **Other observational study without a comparison group**

Dubinsky, M. C. Monitoring of AZA/6-MP treatment in children with IBD is necessary. Inflamm Bowel Dis. 2003; 9 (6): 386-8; discussion 392-3. **No original data**

Dubinsky, M. C., Feldman, E. J., Abreu, M. T., Targan, S. R., and Vasiliauskas, E. A. Thioguanine: a potential alternate thiopurine for IBD patients allergic to 6-mercaptopurine or azathioprine. Am J Gastroenterol. 2003; 98 (5): 1058-63. **Does not evaluate a drug of interest; does not report side effects by medication class**

Dubinsky, M. C., Vasiliauskas, E. A., Singh, H., Abreu, M. T., Papadakis, K. A., et al. 6-thioguanine can cause serious liver injury in inflammatory bowel disease patients. Gastroenterology. 2003; 125 (2): 298-303. **No original data; case report or case series**

Dubinsky, M. C., Yang, H., Hassard, P. V., Seidman, E. G., Kam, L. Y., Abreu, M. T., et al. 6-MP metabolite profiles provide a biochemical explanation for 6-MP resistance in patients with inflammatory bowel disease. Gastroenterology. 2002; 122 (4): 904-15. **Other observational study without a comparison group**

Ducharme, J., Pelletier, C., and Zacharias, R. The safety of infliximab infusions in the community setting. Can J Gastroenterol. 2010; 24 (5): 307-11. **No original data; other observational study without a comparison group**

Dudley-Brown, S., Nag, A., Cullinan, C., Ayers, M., Hass, S., and Panjabi, S. Health-related quality-of-life evaluation of crohn disease patients after receiving natalizumab therapy. Gastroenterol Nurs. 2009; 32 (5): 327-39. **No original data**

Duricova, D., Pedersen, N., Elkjaer, M., Jensen, J. K., and Munkholm, P. 5-aminosalicylic acid dependency in Crohn's disease: a Danish Crohn Colitis Database study. J Crohns Colitis. 2010; 4 (5): 575-81. **Other observational study without a comparison group; does not report side effects by medication class**

Duricova, D., Pedersen, N., Lenicek, M., Hradsky, O., Bronsky, J., Adamcova, M., et al. Infliximab dependency in children with Crohn's disease. Aliment Pharmacol Ther. 2009; 29 (7): 792-9. **Does not report side effects by medication class**

East, J. E., Brooker, J. C., Rutter, M. D., Saunders, B. P. A pilot study of intrastricture steroid versus placebo injection after balloon dilatation of Crohn's strictures. Clin Gastroenterol Hepatol. 2007; 5 (9): 1065-9. **Does not apply to key questions**

Echarri, A., Castro, J., Barreiro, M., Carpio, D., Pereira, S., and Lorenzo, A. Evaluation of adalimumab therapy in multidisciplinary strategy for perianal Crohn's disease patients with infliximab failure. J Crohns Colitis. 2010; 4 (6): 654-60. **Other observational study without a comparison group; does not report side effects by medication class**

Egan, L. J., Sandborn, W. J., Tremaine, W. J., Leighton, J. A., Mays, D. C., Pike, M. G., et al. A randomized dose-response and pharmacokinetic study of methotrexate for refractory inflammatory Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther. 99; 13 (12): 1597-604. **Does not evaluate a drug of interest; other observational study without a comparison group**

Eland, I. A., De Gooyer, D. J., Stokkers, P., Westerveld, B. D., Wilson, J. H. P., and Stricker, B. H. C. [Acute pancreatitis attributed to use of mesalazine]. Tijdschr. Geneeskd. 98; 54 (6): 417-420. **Not written in English**

El-Nachef, N., Terdiman, J., and Mahadevan, U. Anti-tumor necrosis factor therapy for inflammatory bowel disease in the setting of immunosuppression for solid organ transplantation. Am J Gastroenterol. 2010; 105 (5): 1210-1. **Case report or case series**

Elseviers, M. M., D'Haens, G., Lerebours, E., Plane, C., Stolear, J. C., Riegler, G., et al. Renal impairment in patients with inflammatory bowel disease: association with aminosalicylate therapy?. Clin Nephrol. 2004; 61 (2): 83-9. **Does not report side effects by medication class**

Escher JC, van den Brink G, Kate FT, te Velde A, and van Deventer S. Mucosal healing and down-regulation of inflammation with anti-tumor necrosis factor a (INFLIXIMAB) in children with refractory Crohn's disease. Journal of Pediatric Gastroenterology & Nutrition. 2000; 31 (Suppl 2): S19. **Abstract only**

Eshuis, E. J., Bemelman, W. A., van Bodegraven, A. A., Sprangers, M. A., Bossuyt, P. M., van Milligen de Wit, A. W., et al. Laparoscopic ileocolic resection versus infliximab treatment of distal ileitis in Crohn's disease: a randomized multicenter trial (LIR!C-trial). BMC Surg. 2008; 8 15. **Other reason**

Eshuis, E. J., Polle, S. W., Slors, J. F., Hommes, D. W., Sprangers, M. A., Gouma, D. J., et al. Long-term surgical recurrence, morbidity, quality of life, and body image of laparoscopic-assisted vs. open ileocolic resection for Crohn's disease: a comparative study. Dis Colon Rectum. 2008; 51 (6): 858-67. **Does not evaluate a drug of interest**

Ezzat, Y. and Hamdy, K. The frequency of low bone mineral density and its associated risk factors in patients with inflammatory bowel diseases. Int. J. Rheum. Dis. 2010; 13 (3): 259-265. **Does not evaluate a drug of interest; does not report side effects by medication class**

Faber, S. M. and Korelitz, B. I. Experience with Eudragit-S-coated mesalamine (Asacol) in inflammatory bowel disease. An open study. J Clin Gastroenterol. 93; 17 (3): 213-8. **Other observational study without a comparison group**

Fahrlaender, H. and Shalev, E. Regional enteritis (Crohn's disease). [A follow up and comparative study of 182 patients]. Dtsch. Med. Wochenschr. 74; 99 (44): 2207-2214. **Not written in English**

Fanning, S. B., Chapman, G., Yau, Y., Leong, R. W. Education and imaging. Gastrointestinal: Improvement of granuloma annulare with anti-tumour necrosis factor alpha therapy for Crohn's disease. J Gastroenterol Hepatol. 2010; 25 (1): 215. **Does not apply to key questions; case report or case series**

Farrell, R. J., Shah, S. A., Lodhavia, P. J., Alsahli, M., Falchuk, K. R., Michetti, P., et al. Clinical experience with infliximab therapy in 100 patients with Crohn's disease. Am J Gastroenterol. 2000; 95 (12): 3490-7. **Other observational study without a comparison group; does not report side effects by medication class**

Faubion, W. A. Jr, Loftus, E. V. Jr, Harmsen, W. S., Zinsmeister, A. R., and Sandborn, W. J. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology. 2001; 121 (2): 255-60. **Other observational study without a comparison group**

Fausa, O. and Gjone, E. Azathioprine (Imurel) therapy in Crohn's disease. Acta Med Scand. 71; 190 (3): 211-2. **Case report or case series; other observational study without a comparison group**

Feagan B, Greenberg GR, Lofberg R, Ferguson A, and Persson T. Budesonide controlled ileal release prolonged remission in Crohn's disease: A pooled analysis [abstract]. Gut. 97; 41 Suppl 3 A17 **Abstract only**

Feagan BG, Sandborn WJ, Baker JP, Cominellis F, Sutherland LR, Elson CO, et al. A randomized, double-blind, placebo-controlled trial of CDP571, a humanized monoclonal antibody to tumour necrosis factor-a, in patients with corticosteroid-dependent Crohn's disease. Alimentary Pharmacology & Therapeutics. 2005; 21 (4): 373-84. **Does not evaluate a drug of interest**

Feagan, B. G. Aminosalicylates for active disease and in the maintenance of remission in Crohn's disease. Eur J Surg. 98; 164 (12): 903-9. **No original data**

Feagan, B. G. Methotrexate treatment for Crohn's disease. Inflamm Bowel Dis. 98; 4 (2): 120-1. **No original data**

Feagan, B. Infliximab in the treatment of Crohn's disease. Can J Gastroenterol. 2000; 14 Suppl C 6C. **No original data**

Feagins, L. A. and Spechler, S. J. Biologic agent use varies inversely with age at diagnosis in Crohn's disease. Dig Dis Sci. 2010; 55 (11): 3164-70. **Does not apply to key questions**

Fefferman, D. S., Lodhavia, P. J., Alsahli, M., Falchuk, K. R., Peppercorn, M. A., Shah, S. A., et al. Smoking and immunomodulators do not influence the response or duration of response to infliximab in Chrohn's disease. Inflammatory Bowel Dis. 2004; 10 (4): 346-351. **Does not apply to key questions; does not report side effects by medication class**

Felder, J. B., Adler, D. J., and Korelitz, B. I. The safety of corticosteroid therapy in Crohn's disease with an abdominal mass. Am J Gastroenterol. 91; 86 (10): 1450-5. **Case report or case series**

Felekis, T., Katsanos, K., Kitsanou, M., Trakos, N., Theopistos, V., Christodoulou, D., et al. Spectrum and frequency of ophthalmologic manifestations in patients with inflammatory bowel disease: a prospective single-center study. Inflamm Bowel Dis. 2009; 15 (1): 29-34. **Does not evaluate a drug of interest; does not report side effects by medication class**

Ferlitsch, A., Teml, A., Reinisch, W., Ulbrich, G., Wrba, F., Homoncik, M., et al. 6-Thioguanine associated nodular regenerative hyperplasia in patients with inflammatory bowel disease may induce portal hypertension. Am. J. Gastroenterol. 2007; 102 (11): 2495-2503. **Does not evaluate a drug of interest; does not apply to key questions**

Fernando del Rosario, J., Orenstein, S. R., Neigut, D. A., Giarrusso, V., Wolfson, N., and Kocoshis, S. A. Retrospective analysis of alternate-day prednisone maintenance therapy for Crohn's disease. Clin Pediatr (Phila). 98; 37 (7): 413-9. **Does not evaluate a drug of interest; other observational study without a comparison group**

Fieschi, C., Allez, M., and Casanova, J. L. High risk of infectious disease caused by salmonellae and mycobacteria infections in patients with Crohn disease treated with anti-interleukin-12 antibody. Clin Infect Dis. 2005; 40 (9): 1381. **No original data; does not evaluate a drug of interest**

Fiorino, G., Allez, M., Malesci, A., and Danese, S. Review article: anti TNF-alpha induced psoriasis in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2009; 29 (9): 921-7. **No original data**

Fishman, M. Methotrexate and maintenance of remission in Crohn's disease. Can J Gastroenterol. 2001; 15 (7): 428. **No original data**

Floren, C. H., Ahren, B., Bengtsson, M., Bartosik, J., and Obrant, K. Bone mineral density in patients with Crohn's disease during long-term treatment with azathioprine. J Intern Med. 98; 243 (2): 123-6. **Does not apply to key questions**

Florent, C., Cortot, A., Quandale, P., Sahmound, T., Modigliani, R., Sarfaty, E., et al. Placebo-controlled clinical trial of mesalazine in the prevention of early endoscopic recurrences after resection for Crohn's disease. Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). Eur J Gastroenterol Hepatol. 96; 8 (3): 229-33. **Does not apply to key questions**

Fogo, A. J., Hunt, J. B., and Clement, M. Multiple cutaneous malignancies arising in a patient with Crohn disease treated with concomitant azathioprine and antitumour necrosis factor-alpha. Clin Exp Dermatol. 2010. **Case report or case series**

Forbes, A. Is there a role for multidrug therapy in active Crohn's disease?. Inflamm Bowel Dis. 2008; 14 Suppl 2 S257-8. **No original data**

Fournier, M. R., Klein, J., Minuk, G. Y., and Bernstein, C. N. Changes in Liver Biochemistry During Methotrexate Use for Inflammatory Bowel Disease. Am J Gastroenterol. 2010. **Does not apply to key questions; other observational study without a comparison group**

Francella, A., Dyan, A., Bodian, C., Rubin, P., Chapman, M., and Present, D. H. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. Gastroenterology. 2003; 124 (1): 9-17. **Does not apply to key questions**

Franklin, J. L. and Rosenberg, H. H. Impaired folic acid absorption in inflammatory bowel disease: effects of salicylazosulfapyridine (Azulfidine). Gastroenterology. 73; 64 (4): 517-25. **Does not apply to key questions**

Fraser, A. G., Morton, D., McGovern, D., Travis, S., and Jewell, D. P. The efficacy of methotrexate for maintaining remission in inflammatory bowel disease. Aliment Pharmacol Ther. 2002; 16 (4): 693-7. **Other observational study without a comparison group**

Fraser, J. S., Muller, A. F., Smith, D. J., Newman, D. J., and Lamb, E. J. Renal tubular injury is present in acute inflammatory bowel disease prior to the introduction of drug therapy. Aliment Pharmacol Ther. 2001; 15 (8): 1131-7. **Other observational study without a comparison group**

Friedman, L. S. Male infertility related to 5-ASA enemas. Dig Dis Sci. 89; 34 (5): 803. **No original data; does not report side effects by medication class**

Friesen, C. A., Calabro, C., Christenson, K., Carpenter, E., Welchert, E., Daniel, J. F., et al. Safety of infliximab treatment in pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2004; 39 (3): 265-9. **Does not report side effects by medication class**

Fuentes, D., Torrente, F., Keady, S., Thirrupathy, K., Thomson, M. A., Walker-Smith, J. A., et al. High-dose azathioprine in children with inflammatory bowel disease. Aliment Pharmacol Ther. 2003; 17 (7): 913-21. **Other observational study without a comparison group; does not report side effects by medication class**

Fuster Sanjurjo, L., Salazar Laya, B., Rodriguez Penin, I., Lopez Sandomingo, L., Dominguez Urbistondo, G., and Iglesias Barreira, R. [Quality of life in patients with Crohn's disease under treatment with adalimumab]. Aten. Farm. 2010; 12 (6): 375-378. **Not written in English**

Gabalec, L., Bures, J., Sedova, M., and Valenta, Z. [Quality of life of Crohn's disease patients]. Cas Lek Cesk. 2009; 148 (5): 201-5. **Not written in English**

Gaertner, W. B., Madoff, R. D., Spencer, M. P., Mellgren, A., Goldberg, S. M., and Lowry, A. C. Results of combined medical and surgical treatment of rectovaginal fistula in Crohn's disease. Colorectal Dis. 2010. **Does not apply to key questions**

Garcia Vidal, C., Rodriguez Fernandez, S., Martinez Lacasa, J., Salavert, M., Vidal, R., Rodriguez Carballeira, M., et al. Paradoxical response to antituberculous therapy in infliximab-treated patients with disseminated tuberculosis. Clin Infect Dis. 2005; 40 (5): 756-9. **Case report or case series**

Garcia-Ferrer, L., Estornell, J., and Palanca, V. Myocarditis by mesalazine with cardiac magnetic resonance imaging. Eur Heart J. 2009; 30 (8): 1015. **Case report or case series**

Garcia-Vidal, C., Rodriguez-Fernandez, S., Teijon, S., Esteve, M., Rodriguez-Carballeira, M., et al. Risk factors for opportunistic infections in infliximab-treated patients: the importance of screening in prevention. Eur J Clin Microbiol Infect Dis. 2009; 28 (4): 331-7. **Does not report side effects by medication class**

Gassull, M. A., Fernandez-Banares, F., Cabre, E., Papo, M., Giaffer, M. H., Sanchez-Lombrana, J. L., et al. Fat composition may be a clue to explain the primary therapeutic effect of enteral nutrition in Crohn's disease: results of a double blind randomised multicentre European trial. Gut. 2002; 51 (2): 164-8. **Does not evaluate a drug of interest**

Gazouli, M., Pachoula, I., Panayotou, I., Mantzaris, G., Syriopoulou, V. P., Goutas, N., et al. Thiopurine S-methyltransferase genotype and the use of thiopurines in paediatric inflammatory bowel disease Greek patients. J Clin Pharm Ther. 2010; 35 (1): 93-7. **Does not apply to key questions; does not report side effects by medication class**

Gearry, R. B., Barclay, M. L., Burt, M. J., Collett, J. A., and Chapman, B. A. Thiopurine drug adverse effects in a population of New Zealand patients with inflammatory bowel disease. Pharmacoepidemiol Drug Saf. 2004; 13 (8): 563-7. **Does not report side effects by medication class**

Gelb, A. and Zalusky, R. The use of azathiaprine and 6-mercaptopurine (6-MP) as immunosuppressive therapy in inflammatory bowel disease and its role in the etiology of lymphocytic lymphoma. Am J Gastroenterol. 83; 78 (5): 316. **No original data; case report or case series**

Gelbmann, C. M., Rogler, G., Gross, V., Gierend, M., Bregenzer, N., Andus, T., et al. Prior bowel resections, perianal disease, and a high initial Crohn's disease activity index are associated with corticosteroid resistance in active Crohn's disease. Am J Gastroenterol. 2002; 97 (6): 1438-45. **Other observational study without a comparison group; does not report side effects by medication class**

Gellona V, J., Zarraonandia A, A., Zuniga D, A., Palma C, R., Contreras P, J., Silva Ch, J., et al. Infliximab in the treatment of patients with Crohn's disease. Preliminary report: Infliximab en el tratamiento de la enfermedad de Crohn. Estudio preliminar. Rev. Med. Chile. 2006; 134 (3): 320-325. **Not written in English**

Gellona, V. J, Zarraonandia, A. A, Zuniga, D. A, Palma, C. R, Contreras, P. J, Silva Ch, J., et al. [Infliximab in the treatment of patients with Crohn's disease: preliminary report]. Rev Med Chil. 2006; 134 (3): 320-5. **Not written in English**

Generini, S., Giacomelli, R., Fedi, R., Fulminis, A., Pignone, A., Frieri, G., et al. Infliximab in spondyloarthropathy associated with Crohn's disease: an open study on the efficacy of inducing and maintaining remission of musculoskeletal and gut manifestations. Ann Rheum Dis. 2004; 63 (12): 1664-9. **Other observational study without a comparison group**

Geyer, A. S., Anhalt, G. J., and Nousari, H. C. Effectiveness of infliximab in the treatment of refractory perineal cutaneous Crohn disease. Arch Dermatol. 2000; 136 (4): 459-60. **Case report or case series**

Gheorghe, L., Gheorghe, C., Badea, M., Vadan, R., Parvulescu, I., Toader, C., et al. Infliximab for Crohn's disease in clinical practice: the experience of a single center in romania. Rom J Gastroenterol. 2003; 12 (1): 7-13. **Does not evaluate a drug of interest; other reason**

Ghosh, S. Top down therapy in Crohn's disease. Dig. Liver Dis. Suppl. 2008; 2 (1): 15-16. **No original data**

Ghosh, S., Goldin, E., Gordon, F. H., Malchow, H. A., Rask-Madsen, J., Rutgeerts, P., et al. Natalizumab for active Crohn's disease. N Engl J Med. 2003; 348 (1): 24-32. **No original data**

Giaffer, M. H., O'Brien, C. J., and Holdsworth, C. D. Clinical tolerance to three 5-aminosalicylic acid releasing preparations in patients with inflammatory bowel disease intolerant or allergic to sulphasalazine. Aliment Pharmacol Ther. 92; 6 (1): 51-9. **Does not evaluate a drug of interest**

Gilissen, L. P., Derijks, L. J., Bos, L. P., Bus, P. J., Hooymans, P. M., and Engels, L. G. Therapeutic drug monitoring in patients with inflammatory bowel disease and established azathioprine therapy. Clin Drug Investig. 2004; 24 (8): 479-86. **Does not apply to key questions**

Gilissen, L. P., Derijks, L. J., Driessen, A., Bos, L. P., Hooymans, P. M., Stockbrugger, R. W., et al. Toxicity of 6-thioguanine: no hepatotoxicity in a series of IBD patients treated with long-term, low dose 6-thioguanine. Some evidence for dose or metabolite level dependent effects? Dig Liver Dis. 2007; 39 (2): 156-9. **Does not evaluate a drug of interest; other observational study without a comparison group**

Gill, AM, Otaki, AT, Daly, JR, Spencer-Peet, J. Oral Betamethasone 17-Valerate in Chronic Ulcerative Colitis and Crohn's Disease. Br Med J. 65; 2 (5452): 29-31. **Does not evaluate a drug of interest; other observational study without a comparison group**

Ginard, D. and Marino, Z. [Inflammatory bowel disease: should all patients be premedicated when infliximab is administered to reduce infusion reactions and/or immunogenicity?]. Gastroenterol Hepatol. 2008; 31 (8): 542-3. **No original dataNot written in English**

Gionchetti, P., Campieri, M., Belluzzi, A., Boschi, S., Brignola, C., Miglioli, M., et al. Bioavailability of single and multiple doses of a new oral formulation of 5-ASA in patients with inflammatory bowel disease and healthy volunteers. Aliment Pharmacol Ther. 94; 8 (5): 535-40. **Does not evaluate a drug of interest; other observational study without a comparison group**

Gionchetti, P., Tambasco, R., and Campieri, M. How do biological drugs meet treatment goals in anti-TNF naive patients, in patients with anti-TNF failure and in fistulizing patients?. Dig. Liver Dis. Suppl. 2008; 2 (1): 13-14. **No original data**

Girodengo, L., Barthet, M., Desjeux, A., Berdah, S., Berthezene, P., Bellon, P., et al. [Risk factors for Crohn's disease relapse after treatment of intestinal stenosis]. Ann Chir. 2001; 126 (4): 296-301. **Not written in English**

Gisbert, J. P., Gomollon, F., Mate, J., and Pajares, J. M. Pharmacological treatment of fistulizing Crohn's disease: Tratamiento farmacologico de las fistulas en la enfermedad de Crohn. Med. Clin. 2001; 116 (17): 664-671. **Not written in English**

Gisbert, J. P., Luna, M., Gonzalez-Lama, Y., Pousa, I. D., Velasco, M., Moreno-Otero, R., et al. Effect of 5-aminosalicylates on renal function in patients with inflammatory bowel disease: 4-year follow-up study. Gastroenterol Hepatol. 2008; 31 (8): 477-84. **Other observational study without a comparison group; does not report side effects by medication class**

Gisbert, J. P., Luna, M., Gonzalez-Lama, Y., Pousa, I. D., Velasco, M., Moreno-Otero, R., et al. Liver injury in inflammatory bowel disease: long-term follow-up study of 786 patients. Inflamm Bowel Dis. 2007; 13 (9): 1106-14. **Other observational study without a comparison group; does not report side effects by medication class**

Gisbert, J. P., Nino, P., Cara, C., and Rodrigo, L. Comparative effectiveness of azathioprine in Crohn's disease and ulcerative colitis: prospective, long-term, follow-up study of 394 patients. Aliment Pharmacol Ther. 2008; 28 (2): 228-38. **Does not evaluate a drug of interestDoes not report side effects by medication class**

Glazier, K. D., Palance, A. L., Griffel, L. H., and Das, K. M. The ten-year single-center experience with 6-mercaptopurine in the treatment of inflammatory bowel disease. J Clin Gastroenterol. 2005; 39 (1): 21-6. **Does not report side effects by medication class; other reason**

Gokhale, R., Favus, M. J., Karrison, T., Sutton, M. M., Rich, B., and Kirschner, B. S. Bone mineral density assessment in children with inflammatory bowel disease. Gastroenterology. 98; 114 (5): 902-11. **Does not evaluate a drug of interest; does not report side effects by medication class**

Goldberg, H. I., Caruthers, S. B. Jr, Nelson, J. A., and Singleton, J. W. Radiographic findings of the National Cooperative Crohn's Disease Study. Gastroenterology. 79; 77 (4 Pt 2): 925-37. **Other reason**

Goldstein, F. and Murdock, M. G. Clinical and radiologic improvement of regional enteritis and enterocolitis after treatment with salicylazosulfapyridine. Am J Dig Dis. 71; 16 (5): 421-31. **Case report or case series**

Goldstein, F., Menduke, H., Thornton, J. J. 3rd, and Abramson, J. Anti-inflammatory drug treatment of Crohn's disease: a prospective evaluation of 100 consecutively treated patients. J Clin Gastroenterol. 80; 2 (1): 77-85. **Does not report side effects by medication class**

Gomollon, F., Hinojosa, J., and Nos, P. [Budesonide and inflammatory bowel disease]. Gastroenterol Hepatol. 99; 22 (10): 525-32. **Not written in English**

Gonzaga, J. E., Ananthakrishnan, A. N., Issa, M., Beaulieu, D. B., Skaros, S., Zadvornova, Y., et al. Durability of infliximab in Crohn's disease: A single-center experience. Inflamm Bowel Dis. 2009; 15 (12): 1837-1843. **Other observational study without a comparison group; does not report side effects by medication class**

Gonzalez-Lama, Y., Lopez-San Roman, A., Marin-Jimenez, I., Casis, B., Vera, I., Bermejo, F., et al. Open-label infliximab therapy in Crohn's disease: a long-term multicenter study of efficacy, safety and predictors of response. Gastroenterol Hepatol. 2008; 31 (7): 421-6. **Does not report side effects by medication class**

Goodacre, R. L., Ali, M. A., Vanderlinden, B., Hamilton, J. D., Castelli, M., and Seaton, T. Hemolytic anemia in patients receiving sulfasalazine. Digestion. 78; 17 (6): 503-8. **Other reason**

Goodhand, J., Dawson, R., Hefferon, M., Tshuma, N., Swanson, G., Wahed, M., et al. Inflammatory bowel disease in young people: the case for transitional clinics. Inflamm Bowel Dis. 2010; 16 (6): 947-52. **Does not apply to key questionsDoes not report side effects by medication class**

Gorard, D. A., Hunt, J. B., Payne-James, J. J., Palmer, K. R., Rees, R. G., Clark, M. L., et al. Initial response and subsequent course of Crohn's disease treated with elemental diet or prednisolone. Gut. 93; 34 (9): 1198-202. **Does not evaluate a drug of interest**

Grand, R. J. Management of severe colitis/ileocolitis. Inflamm Bowel Dis. 98; 4 (3): 225-7. **No original data**

Green, C. J. and Mee, A. S. Re-introduction of azathioprine in previously intolerant patients. Eur J Gastroenterol Hepatol. 2006; 18 (1): 17-9. **Does not apply to key questionsOther observational study without a comparison group**

Green, J. R., Lobo, A. J., Giaffer, M., Travis, S., and Watkins, H. C. Maintenance of Crohn's disease over 12 months: fixed versus flexible dosing regimen using budesonide controlled ileal release capsules. Aliment Pharmacol Ther. 2001; 15 (9): 1331-41. **Does not evaluate a drug of interest; other observational study without a comparison group**

Greenberger, N. J. and Miner, P. B. Is maintenance therapy effective in Crohn's disease? Lancet. 94; 344 (8927): 900-1. **No original data**

Griffiths, A. M. Monitoring of azathioprine/6-mercaptopurine treatment in children with IBD is not necessary. Inflamm Bowel Dis. 2003; 9 (6): 389-91; discussion 392-3. **No original data**

Griffiths, A. M., Nguyen, P., Smith, C., MacMillan, J. H., and Sherman, P. M. Growth and clinical course of children with Crohn's disease. Gut. 93; 34 (7): 939-43. **Does not evaluate a drug of interest; does not report side effects by medication class**

Gross, R. and Scapa, E. Hepatotoxicity of 6-mercaptopurine in Crohn's disease. Am J Gastroenterol. 92; 87 (12): 1885-6. **Case report or case series**

Grossman, A. B., Noble, A. J., Mamula, P., and Baldassano, R. N. Increased dosing requirements for 6-mercaptopurine and azathioprine in inflammatory bowel disease patients six years and younger. Inflamm Bowel Dis. 2008; 14 (6): 750-5. **Other observational study without a comparison group; does not report side effects by medication class**

Gruenagel, H. H., Orth, E., and Beglau, E. [Crohn's disease: Follow-up, conservative and operative treatment. Review of 55 patients]. MED. WELT. 81; 32 (48): 1832-1836. **Not written in English**

Gujral, N., Friedenberg, F., Friedenberg, J., Gabriel, G., Kotler, M., and Levine, G. Pleuropericarditis related to the use of mesalamine. Dig Dis Sci. 96; 41 (3): 624-6. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; case report or case series**

Gunnarsson, I., Forslid, J., and Ringertz, B. Mesalazine-induced lupus syndrome. Lupus. 99; 8 (6): 486-8. **Case report or case series**

Guslandi, M. Respiratory distress during mesalamine therapy. Dig Dis Sci. 99; 44 (1): 48-9. **Case report or case series**

Haapamaki, J., Turunen, U., Roine, R. P., Farkkila, M. A., and Arkkila, P. E. Impact of demographic factors, medication and symptoms on disease-specific quality of life in inflammatory bowel disease. Qual Life Res. 2009; 18 (8): 961-9. **Does not apply to key questions**

Haber, C. J., Meltzer, S. J., Present, D. H., and Korelitz, B. I. Nature and course of pancreatitis caused by 6-mercaptopurine in the treatment of inflammatory bowel disease. Gastroenterology. 86; 91 (4): 982-6. **Does not evaluate a drug of interest; does not report side effects by medication class**

Hadigan CBR, Braegger CP, Vasilauskis E, Escher JC, Sinaasappel M, Ferry GD, et al. Pharmacokinetics of infliximab (Anti-TNFx) in children with Crohn's disease: A multicenter trial. Journal of Pediatric Gastroenterology & Nutrition. 99; 29 (4): 525. **Abstract only**

Hadziselimovic, F. Adalimumab induces and maintains remission in severe, resistant paediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2008; 46 (2): 208-11. **Case report or case series**

Haennig, A., Bonnet, D., Thebault, S., and Alric, L. Infliximab-induced acute hepatitis during Crohn's disease therapy: Absence of cross-toxicity with adalimumab. Gastroenterol Clin Biol. 2010. **Case report or case series**

Hagel, S., Bruns, T., Kantowski, M., Fix, P., Seidel, T., and Stallmach, A. Cholestatic hepatitis, acute acalculous cholecystitis, and hemolytic anemia: primary Epstein-Barr virus infection under azathioprine. Inflamm Bowel Dis. 2009; 15 (11): 1613-6. **Case report or case series**

Haines, M. L., Ajlouni, Y., Irving, P. M., Sparrow, M. P., Rose, R., Gearry, R. B., et al. Clinical usefulness of therapeutic drug monitoring of thiopurines in patients with inadequately controlled inflammatory bowel disease. Inflammatory Bowel Dis. 2011; 17 (6): 1301-1307. **Does not evaluate a drug of interestDoes not report side effects by medication class**

Hanauer, S. B. Natural history of corticosteroid therapy for inflammatory bowel disease. Rev. Gastroenterol. Disord. 2002; 2 (2): 93-94. **Other observational study without a comparison groupOther reason**

Hanauer, S. B., Korelitz, B. I., Rutgeerts, P., Peppercorn, M. A., Thisted, R. A., Cohen, R. D., and Present, D. H. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. Gastroenterology. 2004; 127 (3): 723-9. **Does not apply to key questions**

Hanauer, S. B., Krawitt, E. L., Robinson, M., Rick, G. G., and Safdi, M. A. Long-term management of Crohn's disease with mesalamine capsules (Pentasa). Pentasa Crohn's Disease Compassionate Use Study Group. Am J Gastroenterol. 93; 88 (9): 1343-51. **Other observational study without a comparison group**

Harries, J. T. and Lloyd, J. K. Azathioprine in the treatment of Crohn's disease. Acta Paediatr Scand. 71; 60 (3): 376. **Does not evaluate a drug of interest; case report or case series**

Hausmann, J., Zabel, K., Herrmann, E., and Schroder, O. Methotrexate for maintenance of remission in chronic active Crohn's disease: long-term single-center experience and meta-analysis of observational studies. Inflamm Bowel Dis. 2010; 16 (7): 1195-202. **Does not report side effects by medication class**

Hausmann, M., Herfarth, H., Scholmerich, J., and Rogler, G. Glucocorticoid receptor isoform expression does not predict steroid treatment response in IBD. Gut. 2007; 56 (9): 1328-9. **Does not evaluate a drug of interest**

Haveran, L. A., Sehgal, R., Poritz, L. S., McKenna, K. J., Stewart, D. B., and Koltun, W. A. Infliximab and/or azathioprine in the treatment of Crohn's disease-like complications after IPAA. Dis. Colon Rectum. 2011; 54 (1): 15-20. **Does not apply to key questions**

Hawwa, A. F., Millership, J. S., Collier, P. S., Vandenbroeck, K., McCarthy, A., Dempsey, S., et al. Pharmacogenomic studies of the anticancer and immunosuppressive thiopurines mercaptopurine and azathioprine. Br J Clin Pharmacol. 2008; 66 (4): 517-28. **Other observational study without a comparison group**

Heijman, J. A., Vroegh, A. N., Van Dullemen, H. M., Postma, M. J., and Rutten, W. J. M. J. [Costs and effectiveness: Azathioprine for the treatment of inflammatory bowel diseases]. Pharm. Weekbl. 2002; 137 (11): 402-405. **Not written in English**

Hellers, G., Cortot, A., Jewell, D., Leijonmarck, C. E., Lofberg, R., Malchow, H., et al. Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group. Gastroenterology. 99; 116 (2): 294-300. **Does not apply to key questions**

Herfarth, H., Gross, V., Andus, T., Caesar, I., Vogelsang, H., Adler, G., et al. Analysis of the therapeutic efficacy of different doses of budesonide in patients with active Crohn's ileocolitis depending on disease activity and localization. Int J Colorectal Dis. 2004; 19 (2): 147-52. **Does not evaluate a drug of interest**

Herfarth, H., Tjaden, C., Lukas, M., Obermeier, F., Dilger, K., Muller, R., et al. Adverse events in clinical trials with azathioprine and mesalamine for prevention of postoperative recurrence of Crohn's disease. Gut. 2006; 55 (10): 1525-6. **No original data**

Hermann, G. G. Sulfasalazine: adverse effects. Dig Dis Sci. 84; 29 (8): 781-2. **Case report or case series**

Hermida C, Cantero J, Moreno-Otero R, and Mate-Jimenez J Methotrexate and 6-mercaptopurine in steroid-dependent inflammatory bowel disease patients: A randomized controlled clinical trial.[abstract]. GUT. 99; 45 (Suppl V): A132. **Abstract only**

Herrlinger, K. R., Deibert, P., Schwab, M., Kreisel, W., Fischer, C., Fellermann, K., et al. Remission maintenance by tioguanine in chronic active Crohn's disease. Aliment Pharmacol Ther. 2003; 17 (12): 1459-64. **Does not evaluate a drug of interest**

Herrlinger, K. R., Fellermann, K., Fischer, C., Kreisel, W., Deibert, P., Schoelmerich, J., et al. Thioguanine-nucleotides do not predict efficacy of tioguanine in Crohn's disease. Aliment Pharmacol Ther. 2004; 19 (12): 1269-76. **Does not evaluate a drug of interest; does not apply to key questions**

Herrlinger, K. R., Witthoeft, T., Raedler, A., Bokemeyer, B., Krummenerl, T., Schulzke, J. D., et al. Randomized, double blind controlled trial of subcutaneous recombinant human interleukin-11 versus prednisolone in active Crohn's disease. Am J Gastroenterol. 2006; 101 (4): 793-7. **Does not evaluate a drug of interest**

Hibi, T., Iwao, Y., Yajima, T., Inoue, N., Ueno, Y., Takaishi, H., et al. Immunosuppressive agents in the treatment of Crohn's disease and ulcerative colitis. J Gastroenterol. 95; 30 Suppl 8 121-3. **Does not evaluate a drug of interest; other reason**

Hindorf, U., Johansson, M., Eriksson, A., Kvifors, E., and Almer, S. H. Mercaptopurine treatment should be considered in azathioprine intolerant patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2009; 29 (6): 654-61. **Does not report side effects by medication class**

Hinojosa del Val, J., Moles, J. R., Nos, P., Hoyos, M., Ramirez, J. J., Primo, J., et al. [Efficacy of 6-mercaptopurine in the treatment of inflammatory bowel disease]. Rev. Esp. Enferm. Dig. 95; 87 (11): 775-780. **Not written in English**

Hinojosa, J., Gomollon, F., Garcia, S., Bastida, G., Cabriada, J. L., Saro, C., et al. Efficacy and safety of short-term adalimumab treatment in patients with active Crohn's disease who lost response or showed intolerance to infliximab: a prospective, open-label, multicentre trial. Aliment Pharmacol Ther. 2007; 25 (4): 409-18. **Other observational study without a comparison group; does not report side effects by medication class**

Ho, G. T., Mowat, A., Potts, L., Cahill, A., Mowat, C., Lees, C. W., et al. Efficacy and complications of adalimumab treatment for medically-refractory Crohn's disease: analysis of nationwide experience in Scotland (2004-2008). Aliment Pharmacol Ther. 2009; 29 (5): 527-34. **Does not report side effects by medication class**

Ho, G. T., Smith, L., Aitken, S., Lee, H. M., Ting, T., Fennell, J., et al. The use of adalimumab in the management of refractory Crohn's disease. Aliment Pharmacol Ther. 2008; 27 (4): 308-15. **Other observational study without a comparison group; does not report side effects by medication class**

Hoang, P., Fontaine, P., Dalton, H. R., Gehenot, M., Sibille, C., et al. Immunosuppressive therapy in inflammatory bowel disease. Acta Gastroenterol Belg. 94; 57 (5-6): 333-8. **No original data**

Holdsworth, C. D. Sulphasalazine hepatotoxicity after 15 years' treatment. Br Med J (Clin Res Ed). 83; 287 (6394): 759. **No original data**

Holtmann, M. H., Galle, P. R., and Neurath, M. F. Treatment of patients with Crohn's disease and concomitant chronic hepatitis C with a chimeric monoclonal antibody to TNF. Am J Gastroenterol. 2003; 98 (2): 504-5. **Case report or case series**

Holtmann, M. H., Krummenauer, F., Claas, C., Kremeyer, K., Lorenz, D., Rainer, O., et al. Significant differences between Crohn's disease and ulcerative colitis regarding the impact of body mass index and initial disease activity on responsiveness to azathioprine: results from a European multicenter study in 1,176 patients. Dig Dis Sci. 2010; 55 (4): 1066-78. **Other observational study without a comparison group; does not report side effects by medication class**

Holtmann, M. H., Krummenauer, F., Claas, C., Kremeyer, K., Lorenz, D., Rainer, O., et al. Long-term effectiveness of azathioprine in IBD beyond 4 years: a European multicenter study in 1176 patients. Dig Dis Sci. 2006; 51 (9): 1516-24. **Other observational study without a comparison group**

Hommel, K. A. and Baldassano, R. N. Brief Report: Barriers to Treatment Adherence in Pediatric Inflammatory Bowel Disease. J Pediatr Psychol. 2009. **Does not apply to key questions**

Hommes, D. W., Parlevliet, W., Sterringa, G. J., Hermans, M., Bartelsman, J. F. W. M., and Van Deventer, S. J. H. [Infliximab therapy in patients with Crohn's disease; experience with 132 patients]. Ned. Tijdschr. Geneeskd. 2002; 146 (25): 1187-1191. **Not written in English**

Hommes, D. W., van de Heisteeg, B. H., van der Spek, M., Bartelsman, J. F., and van Deventer, S. J. Infliximab treatment for Crohn's disease: one-year experience in a Dutch academic hospital. Inflamm Bowel Dis. 2002; 8 (2): 81-6. **Other observational study without a comparison group; does not report side effects by medication class**

Huang, L. J., Zhu, Q., Lei, M., and Cao, Q. Current use of immunosuppressive agents in inflammatory bowel disease patients in East China. World J Gastroenterol. 2009; 15 (24): 3055-9. **Does not report side effects by medication class**

Huber, W., Herrmann, G., Schuster, T., Phillip, V., Saugel, B., Schultheiss, C., et al. Life-threatening complications of Crohns disease and ulcerative colitis: A systematic analysis of admissions to an ICU during 18 years: Lebensbedrohliche Komplikationen von Morbus Crohn und Colitis ulcerosa. Dtsch. Med. Wochenschr. 2010; 135 (14): 668-674. **Not written in English**

Hudson, E., Dore, C., Sowter, C., Toovey, S., and Levi, A. J. Sperm size in patients with inflammatory bowel disease on sulfasalazine therapy. Fertil Steril. 82; 38 (1): 77-84. **Does not apply to key questions**

Huerta, C., Johansson, S., Wallander, M. A., and Garcia Rodriguez, L. A. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med. 2007; 167 (9): 935-43. **Does not evaluate a drug of interest**

Hyams, J. S., Markowitz, J., and Wyllie, R. Use of infliximab in the treatment of Crohn's disease in children and adolescents. J Pediatr. 2000; 137 (2): 192-6. **Other observational study without a comparison group**

Hyams, J. S., Wilson, D. C., Thomas, A., Heuschkel, R., Mitton, S., Mitchell, B., et al. Natalizumab therapy for moderate to severe Crohn disease in adolescents. J Pediatr Gastroenterol Nutr. 2007; 44 (2): 185-91. **Other observational study without a comparison group**

Hyams, J., Crandall, W., Kugathasan, S., Griffiths, A., Olson, A., Johanns, J., et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007; 132 (3): 863-73; quiz 1165-6. **Other observational study without a comparison group; does not report side effects by medication class**

Hyams, J., Walters, T. D., Crandall, W., Kugathasan, S., Griffiths, A., Blank, M., et al. Safety and efficacy of maintenance infliximab therapy for moderate-to-severe Crohn's disease in children: REACH open-label extension. Curr. Med. Res. Opin. 2011; 27 (3): 651-662. **Does not evaluate a drug of interestOther observational study without a comparison group**

Hyder, S. A., Travis, S. P., Jewell, D. P., McC Mortensen, N. J., and George, B. D. Fistulating anal Crohn's disease: results of combined surgical and infliximab treatment. Dis Colon Rectum. 2006; 49 (12): 1837-41. **Other observational study without a comparison group**

Iglesias, M., Barreiro de Acosta, M., Vazquez, I., Figueiras, A., Nieto, L., Lorenzo, A., et al. Psychological impact of Crohn's disease on patients in remission: anxiety and depression risks. Rev Esp Enferm Dig. 2009; 101 (4): 249-57. **Does not apply to key questions**

Iofel, E., Chawla, A., Daum, F., and Markowitz, J. Mesalamine intolerance mimics symptoms of active inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2002; 34 (1): 73-6. **Case report or case series**

Irving, P. M. Recent advances in the management of inflammatory bowel disease. Clin Med. 2009; 9 (6): 605-8. **No original data**

Ito, H., Furuta, S., Sasaki, H., Yoshida, T., Takano, Y., and Hibi, T. Pharmacokinetics and safety of single and multiple doses of Asacol tablets in Japanese healthy volunteers. Adv Ther. 2009; 26 (8): 749-61. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD**

Izuel-Rami, M., Carcelen Andres, J., Allende-Bandre, Ma. A., Agustin Ferrandez, Ma. J., Urbieta Sanz, E., et al. Study of the use of infliximab in Crohn' disease: Estudio de utilizacion de infliximab en la enfermedad de Crohn. Aten. Farm. 2004; 6 (5): 333-342. **Not written in English**

Jacobstein, D. A., Markowitz, J. E., Kirschner, B. S., Ferry, G., Cohen, S. A., Gold, B. D., et al. Premedication and infusion reactions with infliximab: results from a pediatric inflammatory bowel disease consortium. Inflamm Bowel Dis. 2005; 11 (5): 442-6. **Does not report side effects by medication class**

Jahnsen, J., Falch, J. A., Mowinckel, P., and Aadland, E. Body composition in patients with inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2003; 98 (7): 1556-62. **Does not apply to key questions**

Jakobsen, C., Munkholm, P., Paerregaard, A., and Wewer, V. Steroid dependency and pediatric inflammatory bowel disease in the era of immunomodulators-A population-based study. Inflamm Bowel Dis. 2010. **Other observational study without a comparison group; does not report side effects by medication class**

Jakobsen, C., Paerregaard, A., Munkholm, P., Faerk, J., Lange, A., Andersen, J., et al. Pediatric inflammatory bowel disease: Increasing incidence, decreasing surgery rate, and compromised nutritional status: A prospective population-based cohort study 2007-2009. Inflammatory Bowel Dis. 2011. **Case report or case series; does not report side effects by medication class**

Jalocha, L., Wojtun, S., Gil, J., and Dyrla, P. Efficacy of anti-TNF-(alpha) agents in mucosal healing in Crohn disease: Skutecznosc lekow anty-TNF-(alpha) w gojeniu sluzowkowym u osob z choroba lesniowskiego- Crohna. Prz. Gastroenterol. 2009; 4 (4): 184-187. **Not written in English**

Jankovic, G. Aminosalicylates in Crohn's disease. Arch. Gastroenterohepatol. 2008; 27 (1-2): 17-22. **No original data**

Jantschek G, Zeitz M, Pritsch M, Wirsching M, Klor H U, Studt HH, et al. Effect of psychotherapy on the course of crohn's disease: results of the prospective multicenter psychotherapy treatment study on crohn's disease. Scandinavian Journal of Gastroenterology. 98; 33 1289-96. **Does not evaluate a drug of interest; does not apply to key questions**

Jaspers, G. J., Verkade, H. J., Escher, J. C., de Ridder, L., Taminiau, J. A., and Rings, E. H. Azathioprine maintains first remission in newly diagnosed pediatric Crohn's disease. Inflamm Bowel Dis. 2006; 12 (9): 831-6. **Does not report side effects by medication class**

Javett, S. L. and Hoffmann, V. J. Azathioprine in acute Crohn's disease. S Afr Med J. 72; 46 (38): 1369. **Case report or case series**

Jenss H, Hartmann F, Schulmerich J, and Deutsche 5-ASA Studiengruppe 5-Aminosalicylic acid versus methylprednisolone in the therapy of acute Crohn's disease - Results of a double-blind multicentric clinical study. Klinische Wochenschrift. 90; 68 (Suppl 19): 34. **Not written in EnglishAbstract only**

Jharap, B., Seinen, M. L., de Boer, N. K., van Ginkel, J. R., Linskens, R. K., Kneppelhout, J. C., et al. Thiopurine therapy in inflammatory bowel disease patients: Analyses of two 8-year intercept cohorts. Inflamm Bowel Dis. 2010. **Does not report side effects by medication class**

Jick, H., Myers, M. W., and Dean, A. D. The risk of sulfasalazine- and mesalazine-associated blood disorders. Pharmacotherapy. 95; 15 (2): 176-81. **Does not report side effects by medication class**

John, A., Dickey, K., Fenwick, J., Sussman, B., and Beeken, W. Pneumatosis intestinalis in patients with Crohn's disease. Dig Dis Sci. 92; 37 (6): 813-7. **Other reason**

Judit, B. K., Nagy, A., Szabo, A., and Lorincz, M. To grow up with Crohn's disease: (A follow-up of 81 patients until the 18th year of age): Felnoni Crohn-betegseggel: (81 gyermek kovetese 18 eves korig). Orvosi Hetil. 2011; 152 (14): 546-554. **Not written in English**

Jung, Y. S., Cheon, J. H., Park, J. J., Moon, C. M., Kim, E. S., Lee, J. H., et al. Correlation of genotypes for thiopurine methyltransferase and inosine triphosphate pyrophosphatase with long-term clinical outcomes in Korean patients with inflammatory bowel diseases during treatment with thiopurine drugs. J Hum Genet. 2010; 55 (2): 121-3. **Does not apply to key questions**

Jurgens, M., Mahachie John, J. M., Cleynen, I., Schnitzler, F., Fidder, H., van Moerkercke, W., et al. Levels of C-reactive Protein Are Associated With Response to Infliximab Therapy in Patients With Crohn's Disease. Clin. Gastroenterol. Hepatol. 2011; 9 (5): 421-427.e1. **Does not evaluate a drug of interest**

Kabacam, G. and Toruner, M. What is the importance of anti-TNF agents in the treatment of luminal (inflammatory type) Crohn's disease?. Turk J Gastroenterol. 2010; 21 (1): 107-12. **No original data**

Kader, H. A., Raynor, S. C., Young, R., Kaufman, S. S., Vanderhoof, J., Ruby, E. I., et al. Introduction of 6-mercaptopurine in Crohn's disease patients during the perioperative period: a preliminary evaluation of recurrence of disease. J Pediatr Gastroenterol Nutr. 97; 25 (1): 93-7. **Does not apply to key questions; does not report side effects by medication class**

Kader, H. A., Wenner, W. J. Jr, Telega, G. W., Maller, E. S., and Baldassano, R. N. Normal thiopurine methyltransferase levels do not eliminate 6-mercaptopurine or azathioprine toxicity in children with inflammatory bowel disease. J Clin Gastroenterol. 2000; 30 (4): 409-13. **Does not evaluate a drug of interest; does not apply to key questions**

Kane, S. and Dixon, L. Adherence rates with infliximab therapy in Crohn's disease. Aliment Pharmacol Ther. 2006; 24 (7): 1099-103. **Other observational study without a comparison group**

Kane, S. V., Chao, J., and Mulani, P. M. Adherence to infliximab maintenance therapy and health care utilization and costs by Crohn's disease patients. Adv Ther. 2009; 26 (10): 936-46. **Does not apply to key questions; does not report side effects by medication class**

Kaplan, G. and Panaccione, R. Use of combination therapy in IBD. Inflamm Bowel Dis. 2008; 14 Suppl 2 S219-21. **No original data**

Karmiris, K. and Koutroubakis, I. E. Role of infliximab in the treatment of fistulizing Crohn's disease. Ann. Gastroenterol. 2005; 18 (3): 297-302. **No original data**

Karmiris, K., Paintaud, G., Noman, M., Magdelaine-Beuzelin, C., Ferrante, M., Degenne, D., et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. Gastroenterology. 2009; 137 (5): 1628-40. **Does not evaluate a drug of interest; other observational study without a comparison group**

Karoui, S., Ben Yaghlene, L., Fekih, M., Boubaker, J., and Filali, A. [Corticosteroid dependence and resistance in Crohn's disease: prevalence and predictive factors]. Tunis Med. 2003; 81 (1): 15-9. **Not written in English**

Katsanos, K. H., Stamou, P., Tatsioni, A., Tsianos, V. E., Zoumbas, S., Kavvadia, S., et al. Prevalence of inflammatory bowel disease related dysplasia and cancer in 1500 colonoscopies from a referral center in northwestern Greece. J. Crohn's Colitis. 2011; 5 (1): 19-23. **Does not evaluate a drug of interest; does not report side effects by medication class**

Katsanos, K. H., Tsianos, V. E., Zois, C. D., Zioga, H., Vagias, I., Zervou, E., et al. Inflammatory bowel disease and hepatitis B and C in Western Balkans: A referral centre study and review of the literature. J. Crohn's Colitis. 2010; 4 (4): 450-465. **Other reason**

Katz, J. A. How long is it advisable to continue maintenance treatment of Crohn's disease?. Inflamm Bowel Dis. 2008; 14 Suppl 2 S264-5. **No original data**

Kawanishi, H., Rudolph, E., and Bull, F. E. Azathioprine-induced acute pancreatitis. N Engl J Med. 73; 289 (7): 357. **Case report or case series**

Kerbleski, J. F. and Gottlieb, A. B. Dermatological complications and safety of anti-TNF treatments. Gut. 2009; 58 (8): 1033-1039. **No original data**

Kevans, D., Keegan, D., Mulcahy, H. E., and O'Donoghue, D. P. Infliximab therapy in Crohn's disease: a pragmatic approach?. Aliment Pharmacol Ther. 2006; 24 (2): 351-9. **Other observational study without a comparison group; does not report side effects by medication class**

Khadgawat, R., Makharia, G. K., and Puri, K. Evaluation of bone mineral density among patients with inflammatory bowel disease in a tertiary care setting in India. Indian J Gastroenterol. 2008; 27 (3): 103-6. **Does not report side effects by medication class**

Kiefer, K. and El-Matary, W. 6-mercaptopurine as an alternative to azathioprine in azathioprine-induced hepatoxicity. Inflamm Bowel Dis. 2009; 15 (2): 318-9. **Case report or case series**

Kim, D. U., Kim, Y. H., Kim, B. J., Chang, D. K., Son, H. J., Rhee, P. L., et al. The efficacy of low dose azathioprine/6-mercaptopurine in patients with inflammatory bowel disease. Hepatogastroenterology. 2009; 56 (94-95): 1395-402. **Does not evaluate a drug of interest; other observational study without a comparison group**

Kim, J. H., Cheon, J. H., and Kim, W. H. [The frequency and the course of the adverse effects of azathioprine/6-mercaptopurine treatment in patients with inflammatory bowel disease]. Korean J Gastroenterol. 2008; 51 (5): 291-7. **Not written in English**

Kim, P. S., Zlatanic, J., Korelitz, B. I., and Gleim, G. W. Optimum duration of treatment with 6-mercaptopurine for Crohn's disease. Am J Gastroenterol. 99; 94 (11): 3254-7. **Other observational study without a comparison group; does not report side effects by medication class**

Kim, S. H., Yang, S., Kim, K. J., Kim, E. H., Yoon, S. M., Ye, B. D., et al. [Efficacy of infliximab in the treatment of korean patients with crohns disease]. Korean J Gastroenterol. 2009; 54 (2): 108-16. **Other observational study without a comparison group; not written in English**

Kirschner, B. S. Methotrexate therapy for pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 98; 4 (2): 121-3. **No original data**

Kirschner, B. S. Safety of azathioprine and 6-mercaptopurine in pediatric patients with inflammatory bowel disease. Gastroenterology. 98; 115 (4): 813-21. **Does not evaluate a drug of interest; does not report side effects by medication class**

Kitano, A., Okabe, H., Nakagawa, M., Watanabe, Y., Tabata, A., Obayashi, M., et al. Medication for and perianal lesions in Crohn's disease: A clinical study of 102 cases. J. JPN. SOC. COLO-PROCTOL. 92; 45 (8): 1079-1083. **Not written in English**

Kitis, G. Maintenance azathioprine in Crohn's disease. Lancet. 78; 2 (8103): 1306. **No original data**

Klein, R. Q., Spivack, J., and Choate, K. A. Psoriatic skin lesions induced by certolizumab pegol. Arch Dermatol. 2010; 146 (9): 1055-6. **Case report or case series**

Klingenstein, G., Levy, R. N., Kornbluth, A., Shah, A. K., and Present, D. H. Inflammatory bowel disease related osteonecrosis: report of a large series with a review of the literature. Aliment Pharmacol Ther. 2005; 21 (3): 243-9. **Case report or case series**

Klotz, U. Clinical efficacy of oral 5-aminosalicylic acid in the treatment of inflammatory bowel disease. Am J Gastroenterol. 85; 80 (8): 660. **No original data**

Klotz, U., Maier, K., Fischer, C., and Heinkel, K. Therapeutic efficacy of sulfasalazine and its metabolites in patients with ulcerative colitis and Crohn's disease. N Engl J Med. 80; 303 (26): 1499-502. **Other reason**

Klugmann, T. and Bokemeyer, B. Long-term-tolerance of 6-thioguanine in outpatients with IBD: Langzeit-vertraglichkeit der 6-thioguanin-therapie bei CED-patienten in der gastroenterologischen fachpraxis. Verdauungskrankheiten. 2005; 23 (4): 181-185. **Not written in English**

Ko, J. M., Gottlieb, A. B., and Kerbleski, J. F. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. J Dermatolog Treat. 2009; 20 (2): 100-8. **No original data; case report or case series**

Kochi, S., Matsumoto, T., Esaki, M., Jo, Y., and Iida, M. Prediction of 6-thioguanine nucleotides levels in Japanese patients with inflammatory bowel diseases during long-term thiopurine administration. Scand J Gastroenterol. 2010; 45 (5): 608-14. **Does not apply to key questions; does not report side effects by medication class**

Koelewijn, C., Schrijvers, A., and Oldenburg, B. Infliximab use in patients with Crohn's disease: Quality of life, costs and resource use. Neth. J. Med. 2006; 64 (7): 212-218. **No original data; does not apply to key questions**

Kopylov, U., Mantzaris, G. J., Katsanos, K. H., Reenaers, C., Ellul, P., Rahier, J. F., et al. The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab. Aliment. Pharmacol. Ther. 2011; 33 (3): 349-357. **Does not evaluate a drug of interest; other observational study without a comparison group**

Korelitz, B. I. and Present, D. H. Favorable effect of 6-mercaptopurine on fistulae of Crohn's disease. Dig Dis Sci. 85; 30 (1): 58-64. **Does not evaluate a drug of interest; does not report side effects by medication class**

Korelitz, B. I. Therapy of inflammatory bowel disease, including use of immunosuppressive agents. Clin Gastroenterol. 80; 9 (2): 331-49. **No original data; does not evaluate a drug of interest**

Korelitz, B. I., Adler, D. J., Mendelsohn, R. A., and Sacknoff, A. L. Long-term experience with 6-mercaptopurine in the treatment of Crohn's disease. Am J Gastroenterol. 93; 88 (8): 1198-205. **Other observational study without a comparison group**

Korelitz, B. I., Fuller, S. R., Warman, J. I., and Goldberg, M. D. Shingles during the course of treatment with 6-mercaptopurine for inflammatory bowel disease. Am J Gastroenterol. 99; 94 (2): 424-6. **Case report or case series; does not report side effects by medication class**

Korelitz, B. I., Mirsky, F. J., Fleisher, M. R., Warman, J. I., Wisch, N., and Gleim, G. W. Malignant neoplasms subsequent to treatment of inflammatory bowel disease with 6-mercaptopurine. Am J Gastroenterol. 99; 94 (11): 3248-53. **Other observational study without a comparison group; does not report side effects by medication class**

Korelitz, B. I., Zlatanic, J., Goel, F., and Fuller, S. Allergic reactions to 6-mercaptopurine during treatment of inflammatory bowel disease. J Clin Gastroenterol. 99; 28 (4): 341-4. **Other observational study without a comparison group; does not report side effects by medication class**

Kothe MJC, van Hogezand R, DeWoody K, Braakman T, Schaible T, and van Deventer Controlled study of anti-TNF-alpha treatment for enterocutaneous fistulae complicating Crohn`s disease [abstract]. Eur-j-gastroenterol-hepatol. 97; 9 (Suppl 12): A57. **Abstract only**

Kotlyar, D. S., Blonski, W., Diamond, R. H., Wasik, M., and Lichtenstein, G. R. Hepatosplenic T-cell lymphoma in inflammatory bowel disease: a possible thiopurine-induced chromosomal abnormality. Am J Gastroenterol. 2010; 105 (10): 2299-301. **No original data**

Koutroubakis, I. E., Oustamanolakis, P., Malliaraki, N., Karmiris, K., Chalkiadakis, I., Ganotakis, E., et al. Effects of tumor necrosis factor alpha inhibition with infliximab on lipid levels and insulin resistance in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2009; 21 (3): 283-8. **Does not report side effects by medication class**

Koutroubakis, I. E., Zavos, C., Damilakis, J., Papadakis, G. Z., Neratzoulakis, J., Karkavitsas, N., et al. Low bone mineral density in Greek patients with inflammatory bowel disease: Prevalence and risk factors. Ann. Gastroenterol. 2011; 24 (1): 41-46. **Does not apply to key questions; does not report side effects by medication class**

Kozarek, R. A., Patterson, D. J., Gelfand, M. D., Botoman, V. A., Ball, T. J., and Wilske, K. R. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. Ann Intern Med. 89; 110 (5): 353-6. **Does not evaluate a drug of interest; other observational study without a comparison group**

Kraemer, M., Kirschmeier, A., and Marth, T. Perioperative adjuvant therapy with infliximab in complicated anal Crohn's disease. Int J Colorectal Dis. 2008; 23 (10): 965-9. **Other observational study without a comparison group**

Krupoves, A., Mack, D. R., Seidman, E. G., Deslandres, C., Bucionis, V., and Amre, D. K. Immediate and long-term outcomes of corticosteroid therapy in pediatric Crohn's disease patients. Inflammatory Bowel Dis. 2011; 17 (4): 954-962. **Other observational study without a comparison group; does not report side effects by medication class**

Kugathasan, S. Prolonged duration of response to infliximab in early pediatric Crohn's disease. J Pediatr Gastroenterol Nutr. 2001; 33 Suppl 1 S40-3. **Other observational study without a comparison group; does not report side effects by medication class**

Kugathasan, S., Levy, M. B., Saeian, K., Vasilopoulos, S., Kim, J. P., Prajapati, D., et al. Infliximab retreatment in adults and children with Crohn's disease: risk factors for the development of delayed severe systemic reaction. Am J Gastroenterol. 2002; 97 (6): 1408-14. **Does not evaluate a drug of interestDoes not report side effects by medication class**

Kugathasan, S., Werlin, S. L., Martinez, A., Rivera, M. T., Heikenen, J. B., and Binion, D. G. Prolonged duration of response to infliximab in early but not late pediatric Crohn's disease. Am J Gastroenterol. 2000; 95 (11): 3189-94. **Other observational study without a comparison group; does not report side effects by medication class**

Kull, E. and Beau, P. [Compared azathioprine efficacy in ulcerative colitis and in Crohn's disease]. Gastroenterol Clin Biol. 2002; 26 (4): 367-71. **Not written in English**

Kundhal, P., Zachos, M., Holmes, J. L., and Griffiths, A. M. Controlled ileal release budesonide in pediatric Crohn disease: efficacy and effect on growth. J Pediatr Gastroenterol Nutr. 2001; 33 (1): 75-80. **Does not evaluate a drug of interest; other observational study without a comparison group**

Kunisaki, R., Chaki, O., Taguchi, T., Sugiyama, T., and Sugita, A. Infliximab and the bone in Crohn's disease. Aliment Pharmacol Ther. 2005; 21 (6): 789-90. **No original data**

Kuzela, L., Oltman, M., Sutka, J., Zacharova, B., Paulen, P., Repakova, B., et al. [Results of prospective evaluation of mucosal changes in the small bowel by capsule enteroscopy in patients with Crohn's disease treated with infliximab and adalimumab]. Ceska Slov. Gastroenterol. Hepatol. 2010; 64 (2): 22-30. **Not written in English**

Laasila, K. and Leirisalo-Repo, M. Side effects of sulphasalazine in patients with rheumatic diseases or inflammatory bowel disease. Scand J Rheumatol. 94; 23 (6): 338-40. **Does not report side effects by medication class**

Laharie, D., Chanteloup, E., Chabrun, E., Subtil, C., Kowo, M., El Hanafi, K., et al. The tolerance and efficacy of a postponed retreatment with infliximab in Crohn's disease primary responders. Aliment Pharmacol Ther. 2009; 29 (12): 1240-8. **Other observational study without a comparison group; does not report side effects by medication class**

Laharie, D., Reffet, A., Belleannee, G., Chabrun, E., Subtil, C., Razaire, S., et al. Mucosal healing with methotrexate in Crohns disease: A prospective comparative study with azathioprine and infliximab. Aliment. Pharmacol. Ther. 2011; 33 (6): 714-721. **Other observational study without a comparison group; does not report side effects by medication class**

Lamireau, T., Cezard, J. P., Dabadie, A., Goulet, O., Lachaux, A., Turck, D., et al. Efficacy and tolerance of infliximab in children and adolescents with Crohn's disease. Inflamm Bowel Dis. 2004; 10 (6): 745-50. **Other observational study without a comparison group; does not report side effects by medication class**

Landi, B., Anh, T. N., Cortot, A., Soule, J. C., Rene, E., Gendre, J. P., et al. Endoscopic monitoring of Crohn's disease treatment: a prospective, randomized clinical trial. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gastroenterology. 92; 102 (5): 1647-53. **Other reason**

Langer-Gould, A. and Steinman, L. Progressive multifocal leukoencephalopathy and multiple sclerosis: lessons from natalizumab. Curr Neurol Neurosci Rep. 2006; 6 (3): 253-8. **No original data**

Lankarani, K. B. Mortality associated with infliximab. J Clin Gastroenterol. 2001; 33 (3): 255-6. **Case report or case series; other reason**

Larvol, L., Soule, J. C., and Le Tourneau, A. Reversible lymphoma in the setting of azathioprine therapy for Crohn's disease. N Engl J Med. 94; 331 (13): 883-4. **Case report or case series**

Laverdant, C., Molinie, C., and Essioux, H. [Treatment of Crohn's disease by metronidazole or its by-products]. Med. Chir. Dig. 82; 11 (5): 315-319. **Not written in English**

Lecomte, T., Contou, J. F., Beaugerie, L., Carbonnel, F., Cattan, S., Gendre, J. P., et al. Predictive factors of response of perianal Crohn's disease to azathioprine or 6-mercaptopurine. Dis Colon Rectum. 2003; 46 (11): 1469-75. **Does not apply to key questions; does not report side effects by medication class**

Lee, J. S., Lee, J. H., Lee, J. H., Lee, H. J., Kim, M. J., Lee, H. J., et al. Efficacy of early treatment with infliximab in pediatric Crohn's disease. World J Gastroenterol. 2010; 16 (14): 1776-81. **Does not report side effects by medication class**

Lee, K. M., Kim, J. S., Shin, D. H., Cheong, J. Y., Yoo, B. M., Kim, J. K., et al. [Effect of infliximab in the treatment of refractory inflammatory bowel disease with complication]. Korean J Gastroenterol. 2004; 44 (5): 259-66. **Not written in English**

Lee, W. S. The use of infliximab in South-east Asian children with severe Crohn's disease. Pediatr Int. 2004; 46 (2): 198-201. **Case report or case series; other observational study without a comparison group**

Lees, C. W., Maan, A. K., Hansoti, B., Satsangi, J., and Arnott, I. D. Tolerability and safety of mercaptopurine in azathioprine-intolerant patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2008; 27 (3): 220-7. **Does not apply to key questions; does not report side effects by medication class**

Leite, S., Ribeiro, J. M., Lima, S. C., Barroso, S., and Cotter, J. [Azathioprine in inflammatory bowel disease]. Acta Med Port. 2009; 22 (1): 33-40. **Not written in English**

Lemann, M., Chamiot-Prieur, C., Mesnard, B., Halphen, M., Messing, B., Rambaud, J. C., et al. Methotrexate for the treatment of refractory Crohn's disease. Aliment Pharmacol Ther. 96; 10 (3): 309-14. **Other observational study without a comparison group**

Lemann, M., Zenjari, T., Bouhnik, Y., Cosnes, J., Mesnard, B., Rambaud, J. C., et al. Methotrexate in Crohn's disease: long-term efficacy and toxicity. Am J Gastroenterol. 2000; 95 (7): 1730-4. **Other observational study without a comparison group; does not report side effects by medication class**

Lennard-Jones, J. E. Azathioprine and 6-mercaptopurine have a role in the treatment of Crohn's disease. Dig Dis Sci. 81; 26 (4): 364-8. **No original data**

Lennard-Jones, J. E. Azathioprine in the treatment of Crohn's disease. Proc R Soc Med. 72; 65 (3): 291-3. **Case report or case series; other observational study without a comparison group**

Leung, Y., Sparrow, M. P., Schwartz, M., and Hanauer, S. B. Long term efficacy and safety of allopurinol and azathioprine or 6-mercaptopurine in patients with inflammatory bowel disease. J. Crohn's Colitis. 2009; 3 (3): 162-167. **Other observational study without a comparison group; does not report side effects by medication class**

Leveque, N., Brixi-Benmansour, H., Reig, T., Renois, F., Talmud, D., Brodard, V., et al. Low frequency of cytomegalovirus infection during exacerbations of inflammatory bowel diseases. J. Med. Virol. 2010; 82 (10): 1694-1700. **Does not evaluate a drug of interest; does not apply to key questions**

Levi, Z., Fraser, E., Krongrad, R., Hazazi, R., benjaminov, O., meyerovitch, J., et al. Factors associated with radiation exposure in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2009; 30 (11-12): 1128-36. **Does not apply to key questions**

Levine, A., Kori, M., Dinari, G., Broide, E., Shaoul, R., Yerushalmi, B., et al. Comparison of two dosing methods for induction of response and remission with oral budesonide in active pediatric Crohn's disease: a randomized placebo-controlled trial. Inflamm Bowel Dis. 2009; 15 (7): 1055-61. **Does not evaluate a drug of interest; other reason**

Lewis, J. D., Gelfand, J. M., Troxel, A. B., Forde, K. A., Newcomb, C., Kim, H., et al. Immunosuppressant medications and mortality in inflammatory bowel disease. Am J Gastroenterol. 2008; 103 (6): 1428-35; quiz 1436. **Does not apply to key questions**

Lewis, J. D., Schwartz, J. S., and Lichtenstein, G. R. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. Gastroenterology. 2000; 118 (6): 1018-24. **Does not evaluate a drug of interest; does not apply to key questions**

Lichtenstein, G. R. Use of laboratory testing to guide 6-mercaptopurine/azathioprine therapy. Gastroenterology. 2004; 127 (5): 1558-64. **No original data**

Lichtenstein, G. R., Bala, M., Han, C., DeWoody, K., and Schaible, T. Infliximab improves quality of life in patients with Crohn's disease. Inflamm Bowel Dis. 2002; 8 (4): 237-43. **Other reason**

Lichtenstein, G. R., Olson, A., Travers, S., Diamond, R. H., Chen, D. M., Pritchard, M. L., et al. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. Am J Gastroenterol. 2006; 101 (5): 1030-8. **No original data**

Lichtenstein, G. R., Thomsen, O. O., Schreiber, S., Lawrance, I. C., Hanauer, S. B., Bloomfield, R., et al. Continuous Therapy With Certolizumab Pegol Maintains Remission of Patients With Crohn's Disease for up to 18 Months. Clin Gastroenterol Hepatol. 2010. **Does not evaluate a drug of interest**

Lidar, M., Langevitz, P., Barzilai, O., Ram, M., Porat-Katz, B. S., Bizzaro, N., et al. Infectious serologies and autoantibodies in inflammatory bowel disease: insinuations at a true pathogenic role. Ann N Y Acad Sci. 2009; 1173 640-8. **Does not evaluate a drug of interest; does not report side effects by medication class**

Lindor, K. D., Fleming, C. R., and Ilstrup, D. M. Preoperative nutritional status and other factors that influence surgical outcome in patients with Crohn's disease. Mayo Clin Proc. 85; 60 (6): 393-6. **Other reason**

Lindor, K. D., Fleming, C. R., Burnes, J. U., Nelson, J. K., and Ilstrup, D. M. A randomized prospective trial comparing a defined formula diet, corticosteroids, and a defined formula diet plus corticosteroids in active Crohn's disease. Mayo Clin Proc. 92; 67 (4): 328-33. **Does not evaluate a drug of interest**

Lionetti, P., Bronzini, F., Salvestrini, C., Bascietto, C., Canani, R. B., De Angelis, G. L., et al. Response to infliximab is related to disease duration in paediatric Crohn's disease. Aliment Pharmacol Ther. 2003; 18 (4): 425-31. **Other observational study without a comparison group**

Ljung, T., Axelsson, L. G., Herulf, M., Lundberg, J. O., and Hellstrom, P. M. Early changes in rectal nitric oxide and mucosal inflammatory mediators in Crohn's colitis in response to infliximab treatment. Aliment Pharmacol Ther. 2007; 25 (8): 925-32. **Does not apply to key questions; other reason**

Ljung, T., Karlen, P., Schmidt, D., Hellstrom, P. M., Lapidus, A., Janczewska, I., et al. Infliximab in inflammatory bowel disease: clinical outcome in a population based cohort from Stockholm County. Gut. 2004; 53 (6): 849-53. **Other observational study without a comparison group; does not report side effects by medication class**

Ljung, T., Lundberg, S., Varsanyi, M., Johansson, C., Schmidt, P. T., Herulf, M., et al. Rectal nitric oxide as biomarker in the treatment of inflammatory bowel disease: responders versus nonresponders. World J Gastroenterol. 2006; 12 (21): 3386-92. **Does not apply to key questions**

Lloyd-Still JD. Azathioprine and the treatment of chronic inflammatory bowel disease. The Journal of pediatrics. 90; 117 (5): 732-5. **No original data**

Lofberg R, Danielsson O, Floron C-H, Noble I, Brown R, Ericsson K, et al. Cost effectiveness of oral budesonide (Entocort capsules) maintenace therapy versus no maintenance therapy for Crohn's disease in Sweden [abstract]. Gut. 97; 41 Suppl 3 A223. **Abstract only**

Lofberg, R. Treatment of fistulas in Crohn's disease with infliximab. Gut. 99; 45 (5): 642-3. **No original data**

Lofberg, R., Danielsson, A., and Salde, L. Oral budesonide in active Crohn's disease. Aliment Pharmacol Ther. 93; 7 (6): 611-6. **Does not evaluate a drug of interest; other observational study without a comparison group**

Loftus, E. V. Jr, Johnson, S. J., Wang, S. T., Wu, E., Mulani, P. M., and Chao, J. Risk-benefit analysis of adalimumab versus traditional non-biologic therapies for patients with Crohn's disease. Inflamm Bowel Dis. 2011; 17 (1): 127-40. **No original data**

Loftus, E. V. New Data on the Use of Biologic Agents for Crohn. Gastroenterol Hepatol (N Y). 2010; 6 (2 Suppl 3): 4-16. **No original data**

Lonnkvist, M. H., Befrits, R., Lundberg, J. O., Lundahl, J., Fagerberg, U. L., Hjortswang, H., et al. Infliximab in clinical routine: experience with Crohn's disease and biomarkers of inflammation over 5 years. Eur J Gastroenterol Hepatol. 2009; 21 (10): 1168-76. **Does not report side effects by medication class**

Lopez Palacios, N., Mendoza, J. L., Taxonera, C., Lana, R., Fuentes Ferrer, M., and Diaz-Rubio, M. [Adalimumab induction and maintenance therapy for Crohn's disease. An open-label study]. Rev Esp Enferm Dig. 2008; 100 (11): 676-81. **Not written in English**

Lopez-Martin, C., Chaparro, M., Espinosa, L., Bejerano, A., Mate, J., and Gisbert, J. P. Adverse events of thiopurine immunomodulators in patients with inflammatory bowel disease. Gastroenterol. Hepatol. 2011. **Does not evaluate a drug of interest**

Loras, C., Saro, C., Gonzalez-Huix, F., Minguez, M., Merino, O., Gisbert, J. P., et al. Prevalence and factors related to hepatitis B and C in inflammatory bowel disease patients in Spain: a nationwide, multicenter study. Am J Gastroenterol. 2009; 104 (1): 57-63. **Does not report side effects by medication class**

Lou, G. C., Yang, J. M., Huang, W., Zhang, J., and Zhou, B. Esophageal Crohn's disease. Endoscopy. 2009; 41 Suppl 2 E257. **Case report or case series**

Louis, E. J., Watier, H. E., Schreiber, S., Hampe, J., Taillard, F., Olson, A., et al. Polymorphism in IgG Fc receptor gene FCGR3A and response to infliximab in Crohn's disease: a subanalysis of the ACCENT I study. Pharmacogenet Genomics. 2006; 16 (12): 911-4. **Does not apply to key questions**

Louis, E., Boverie, J., Dewit, O., Baert, F., De Vos, M., and D'Haens, G. Treatment of small bowel subocclusive Crohn's disease with infliximab: an open pilot study. Acta Gastroenterol Belg. 2007; 70 (1): 15-9. **Other observational study without a comparison group; does not report side effects by medication class**

Louis, E., Vermeire, S., Rutgeerts, P., De Vos, M., Van Gossum, A., Pescatore, P., et al. A positive response to infliximab in Crohn disease: association with a higher systemic inflammation before treatment but not with -308 TNF gene polymorphism. Scand J Gastroenterol. 2002; 37 (7): 818-24. **Other observational study without a comparison group; does not report side effects by medication class**

Lowry, P. W. and Sandborn, W. J. A comparison of budesonide and mesalamine for active Crohn's disease. Gastroenterology. 99; 116 (5): 1263. **No original data**

Lowry, P. W., Weaver, A. L., Tremaine, W. J., and Sandborn, W. J. Combination therapy with oral tacrolimus (FK506) and azathioprine or 6-mercaptopurine for treatment-refractory Crohn's disease perianal fistulae. Inflamm Bowel Dis. 99; 5 (4): 239-45. **Other observational study without a comparison group; does not report side effects by medication class**

Ludwig, D. and Stange, E. F. Efficacy of azathioprine in the treatment of chronic active Crohn's disease: prospective one-year follow-up study. German Imurek Study Group. Z Gastroenterol. 99; 37 (11): 1085-91. **Other observational study without a comparison group; does not report side effects by medication class**

Lukas, M., Bortlik, M., Novotny, A., Pospisilova, B., Fialova, J., and Vavrova, J. [Nephrotoxicity of mesalazine in long-term treatment of ulcerative colitis and Crohn's disease]. Gastroenterol. 99; 53 (5): 135-139. **Not written in English**

Luna-Chadid, M., Perez Calle, J. L., Mendoza, J. L., Vera, M. I., Bermejo, A. F., Sanchez, F., et al. Predictors of response to infliximab in patients with fistulizing Crohn's disease. Rev Esp Enferm Dig. 2004; 96 (6): 379-81; 382-4. **Does not evaluate a drug of interest; other observational study without a comparison group**

Lust, M. and Travis, S. Is anti-TNF therapy always prohibited in patients with inflammatory bowel disease and previous malignancy?. Pract. Gastroenterol. 2009; 33 (8): 25-30. **No original data**

Lyckegaard, E., Hakansson, K., and Bengtsson, B. Budesonide in Crohn's disease: findings of a compassionate-use program. Hepatogastroenterology. 2007; 54 (79): 2024-7. **Other observational study without a comparison group; does not report side effects by medication class**

Mack, D. R., Young, R., Kaufman, S. S., Ramey, L., and Vanderhoof, J. A. Methotrexate in patients with Crohn's disease after 6-mercaptopurine. J Pediatr. 98; 132 (5): 830-5. **Other observational study without a comparison group; does not report side effects by medication class**

MacLean, L. D. The National Cooperative Crohn's Disease Study. Can J Surg. 80; 23 (1): 7-8. **No original data; does not apply to key questions**

MacLennan, C., Lammas, D. A., and Kumararatne, D. S. Anti-interleukin-12 antibody treatment for Crohn disease: potential risk of invasive disease due to mycobacteria and salmonellae infection. Clin Infect Dis. 2005; 40 (9): 1381-2. **No original data; does not evaluate a drug of interest**

Madonia, S., Orlando, A., Scimeca, D., Olivo, M., Rossi, F., and Cottone, M. Occult hepatitis B and infliximab-induced HBV reactivation. Inflamm Bowel Dis. 2007; 13 (4): 508-9. **Case report or case series**

Mahadevan, U., Marion, J. F., and Present, D. H. Fistula response to methotrexate in Crohn's disease: a case series. Aliment Pharmacol Ther. 2003; 18 (10): 1003-8. **Case report or case series; other observational study without a comparison group**

Mahadevan, U., Terdiman, J. P., Aron, J., Jacobsohn, S., and Turek, P. Infliximab and semen quality in men with inflammatory bowel disease. Inflamm Bowel Dis. 2005; 11 (4): 395-9. **Does not evaluate a drug of interest; does not apply to key questions**

Mahida, Y. R. and Jewell, D. P. Slow-release 5-amino-salicylic acid (Pentasa) for the treatment of active Crohn's disease. Digestion. 90; 45 (2): 88-92. **Other reason**

Maier K, Fruhmorgen P, Bode JC, and et al Successful management of chronic inflammatory gut disease with oral 5-aminosalicylic acid. DTSCH-MED-WOCHENSCHR. 85; 110 (10): 363-368. **Not written in English**

Maier K, Gaisberg Uv, Frohmorgen S, Sinn I, Bode C, and Klotz U. Clinical effectiveness and pharmacokinetics of oral 5-aminosalicylic acod in chronic inflammatory bowel diseases. Klinische Wochenschrift. 85; 63 (Suppl 4): 196 **Not written in English**

Maire, F. Infliximab, azathioprine, or combination therapy for Crohn's disease: Traitement de la maladie de Crohn: Azathioprine, infliximab ou association des deux?. Hepato-Gastro. 2010; 17 (4): 355-360. **Not written in English**

Makhzoum, J., Jobin, G., Dagenais, P., Makhzoum, S., and Perreault, S. Risk for osteoporosis and antiresorptive therapies in patients with Crohn's disease. J. Pharm. Technol. 2006; 22 (1): 9-14. **Other reason**

Malik, M., Tobin, A. M., Shanahan, F., O'Morain, C., Kirby, B., and Bourke, J. Steroid allergy in patients with inflammatory bowel disease. Br J Dermatol. 2007; 157 (5): 967-9. **Does not apply to key questions**

Malireddy, K., Larson, D. W., Sandborn, W. J., Loftus, E. V., Faubion, W. A., Pardi, D. S., et al. Recurrence and impact of postoperative prophylaxis in laparoscopically treated primary ileocolic Crohn disease. Arch Surg. 2010; 145 (1): 42-7. **Does not evaluate a drug of interest; does not report side effects by medication class**

Mamula, P., Cohen, S. A., Ferry, G. D., Kirschner, B. S., Winter, H. S., Innes, A., et al. CDP571, a humanized anti-tumor necrosis factor-alpha monoclonal antibody in pediatric Crohn's disease. Inflamm Bowel Dis. 2004; 10 (6): 723-30. **Does not evaluate a drug of interest; other observational study without a comparison group**

Manosa, M., Naves, J. E., Leal, C., Cabre, E., Moreno, V., Lorenzo-Zuniga, V., et al. Does methotrexate induce mucosal healing in Crohn's disease?. Inflamm Bowel Dis. 2010; 16 (3): 377-8. **Case report or case series; other observational study without a comparison group**

Mantzaris GJ, Archavlis E, Amberiadis P, Kourtessas D, and Triantafullou G. A Prospective Randomized Trial in Active Crohn's Disease Comparing prednisolone, a Polymeric Diet and a Polymeric Diet Plus Prednisolon [abstract]. Gut. 96; 39 Suppl 3 A166. **Abstract only**

Marchal, L., D'Haens, G., Van Assche, G., Vermeire, S., Noman, M., Ferrante, M., et al. The risk of post-operative complications associated with infliximab therapy for Crohn's disease: a controlled cohort study. Aliment Pharmacol Ther. 2004; 19 (7): 749-54. **Does not apply to key questions; does not report side effects by medication class**

Margo, F., Marques, M., and Santos, C. C. Episodic infliximab treatment induces infusion reactions. Inflamm Bowel Dis. 2008; 14 (11): 1608-10. **Case report or case series**

Mariette, X., Tubach, F., Bagheri, H., Bardet, M., Berthelot, J. M., Gaudin, P., et al. Lymphoma in patients treated with anti-TNF: Results of the 3-year prospective French RATIO registry. Ann. Rheum. Dis. 2010; 69 (2): 400-408. **Other reason**

Marinaki, A. M., Ansari, A., Duley, J. A., Arenas, M., Sumi, S., Lewis, C. M., et al. Adverse drug reactions to azathioprine therapy are associated with polymorphism in the gene encoding inosine triphosphate pyrophosphatase (ITPase). Pharmacogenetics. 2004; 14 (3): 181-7. **Does not evaluate a drug of interest**

Marion, J. F. Toxicity of 6-mercaptopurine/ azathioprine in patients with inflammatory bowel disease. Inflamm Bowel Dis. 98; 4 (2): 116-7. **No original data**

Markowitz, J., Grancher, K., Mandel, F., and Daum, F. Immunosuppressive therapy in pediatric inflammatory bowel disease: results of a survey of the North American Society for Pediatric Gastroenterology and Nutrition. Subcommittee on Immunosuppressive Use of the Pediatric IBD Collaborative Research Forum. Am J Gastroenterol. 93; 88 (1): 44-8. **Does not apply to key questions; no human data**

Markowitz, J., Hyams, J., Mack, D., Leleiko, N., Evans, J., Kugathasan, S., et al. Corticosteroid therapy in the age of infliximab: acute and 1-year outcomes in newly diagnosed children with Crohn's disease. Clin Gastroenterol Hepatol. 2006; 4 (9): 1124-9. **Other observational study without a comparison group; does not report side effects by medication class**

Martin-de-Carpi, J., Pociello, N., and Varea, V. Long-term efficacy of adalimumab in Paediatric Crohn's disease patients naive to other anti-TNF therapies. J. Crohn's Colitis. 2010; 4 (5): 594-598. **Case report or case series**

Martreau, P. [A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators.]. Gastroenterol Clin Biol. 2000; 24 (12): 1243-4. **Not written in English**

Matsumoto, T., Iida, M., Motoya, S., Haruma, K., Suzuki, Y., Kobayashi, K., et al. Therapeutic efficacy of infliximab on patients with short duration of Crohn's disease: a Japanese multicenter survey. Dis Colon Rectum. 2008; 51 (6): 916-23. **Other observational study without a comparison group**

Max, M. H., Wolff, M., Broell, J. R., and Gump, F. E. The effect of long-term steroid therapy on the histopathology of regional enteritis. J Surg Res. 73; 14 (2): 124-32. **Does not apply to key questions**

McCullough, J. E., Kim, C. H., and Banks, P. M. Mantle zone lymphoma of the colon simulating diffuse inflammatory bowel disease. Role of immunohistochemistry in establishing the diagnosis. DIG. DIS. SCI. 92; 37 (6): 934-938. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD, Case report or case series**

McDonnell, M. J. and Dhar, A. Azathioprine use in inflammatory bowel disease in South Durham - An insight into clinical practice. J. R. Coll. Phys. Edinburgh. 2009; 39 (2): 100-106. **Other observational study without a comparison group**

McNatty, D. Crohn's disease - Strategies to improve quality of life. 2008; 74 (9): 42+44. **No original data**

Medkour, F., Babai, S., Chanteloup, E., Buffard, V., Delchier, J. C., and Le-Louet, H. Development of diffuse psoriasis with alopecia during treatment of Crohn's disease with infliximab. Gastroenterol Clin Biol. 2010; 34 (2): 140-1. **Case report or case series**

Meier, C., Thonnessen, C., Rothe, U., Henker, J., Quietzsch, J., Prager, J., et al. [Chronic inflammatory bowel disease in childhood and adolescence. Initial symptoms, diagnosis, treatment - Data recorded in the register of chronic inflammatory bowel disease in children and adolescents in Saxony]. Monatsschr. Kinderheilkd. 2006; 154 (12): 1212-1218. **Not written in English**

Melendez, J. D., Larregui, Y., Vazquez, J. M., Carlo, V. L., and Torres, E. A. Medication profiles of patients in the University of Puerto Rico inflammatory bowel disease registry. Puerto Rico Health Sci. J. 2011; 30 (1): 3-8. **Does not evaluate a drug of interest; case report or case series**

Menachem, Y., Avidan, B., Lavy, A., Lang, A., Bardan, E., Fidder, H., et al. Increasing the infliximab dose is beneficial in Crohn's disease patients who responded to a lower dose and relapsed. Digestion. 2005; 72 (2-3): 124-8. **Does not evaluate a drug of interest; does not apply to key questions**

Mendes, F. D., Levy, C., Enders, F. B., Loftus, E. V. Jr, Angulo, P., and Lindor, K. D. Abnormal hepatic biochemistries in patients with inflammatory bowel disease. Am J Gastroenterol. 2007; 102 (2): 344-50. **Does not apply to key questions; does not report side effects by medication class**

Mendoza, J. L., Garcia-Paredes, J., Cruz Santamaria, D. M., Lana, R., Ramirez Fernandez, E., Rodriguez Asteaga, E., et al. Infliximab treatment and prognostic factors for response in patients with Crohn's disease. Rev Esp Enferm Dig. 2002; 94 (5): 269-79. **Not written in English; other reason**

Mendoza, J. L., Urcelay, E., Lana, R., Martin, M. C., Lopez, N., Guijarro, L. G., et al. MDR1 polymorphisms and response to azathioprine therapy in patients with Crohn's disease. Inflamm Bowel Dis. 2007; 13 (5): 585-90. **Does not apply to key questions; other observational study without a comparison group**

Miheller, P., Lakatos, P. L., Horvath, G., Molnar, T., Szamosi, T., Czegledi, Z., et al. Efficacy and safety of infliximab induction therapy in Crohn's Disease in Central Europe--a Hungarian nationwide observational study. BMC Gastroenterol. 2009; 9 66. **Does not report side effects by medication class**

Miheller, P., Muzes, G., Racz, K., Blazovits, A., Lakatos, P., Herszenyi, L., and Tulassay, Z. Changes of OPG and RANKL concentrations in Crohn's disease after infliximab therapy. Inflamm Bowel Dis. 2007; 13 (11): 1379-84. **Does not evaluate a drug of interest; other observational study without a comparison group**

Minderhoud, I. M., Samsom, M., and Oldenburg, B. Crohn's disease, fatigue, and infliximab: is there a role for cytokines in the pathogenesis of fatigue?. World J Gastroenterol. 2007; 13 (14): 2089-93. **Does not apply to key questions other observational study without a comparison group**

Molloy, J. W., Kim, E., and Mahadevan, U. Do Side-by-Side Anastomoses Decrease the Risk of Recurrence in Crohn's Disease?. Gastroenterology. 2010; 138 (5): 2010-2012. **No original data; does not apply to key questions**

Molnar, T., Farkas, K., Miheller, P., Nyari, T., Szepes, Z., Herszenyi, L., et al. Is the efficacy of successful infliximab induction therapy maintained for one year lasting without retreatment in different behavior types of Crohn's disease? J. Crohn's Colitis. 2008; 2 (4): 322-326. **Other observational study without a comparison group**

Molnar, T., Farkas, K., Nagy, F., Szepes, Z., and Wittmann, T. Lymphomas in two IBD patients treated with anti-TNF-alpha mono or combination therapy: Is hepatosplenic lymphoma really the "old maid"?. Inflamm Bowel Dis. 2011. **Case report or case series; other observational study without a comparison group**

Molnar, T., Farkas, K., Nyari, T., Szepes, Z., Nagy, F., Kiss, T., et al. [Frequency and predictors of loss of response to biological therapy in Crohn's disease after one-year treatment period.]. Orv Hetil. 2011; 152 (24): 951-957. **Not written in English**

Molnar, T., Farkas, K., Szepes, Z., Nagy, F., and Wittmann, T. Long-term outcome of infliximab therapy is highly comparable in a Danish and in a Hungarian tertiary center. Scand J Gastroenterol. 2011; 46 (2): 248-9. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; other reason**

Morales, A., Salguti, S., Miao, C. L., and Lewis, J. D. Relationship between 6-mercaptopurine dose and 6-thioguanine nucleotide levels in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2007; 13 (4): 380-5. **Does not evaluate a drug of interest; other observational study without a comparison group**

Morelli, J. and Wilson, F. A. Does administration of infliximab increase susceptibility to listeriosis?. Am J Gastroenterol. 2000; 95 (3): 841-2. **Case report or case series**

Mortimore, M., Gibson, P. R., Selby, W. S., Radford-Smith, G. L., Florin, T. H. J., Ooi, K., et al. Early Australian experience with infliximab, a chimeric antibody against tumour necrosis factor-(alpha), in the treatment of Crohn's disease: Is its efficacy augmented by steroid-sparing immunosuppressive therapy? Intern. Med. J. 2001; 31 (3): 146-150. **Does not evaluate a drug of interest; other observational study without a comparison group**

Motamed, F., Famouri, F., Najafi, M., Moazzami, K., Farahmand, F., Khodadad, A., et al. Response to induction therapy in a pediatric population of inflammatory bowel disease. Z. Gastroenterol. 2010; 48 (7): 748-752. **Does not report side effects by medication class**

Motil, K. J., Grand, R. J., Davis-Kraft, L., Ferlic, L. L., and Smith, E. O. Growth failure in children with inflammatory bowel disease: a prospective study. Gastroenterology. 93; 105 (3): 681-91. **Does not evaluate a drug of interest**

Moum, B. [Follow up of the use of biological drugs against inflammatory bowel diseases]. Tidsskr Nor Laegeforen. 2007; 127 (21): 2841-2. **Not written in English**

Moum, B. [When should anti-TNF-alpha treatment in Crohn disease be terminated?]. Tidsskr Nor Laegeforen. 2010; 130 (5): 474. **Not written in English**

Mudge, T. J. Semen and sulphasalazine. Clin Reprod Fertil. 82; 1 (2): 157-8. **No original data**

Mulder, C. J., Rondas, A. A., Wiltink, E. H., and Tytgat, G. N. Topical corticosteroids in inflammatory bowel disease. Neth J Med. 89; 35 Suppl 1 S27-34. **No original data**

Mulder, C. J., Tytgat, G. N., Dekker, W., and Terpstra, I. J. Pentasa in lieu of sulfasalazine. Ann Intern Med. 88; 108 (6): 911-2. **Other observational study without a comparison group**

Muller, A. F., Stevens, P. E., McIntyre, A. S., Ellison, H., and Logan, R. F. Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. Aliment Pharmacol Ther. 2005; 21 (10): 1217-24. **Does not report side effects by medication class**

Munk, E. M., Pedersen, L., Floyd, A., Norgard, B., Rasmussen, H. H., and Sorensen, H. T. Inflammatory bowel diseases, 5-aminosalicylic acid and sulfasalazine treatment and risk of acute pancreatitis: a population-based case-control study. Am J Gastroenterol. 2004; 99 (5): 884-8. **Does not report side effects by medication class**

Munkholm, P. Crohn's disease-occurrence, course and prognosis: An epidemiologic cohort-study. DAN. MED. BULL. 97; 44 (3): 287-302. **Does not apply to key questions; does not report side effects by medication class**

Munkholm, P., Langholz, E., Davidsen, M., and Binder, V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. Gut. 94; 35 (3): 360-2. **Does not evaluate a drug of interest; other observational study without a comparison group**

Murakami, Y., Matsui, T., Hirai, F., Takatsu, N., Takaki, Y., Nagahama, T., et al. Efficacy of azathioprine in mild or moderate relapse in Crohn's disease: clinical and endoscopic evaluation. Dig Endosc. 2010; 22 (1): 25-32. **Does not evaluate a drug of interest; does not report side effects by medication class**

Myrelid, P., Olaison, G., Sjodahl, R., Nystrom, P.-O., Almer, S., and Andersson, P. Thiopurine therapy is associated with postoperative intra-abdominal septic complications in abdominal surgery for crohn's disease. Dis. Colon Rectum. 2009; 52 (8): 1387-1394. **Does not apply to key questions; does not report side effects by medication class**

Naganuma, M., Hyun, S. B., and Watanabe, M. Diagnosis and treatment for small intestinal lesions in patients with Crohn's disease. J. Jpn. Soc. Gastroenterolog. 2010; 107 (6): 845-854. **Not written in English**

Nagy, F., Molnar, T., Szepes, Z., Farkas, K., Nyari, T., and Lonovics, J. Efficacy of 6-mercaptopurine treatment after azathioprine hypersensitivity in inflammatory bowel disease. World J Gastroenterol. 2008; 14 (27): 4342-6. **Other observational study without a comparison group**

Nagy, G., Pronay, G., and Ujszaszy, L. Therapeutical experiments in ulcerative colitis and Crohn's disease. Acta Med Hung. 85; 42 (3-4): 163-74. **Does not evaluate a drug of interest; does not report side effects by medication class**

Nakshabendi, I. M., Duncan, A., and Russell, R. I. Is Asacol as effective as sulphasalazine in maintaining remission of Crohn's disease and ulcerative colitis?. Postgrad Med J. 92; 68 (797): 189-91. **Other observational study without a comparison group**

Nancey, S., Blanvillain, E., Parmentier, B., Flourie, B., Bayet, C., Bienvenu, J., et al. Infliximab treatment does not induce organ-specific or nonorgan-specific autoantibodies other than antinuclear and anti-double-stranded DNA autoantibodies in Crohn's disease. Inflamm Bowel Dis. 2005; 11 (11): 986-91. **Does not report side effects by medication class**

Nathan, D. M., Iser, J. H., and Gibson, P. R. A single center experience of methotrexate in the treatment of Crohn's disease and ulcerative colitis: a case for subcutaneous administration. J Gastroenterol Hepatol. 2008; 23 (6): 954-8. **Other observational study without a comparison group**

Nayar, M., Cunliffe, W., Cross, P., and Oppong, K. Mesalazine-induced jaundice, eosonophilia, and thrombocytopenia. Inflamm Bowel Dis. 2008; 14 (9): 1320-1. **Case report or case series**

Ng, S. C., Plamondon, S., Gupta, A., Burling, D., and Kamm, M. A. Prospective assessment of the effect on quality of life of anti-tumour necrosis factor therapy for perineal Crohn's fistulas. Aliment Pharmacol Ther. 2009; 30 (7): 757-66. **Does not apply to key questions; does not report side effects by medication class**

Ng, S. C., Plamondon, S., Gupta, A., Burling, D., Swatton, A., Vaizey, C. J., et al. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas. Am J Gastroenterol. 2009; 104 (12): 2973-86. **Other observational study without a comparison group; does not report side effects by medication class**

Nguyen, G. C., Nugent, Z., Shaw, S., and Bernstein, C. N. Outcomes of Patients With Crohn's Disease Improved From 1988 to 2008 and Were Associated With Increased Specialist Care. Gastroenterology. 201. **Does not evaluate a drug of interest; other observational study without a comparison group**

Nguyen, K. D., Alexis, R., and Schwarz, S. M. Oropharyngeal and proximal esophageal involvement during adalimumab treatment of Crohn disease. J Pediatr Gastroenterol Nutr. 2010; 50 (2): 225-6. **Case report or case series**

Nguyen, T. M., Le Gall, C., Lachaux, A., and Boulieu, R. High thiopurine metabolite concentrations associated with lymphopenia in inflammatory bowel disease (IBD) pediatric patients receiving aminosalicylates combined with azathioprine. Int J Clin Pharmacol Ther. 2010; 48 (4): 275-81. **Does not apply to key questions; does not report side effects by medication class**

Nguyen, T., Vacek, P. M., O'Neill, P., Colletti, R. B., and Finette, B. A. Mutagenicity and potential carcinogenicity of thiopurine treatment in patients with inflammatory bowel disease. Cancer Res. 2009; 69 (17): 7004-12. **Does not apply to key questions; other observational study without a comparison group**

Nguyen, T.-M. H., Le Gall, C., Lachaux, A., and Boulieu, R. High thiopurine metabolite concentrations associated with lymphopenia in inflammatory bowel disease (IBD) pediatric patients receiving aminosalicylates combined with azathioprine. Int. J. Clin. Pharmacol. Ther. 2010; 48 (4): 275-281. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; does not apply to key questions**

Nichita, C., Stelle, M., Vavricka, S., El-Wafa Ali, A., Ballabeni, P., de Saussure, P., et al. Clinical experience with adalimumab in a multicenter Swiss cohort of patients with Crohn's disease. Digestion. 2010; 81 (2): 78-85. **Other observational study without a comparison group**

Nielsen, O. H. Sulfasalazine intolerance. A retrospective survey of the reasons for discontinuing treatment with sulfasalazine in patients with chronic inflammatory bowel disease. Scand J Gastroenterol. 82; 17 (3): 389-93. **Does not evaluate a drug of interest; does not apply to key questions**

Nightingale, S. L. From the Food and Drug Administration. JAMA. 98; 280 (13): 1128. **No original data**

Noe, J. D. and Pfefferkorn, M. Short-term response to adalimumab in childhood inflammatory bowel disease. Inflamm Bowel Dis. 2008; 14 (12): 1683-7. **Does not report side effects by medication class**

Nogueira, J. R. and Freedman, M. A. Acute pancreatitis as a complication of Imuran therapy in regional enteritis. Gastroenterology. 72; 62 (5): 1040-1. **Case report or case series**

Norden, D. K., Lichtenstein, G. R., and Williams, W. V. Sulfasalazine-induced myopathy. Am J Gastroenterol. 94; 89 (5): 801-2. **Case report or case series**

Norgard, B., Czeizel, A. E., Rockenbauer, M., Olsen, J., and Sorensen, H. T. Population-based case control study of the safety of sulfasalazine use during pregnancy. Aliment Pharmacol Ther. 2001; 15 (4): 483-6. **Does not apply to key questions**

Norgard, B., Pedersen, L., Fonager, K., Rasmussen, S. N., and Sorensen, H. T. Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. Aliment Pharmacol Ther. 2003; 17 (6): 827-34. **Does not apply to key questions**

Nos Mateu, P. [Locally acting corticosteroids in inflammatory bowel disease. Are they effective? Are they really less toxic?]. Gastroenterol Hepatol. 2008; 31 Suppl 3 16-21. **No original data; not written in English**

Nos, P., Bastida, G., Beltran, B., Aguas, M., and Ponce, J. Crohn's disease in common variable immunodeficiency: treatment with antitumor necrosis factor alpha. Am J Gastroenterol. 2006; 101 (9): 2165-6. **Case report or case series**

Novacek, G., Kleinberger, M., Vogelsang, H., Moser, G., and Lochs, H. Budesonide in glucocorticoid dependent chronic active Crohn's disease; a pilot study. Z Gastroenterol. 95; 33 (5): 251-4. **Other observational study without a comparison group; does not report side effects by medication class**

Nugent, F. W. and Roy, M. A. Duodenal Crohn's disease: An analysis of 89 cases. AM. J. GASTROENTEROL. 89; 84 (3): 249-254. **Does not evaluate a drug of interest; does not apply to key questions**

Nyman, M., Hansson, I., and Eriksson, S. Long-term immunosuppressive treatment in Crohn's disease. Scand J Gastroenterol. 85; 20 (10): 1197-203. **Does not evaluate a drug of interest; other observational study without a comparison group**

Oakes, R. A. Asacol in inflammatory bowel disease. N Z Med J. 87; 100 (824): 325. **No original data**

O'Brien, J. J., Bayless, T. M., and Bayless, J. A. Use of azathioprine or 6-mercaptopurine in the treatment of Crohn's disease. Gastroenterology. 91; 101 (1): 39-46. **Other observational study without a comparison group; does not report side effects by medication class**

Ochsenkuhn, T., Goke, B., and Sackmann, M. Combining infliximab with 6-mercaptopurine/azathioprine for fistula therapy in Crohn's disease. Am J Gastroenterol. 2002; 97 (8): 2022-5. **Other observational study without a comparison group; does not report side effects by medication class**

O'Donnell, S., Murphy, S., Anwar, M. M., O'Sullivan, M., Breslin, N., O'Connor, H. J., et al. Safety of infliximab in 10 years of clinical practice. Eur. J. Gastroenterol. Hepatol. 2011. **Case report or case series**

Ooi, C. Y., Bohane, T. D., Lee, D., Naidoo, D., and Day, A. S. Thiopurine metabolite monitoring in paediatric inflammatory bowel disease. Aliment Pharmacol Ther. 2007; 25 (8): 941-7. **Other observational study without a comparison group; does not report side effects by medication class**

Orlando, A., Colombo, E., Kohn, A., Biancone, L., Viscido, A., Sostegni, R., et al. Infliximab in the treatment of steroid resistant/dependant and fistulating Crohn's disease: An analysis of predictors of response in a italian multicentric open study in 573 patients. Eur. Rev. Med. Pharmacol. Sci. 2004; 8 (5): 230. **Abstract only**

Oshima, T., Taira, S., Nonaka, M., Hayama, Y., Yagi, K., Yukawa, I., et al. A study on bone mineral density in patients with Crohn's disease. Hepatogastroenterology. 2008; 55 (88): 2116-20. **Does not apply to key questions**

Oshitani, N., Kitano, A., Sawa, Y., Sano, K., Ueda, W., Hara, J., et al. Outcome of maintenance therapy in Crohn's disease. J. JPN. SOC. COLO-PROCTOL. 96; 49 (3): 253-259. **Not written in English**

Oussalah, A., Babouri, A., Chevaux, J. B., Stancu, L., Trouilloud, I., Bensenane, M., et al. Adalimumab for Crohn's disease with intolerance or lost response to infliximab: a 3-year single-centre experience. Aliment Pharmacol Ther. 2009; 29 (4): 416-23. **Does not report side effects by medication class**

Oussalah, A., Chevaux, J. B., Fay, R., Sandborn, W. J., Bigard, M. A., and Peyrin-Biroulet, L. Predictors of infliximab failure after azathioprine withdrawal in Crohn's disease treated with combination therapy. Am J Gastroenterol. 2010; 105 (5): 1142-9. **Other observational study without a comparison group**

Palacios, N. L., Mendoza, J. L., Taxonera, C., Lana, R., Ferrer, M. F., and Diaz-Rubio, M. Adalimumab induction and maintenance therapy from Crohn's diseas: An open-label study: Tratamiento de induccion y mantenimiento con adalimumab en la enfermedad de Crohn: Un estudio abierto. Rev. Esp. Enferm. Dig. 2008; 100 (11): 676-681. **Not written in English**

Pallotta, N., Barberani, F., Hassan, N. A., Guagnozzi, D., Vincoli, G., and Corazziari, E. Effect of infliximab on small bowel stenoses in patients with Crohn's disease. World J Gastroenterol. 2008; 14 (12): 1885-90. **Case report or case series; other observational study without a comparison group**

Palmieri, O., Latiano, A., Bossa, F., Vecchi, M., D'Inca, R., Guagnozzi, D., et al. Sequential evaluation of thiopurine methyltransferase, inosine triphosphate pyrophosphatase, and HPRT1 genes polymorphisms to explain thiopurines' toxicity and efficacy. Aliment Pharmacol Ther. 2007; 26 (5): 737-45. **Does not apply to key questions; does not report side effects by medication class**

Papadakis, K. A. Crohn's disease: Adalimumab improves quality of life. Nat Rev Gastroenterol Hepatol. 2009; 6 (4): 200-1. **No original data**

Papadakis, K. A., Shaye, O. A., Vasiliauskas, E. A., Ippoliti, A., Dubinsky, M. C., Birt, J., et al. Safety and efficacy of adalimumab (D2E7) in Crohn's disease patients with an attenuated response to infliximab. Am J Gastroenterol. 2005; 100 (1): 75-9. **Other observational study without a comparison group; does not report side effects by medication class**

Papay, P., Reinisch, W., Ho, E., Gratzer, C., Lissner, D., Herkner, H., et al. The impact of thiopurines on the risk of surgical recurrence in patients with Crohn's disease after first intestinal surgery. Am J Gastroenterol. 2010; 105 (5): 1158-64. **Does not report side effects by medication class**

Papi, C., Festa, V., Leandro, G., Moretti, A., Tanga, M., Koch, M., et al. Long-term outcome of Crohn's disease following corticosteroid-induced remission. Am J Gastroenterol. 2007; 102 (4): 814-9. **Other observational study without a comparison group**

Papp, J. P., Watson, D. W., and Bull, F. E. Azathioprine treatment in Crohn's disease. Am J Gastroenterol. 74; 61 (2): 136-42. **Case report or case series; other observational study without a comparison group**

Parker, R., Dixit, A., Fraser, A., Creed, T. J., and Probert, C. S. Clinical experience of methotrexate in Crohn's disease: response, safety and monitoring of treatment. Postgrad Med J. 2010; 86 (1014): 208-11. **No original data; other observational study without a comparison group**

Parlak, E., Ulker, A., Alkim, C., Tunc, B., Tezel, A., and Dagli, U. [The efficacy of 5-ASA preparations in prevention of postoperative recurrence of crohn's disease (retrospective assessment)]. Turk. J. Gastroenterol. 99; 10 (3): 276-279. **Not written in English**

Parlak, E., Ulker, A., Dagli, U., and Alkim, C. A retrospective trial comparing 5-ASA plus ciprofloxacin and metronidazole with 5-ASA and corticosteroids in the treatment of active Crohn's disease. Turk. J. Gastroenterol. 2000; 11 (3): 227-230. **Does not evaluate a drug of interest; other observational study without a comparison group**

Parsi, M. A. and Lashner, B. A. Safety of infliximab: primum non nocere. The safety profile of infliximab in patients with Crohn's disease: the Mayo Clinic experience in 500 patients. Inflamm Bowel Dis. 2004; 10 (4): 486-7. **No original data; other observational study without a comparison group**

Parsi, M. A. Does smoking decrease the response to infliximab in patients with Crohn's disease?. Inflamm Bowel Dis. 2008; 14 Suppl 2 S18-9. **No original data**

Parsi, M. A., Achkar, J. P., Richardson, S., Katz, J., Hammel, J. P., Lashner, B. A., et al. Predictors of response to infliximab in patients with Crohn's disease. Gastroenterology. 2002; 123 (3): 707-13. **Other observational study without a comparison group; does not report side effects by medication class**

Patel, H., Barr, A., and Jeejeebhoy, K. N. Renal effects of long-term treatment with 5-aminosalicylic acid. Can J Gastroenterol. 2009; 23 (3): 170-6. **Does not apply to key questions; does not report side effects by medication class**

Pelletier, A. L., Kalisazan, B., Wienckiewicz, J., Bouarioua, N., and Soule, J. C. Infliximab treatment for symptomatic Crohn's disease strictures. Aliment Pharmacol Ther. 2009; 29 (3): 279-85. **Does not apply to key questions**

Pena, J. M., Gonzalez-Garcia, J. J., Garcia-Alegria, J., Barbado, F. J., and Vazquez, J. J. Thrombocytopenia and sulfasalazine. Ann Intern Med. 85; 102 (2): 277-8. **No original data; case report or case series**

Perez-Perez, L., Caeiro, J. L., Fabeiro, J. M., Allegue, F., and Zulaica, A. Induction of pustular lesions during infliximab therapy for Crohn's disease. Acta Derm Venereol. 2008; 88 (3): 292-3. **No original data; case report or case series**

Perrett, C. M., Walker, S. L., O'Donovan, P., Warwick, J., Harwood, C. A., Karran, P., et al. Azathioprine treatment photosensitizes human skin to ultraviolet A radiation. Br. J. Dermatol. 2008; 159 (1): 198-204. **Does not apply to key questions; case report or case series**

Persoons, P., Vermeire, S., Demyttenaere, K., Fischler, B., Vandenberghe, J., Van Oudenhove, L., et al. The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. Aliment Pharmacol Ther. 2005; 22 (2): 101-10. **Does not report side effects by medication class**

Petersen, J. A. and Rasmussen, S. N. Biotechnologically manufactured drugs for inflammatory bowel disease. Scand J Gastroenterol. 2001; 36 (12): 1233-8. **No original data**

Petitpain, N., Gambier, N., Wahl, D., Chary-Valckenaere, I., Loeuille, D., and Gillet, P. Arterial and venous thromboembolic events during anti-TNF therapy: a study of 85 spontaneous reports in the period 2000-2006. Biomed Mater Eng. 2009; 19 (4-5): 355-64. **Case report or case series; other observational study without a comparison group**

Petrolati, A., Altavilla, N., Cipolla, R., Fenderico, P., Forlini, G., Nasoni, S., et al. Cutaneous metastatic Crohn's disease responsive to infliximab. Am J Gastroenterol. 2009; 104 (4): 1058. **Case report or case series**

Pettersson, B., Almer, S., Albertioni, F., Soderhall, S., and Peterson, C. Differences between children and adults in thiopurine methyltransferase activity and metabolite formation during thiopurine therapy: possible role of concomitant methotrexate. Ther Drug Monit. 2002; 24 (3): 351-8. **Does not apply to key questions; other observational study without a comparison group**

Peyrin-Biroulet, L. [Anti-TNF therapy and Crohn's disease]. Gastroenterol Clin Biol. 2008; 32 (5 Pt 1): 478-81. **Not written in English**

Peyrin-Biroulet, L., Laclotte, C., and Bigard, M. A. Adalimumab maintenance therapy for Crohn's disease with intolerance or lost response to infliximab: an open-label study. Aliment Pharmacol Ther. 2007; 25 (6): 675-80. **Other observational study without a comparison group; does not report side effects by medication class**

Peyrin-Biroulet, L., Oussalah, A., Williet, N., Pillot, C., Bresler, L., and Bigard, M.-A. Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. Gut. 2011. **Does not evaluate a drug of interest; does not apply to key questions**

Phelan, C. and Wooltorton, E. Infliximab and serious hematologic events. CMAJ. 2004; 171 (9): 1045. **No original data**

Piccin, A., Cortelazzo, S., Rovigatti, U., Bourke, B., and Smith, O. P. Immunosuppressive treatments in Crohn. Am J Hematol. 2010. **No original data; case report or case series**

Picco, M. F., Zubiaurre, I., Adluni, M., Cangemi, J. R., and Shelton, D. Immunomodulators are associated with a lower risk of first surgery among patients with non-penetrating non-stricturing Crohn's disease. Am J Gastroenterol. 2009; 104 (11): 2754-9. **Does not report side effects by medication class**

Pillot, C., Chevaux, J. B., Bigard, M. A., and Peyrin-Biroulet, L. Infliximab 10 mg/kg every 3 weeks for Crohn's disease. Am J Gastroenterol. 2010; 105 (11): 2509-10. **No original data; case report or case series**

Pinto, A. L., Chebli, L. A., Ribeiro, M. S., Pace, F. H., Moraes, J. P., do Amaral, F. J. Jr, et al. Azathioprine therapy in steroid-dependent patients with Crohn disease: results of a 10-year longitudinal follow-up study. Med Sci Monit. 2009; 15 (5): PI19-26. **Other observational study without a comparison group; does not report side effects by medication class**

Pittet, V., Juillerat, P., Michetti, P., Vader, J.-P., Burnand, B., Rogler, G., et al. Appropriateness of therapy for fistulizing Crohn's disease: Findings from a national inflammatory bowel disease cohort. Aliment. Pharmacol. Ther. 2010; 32 (8): 1007-1016. **Does not apply to key questions; other observational study without a comparison group**

Poggioli, G., Laureti, S., Pierangeli, F., Rizzello, F., Ugolini, F., Gionchetti, P., et al. Local injection of Infliximab for the treatment of perianal Crohn's disease. Dis Colon Rectum. 2005; 48 (4): 768-74. **Other observational study without a comparison group**

Pohl C and Kruis W. Oral budesonide - A further step in the prevention of relapse in Crohn's disease? Leber Magen Darm. 97; 27 (4): 235-239. **Not written in English**

Pollak, R. D., Karmeli, F., Eliakim, R., Ackerman, Z., Tabb, K., and Rachmilewitz, D. Femoral neck osteopenia in patients with inflammatory bowel disease. Am J Gastroenterol. 98; 93 (9): 1483-90. **Does not report side effects by medication class**

Poritz, L. S., Rowe, W. A., and Koltun, W. A. Remicade does not abolish the need for surgery in fistulizing Crohn's disease. Dis Colon Rectum. 2002; 45 (6): 771-5. **Other observational study without a comparison group; does not report side effects by medication class**

Poupardin, C., Lemann, M., Gendre, J. P., Sabate, J. M., Marteau, P., Chaussade, S., et al. Efficacy of infliximab in Crohn's disease. Results of a retrospective multicenter study with a 15-month follow-up. Gastroenterol Clin Biol. 2006; 30 (2): 247-52. **Does not report side effects by medication class**

Pozler, O., Maly, J., Bonova, O., Dedek, P., Fruhauf, P., Havlickova, A., et al. Incidence of Crohn disease in the Czech Republic in the years 1990 to 2001 and assessment of pediatric population with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2006; 42 (2): 186-9. **Does not apply to key questions**

Prabhakar, L. P., Laramee, C., Nelson, H., and Dozois, R. R. Role for segmental or abdominal colectomy in Crohn's colitis. DIS. COLON RECTUM. 97; 40 (1): 71-78. **Does not apply to key questions**

Prajapati, D. N., Knox, J. F., Emmons, J., Saeian, K., Csuka, M. E., and Binion, D. G. Leflunomide treatment of Crohn's disease patients intolerant to standard immunomodulator therapy. J Clin Gastroenterol. 2003; 37 (2): 125-8. **Does not evaluate a drug of interest**

Prantera, C., Pallone, F., Brunetti, G., Cottone, M., Miglioli, M., Porro, G. B., et al. Oral 5-aminosalicylic acid (Asacol) in the maintenance treatment of Crohn's disease. GASTROENTEROLOGY. 92; 103 (2): 363-368. **Other reason**

Present DH, Wisch N, Glass JL, and Korelitz BI. The efficacy of immunosuppressive therapy in Crohn's disease. A randomized long term double blind study. Gastroenterology. 77; 72 (5II): A-91. **Abstract only**

Present, D. H., Meltzer, S. J., Krumholz, M. P., Wolke, A., and Korelitz, B. I. 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. Ann Intern Med. 89; 111 (8): 641-9. **Does not report side effects by medication class**

Prokopova, L., Zboril, V., and Abbe, L. M. The Problems of Crohn's Disease Treatment by anti-TNF: A Theory and Our Experience: Uskali lecby Crohnovy nemoci anti-TNF: Teorie a vlastni zkusenosti. Ceska Slov. Gastroenterol. Hepatol. 2003; 57 (5): 167-170. **Not written in English**

Qasim, A., McDonald, S., Sebastian, S., McLoughlin, R., Buckley, M., O'Connor, H., et al. Efficacy and safety of 6-thioguanine in the management of inflammatory bowel disease. Scand J Gastroenterol. 2007; 42 (2): 194-9. **Does not evaluate a drug of interest; does not report side effects by medication class**

Radke, M., Bartolomaeus, G., Muller, M., and Richter, I. Acute pancreatitis in Crohn's disease due to 5-ASA therapy. J Pediatr Gastroenterol Nutr. 93; 16 (3): 337-9. **Case report or case series**

Rahhal, R. M. and Bishop, W. P. Initial clinical experience with allopurinol-thiopurine combination therapy in pediatric inflammatory bowel disease. Inflamm Bowel Dis. 2008; 14 (12): 1678-82. **Does not apply to key questions; other observational study without a comparison group**

Rahier, J. F. and Colombel, J. F. Opportunistic infections and anti-tumor necrosis factor antagonists in patients with IBD: prevention and diagnosis. Dig. Liver Dis. Suppl. 2008; 2 (1): 23-24. **No original data**

Ramadas, A. V., Gunesh, S., Thomas, G. A., Williams, G. T., and Hawthorne, A. B. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986-2003): a study of changes in medical treatment and surgical resection rates. Gut. 2010; 59 (9): 1200-6. **Other observational study without a comparison group**

Rampton, D. S. Methotrexate in Crohn's disease. Gut. 2001; 48 (6): 790-1. **No original data**

Rao, S. S. 5-Aminosalicylic acid enemas in distal colitis. Gastroenterology. 88; 95 (6): 1698-9. **No original data**

Rasmussen, S. N., Binder, V., Maier, K., Bondesen, S., Fischer, C., Klotz, U., et al. Treatment of Crohn's disease with peroral 5-aminosalicylic acid. Gastroenterology. 83; 85 (6): 1350-3. **Other observational study without a comparison group**

Rasmussen, S. N., Lauritsen, K., Tage-Jensen, U., Nielsen, O. H., Bytzer, P., Jacobsen, O., et al. 5-Aminosalicylic acid in the treatment of Crohn's disease. A 16-week double-blind, placebo-controlled, multicentre study with Pentasa. Scand J Gastroenterol. 87; 22 (7): 877-83. **Other reason**

Ravikumara, M., Hinsberger, A., and Spray, C. H. Role of methotrexate in the management of Crohn disease. J Pediatr Gastroenterol Nutr. 2007; 44 (4): 427-30. **Case report or case series; other observational study without a comparison group**

Rayner, C. K., Hart, A. L., Hayward, C. M., Emmanuel, A. V., and Kamm, M. A. Azathioprine dose escalation in inflammatory bowel disease. Aliment Pharmacol Ther. 2004; 20 (1): 65-71. **Does not report side effects by medication class**

Reffitt, D. M., Meenan, J., Sanderson, J. D., Jugdaohsingh, R., Powell, J. J., and Thompson, R. P. Bone density improves with disease remission in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2003; 15 (12): 1267-73. **Does not apply to key questions**

Regadas, F. S., Pinto, R. A., Murad-Regadas, S. M., Canedo, J. A., Leal, M., Nogueras, J. J., et al. Short-term outcome of infliximab and other medications on patients with inflammatory bowel disease undergoing ileostomy reversal. Colorectal Dis. 2010. **Does not apply to key questions, Does not report side effects by medication class**

Regueiro, M. and Mardini, H. Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement. Inflamm Bowel Dis. 2003; 9 (2): 98-103. **Other observational study without a comparison group**

Regueiro, M., Kip, K. E., Schraut, W., Baidoo, L., Sepulveda, A. R., Pesci, M., et al. Crohn's disease activity index does not correlate with endoscopic recurrence one year after ileocolonic resection. Inflammatory Bowel Dis. 2011; 17 (1): 118-126. **Does not apply to key questions**

Regueiro, M., Schraut, W., Baidoo, L., Kip, K. E., Sepulveda, A. R., Pesci, M., et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology. 2009; 136 (2): 441-50.e1; quiz 716. **Does not apply to key questions**

Regueiro, M., Siemanowski, B., Kip, K. E., and Plevy, S. Infliximab dose intensification in Crohn's disease. Inflamm Bowel Dis. 2007; 13 (9): 1093-9. **Does not evaluate a drug of interest; other observational study without a comparison group**

Reichel, C., Streit, J., and Wunsch, S. [Significant changes of pharmacotherapy in gastroenterological rehabilitation of Crohn's disease]. Rehabilitation (Stuttg). 2009; 48 (6): 354-60. **Not written in English**

Reilly, M. C., Gerlier, L., Brabant, Y., and Brown, M. Validity, reliability, and responsiveness of the work productivity and activity impairment questionnaire in Crohn's disease. Clin. Ther. 2008; 30 (2): 393-404. **Does not apply to key questions**

Reinisch, W., Gasche, C., Wyatt, J., Moser, G., Lochs, H., Vogelsang, H., et al. Steroid dependency in Crohn's disease. Lancet. 95; 345 (8953): 859. **No original data**

Reinshagen, M., Schutz, E., Armstrong, V. W., Behrens, C., von Tirpitz, C., Stallmach, A., et al. 6-thioguanine nucleotide-adapted azathioprine therapy does not lead to higher remission rates than standard therapy in chronic active crohn disease: results from a randomized, controlled, open trial. Clin Chem. 2007; 53 (7): 1306-14. **Does not evaluate a drug of interest; other observational study without a comparison group**

Rhodes J, Bainton D, and Beck P Azathioprine in Crohn's disease. Lancet. 70; 2 (7683): 1142. **Other reason**

Rhodes, J. Azathioprine in the treatment of Crohn's disease. Br J Surg. 72; 59 (10): 819-21. **No original data**

Ricart, E. and Sandborn, W. J. Infliximab for the treatment of fistulas in patients with Crohn'S disease. Gastroenterology. 99; 117 (5): 1247-8. **No original data; other reason**

Ricart, E. Thiopurine and the risk of lymphoma in inflammatory bowel disease: Tiopurinas y riesgo de linfoma en la enfermedad inflamatoria intestinal. Gastroenterol. Hepatol. Continuada. 2010; 9 (4): 193-196. **Not written in English**

Riello, L., Talbotec, C., Garnier-Lengline, H., Pigneur, B., Svahn, J., Canioni, D., et al. Tolerance and efficacy of azathioprine in pediatric Crohn's disease. Inflamm Bowel Dis. 2011. **Does not evaluate a drug of interest**

Rijk, M. C., van Hogezand, R. A., van Lier, H. J., and van Tongeren, J. H. Sulphasalazine and prednisone compared with sulphasalazine for treating active Crohn disease. A double-blind, randomized, multicenter trial. Ann Intern Med. 91; 114 (6): 445-50. **Other reason**

Rintamaki, H., Sipponen, T., Salo, H. M., Vaarala, O., and Kolho, K.-L. Serum immune-activation potency and response to anti-TNF-(alpha) therapy in Crohn's disease. World J. Gastroenterol. 2010; 16 (46): 5845-5851. **Does not apply to key questions; does not report side effects by medication class**

Rizzo, G., Armuzzi, A., Pugliese, D., Verbo, A., Papa, A., Mattana, C., et al. Anti-TNF-alpha therapies do not increase early postoperative complications in patients with inflammatory bowel disease. An Italian single-center experience. Int. J. Colorectal Dis. 2011; 1-10. **Does not apply to key questions**

Robinson, R. J., al-Azzawi, F., Iqbal, S. J., Kryswcki, T., Almond, L., Abrams, K., et al. Osteoporosis and determinants of bone density in patients with Crohn's disease. Dig Dis Sci. 98; 43 (11): 2500-6. **Does not report side effects by medication class**

Robinson, R. J., Iqbal, S. J., Wolfe, R., Patel, K., Abrams, K., and Mayberry, J. F. The effect of rectally administered steroids on bone turnover: a comparative study. Aliment Pharmacol Ther. 98; 12 (3): 213-7. **Does not report side effects by medication class**

Roblin, X., Biroulet, L. P., Phelip, J. M., Nancey, S., and Flourie, B. A 6-thioguanine nucleotide threshold level of 400 pmol/8 null 10 8 erythrocytes predicts azathioprine refractoriness in patients with inflammatory bowel disease and normal TPMT activity. Am. J. Gastroenterol. 2008; 103 (12): 3115-3122. **Does not apply to key questions**

Roblin, X., Oussalah, A., Chevaux, J.-B., Sparrow, M., and Peyrin-Biroulet, L. Use of thiopurine testing in the management of inflammatory bowel diseases in clinical practice: A worldwide survey of experts. Inflammatory Bowel Dis. 2011. **Does not report side effects by medication class; other reason**

Roblin, X., Phelip, J. M., Genevois, M., Ducros, V., and Bonaz, B. Hyperhomocysteinaemia is associated with osteoporosis in patients with Crohn's disease. Aliment Pharmacol Ther. 2007; 25 (7): 797-804. **Does not apply to key questions**

Roblin, X., Serre-Debeauvais, F., Phelip, J. M., Faucheron, J. L., Hardy, G., Chartier, A., et al. 6-thioguanine monitoring in steroid-dependent patients with inflammatory bowel diseases receiving azathioprine. Aliment Pharmacol Ther. 2005; 21 (7): 829-39. **Does not apply to key questions, Other observational study without a comparison group**

Rodrigo, L., Perez-Pariente, J. M., Fuentes, D., Cadahia, V., Garcia-Carbonero, A., Nino, P., et al. Retreatment and maintenance therapy with infliximab in fistulizing Crohn's disease. Rev Esp Enferm Dig. 2004; 96 (8): 548-54; 554-8. **Does not report side effects by medication class**

Roggero P, Santus F, Barabino A, Canani RB, Cucchiara S, Guariso G, et al. A prospective pediatric multicenter trial of enteral nutrition and azathioprine in preventing relapses of Crohn disease: preliminary results. Journal of Pediatric Gastroenterology and Nutrition. 2003; 36 (4): 543. **Abstract only**

Romano, C., Cucchiara, S., Barabino, A., Annese, V., and Sferlazzas, C. Usefulness of omega-3 fatty acid supplementation in addition to mesalazine in maintaining remission in pediatric Crohn's disease: a double-blind, randomized, placebo-controlled study. World J Gastroenterol. 2005; 11 (45): 7118-21. **Does not evaluate a drug of interest**

Roseau, E. [Crohn's disease: prevention of relapse with methotrexate or growth hormone]. Presse Med. 2000; 29 (30): 1652-3. **Not written in English**

Rosen, A., Ursing, B., Alm, T., Barany, F., Bergelin, I., Ganrot-Norlin, K., et al. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. I. Design and methodologic considerations. Gastroenterology. 82; 83 (3): 541-9. **No original data; does not evaluate a drug of interest**

Rosen, R., Integlia, M. J., and Bousvaros, A. Severe pancytopenia from thiopurine methyltransferase deficiency: a preventable complication of 6-mercaptopurine therapy in children with Crohn disease. J Pediatr Gastroenterol Nutr. 2002; 35 (5): 695-9. **Does not evaluate a drug of interest; does not apply to key questionsCase report or case series**

Rosh, J. R., Lerer, T., Markowitz, J., Goli, S. R., Mamula, P., Noe, J. D., et al. Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in pediatric Crohn's disease. Am J Gastroenterol. 2009; 104 (12): 3042-9. **Other observational study without a comparison group; does not report side effects by medication class**

Ross, S., Rajwal, S. K., Sugarman, I., Picton, S., Devlin, J., Davison, S., et al. Epstein-Barr Virus-associated Lymphoproliferative Disorder in Crohn Disease Treated With Azathioprine. J Pediatr Gastroenterol Nutr. 2010. **Does not apply to key questionsCase report or case series**

Roth, M., Gross, V., Scholmerich, J., Ueberschaer, B., and Ewe, K. Treatment of active Crohn's disease with an oral slow-release budesonide formulation. Am J Gastroenterol. 93; 88 (6): 968-9. **Does not evaluate a drug of interest; does not report side effects by medication class**

Ruemmele, F. M., Lachaux, A., Cezard, J. P., Morali, A., Maurage, C., Ginies, J. L., et al. Efficacy of infliximab in pediatric Crohn's disease: a randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. Inflamm Bowel Dis. 2009; 15 (3): 388-94. **Does not evaluate a drug of interest**

Russo, E. A., Iacucci, M., Lindsay, J. O., Campbell, S., Hart, A., Hamlin, J., et al. Survey on the use of adalimumab as maintenance therapy in Crohn's disease in England and Ireland. Eur J Gastroenterol Hepatol. 2010; 22 (3): 334-9. **Other observational study without a comparison group; does not report side effects by medication class**

Rutgeerts, P. and Vantrappen, G. New 5-ASA formulations for inflammatory bowel disease: LE NUOVE PREPARAZIONI DI 5-ASA PER LE MALATTIE INFIAMMATORIE INTESTINALI. ARGOMENTI GASTROENTEROL. CLIN. 93; 6 (1): 8-14. **Not written in English**

Rutgeerts, P. Budesonide led to a greater remission rate and fewer severe adverse events than did mesalamine in Crohn's disease. Gut. 99; 45 (1): 13-4. **No original data; other reason**

Rutgeerts, P. Little benefit from mesalazine taken prophylactically after surgery for Crohn's disease. Gut. 2001; 48 (4): 452-3. **No original data**

Sabate, J. M., Villarejo, J., Lemann, M., Bonnet, J., Allez, M., and Modigliani, R. An open-label study of thalidomide for maintenance therapy in responders to infliximab in chronically active and fistulizing refractory Crohn's disease. Aliment Pharmacol Ther. 2002; 16 (6): 1117-24. **Does not evaluate a drug of interest**

Sahmoud, T., Mary, J. Y., and Sahmoud, T. Mesalazine as a maintenance treatment in Crohn's disease: is it the long awaited solution?. Gut. 97; 40 (2): 284-5. **No original data**

Saibeni, S., Virgilio, T., D'Inca, R., Spina, L., Bortoli, A., Paccagnella, M., et al. The use of thiopurines for the treatment of inflammatory bowel diseases in clinical practice. Dig Liver Dis. 2008; 40 (10): 814-20. **Does not evaluate a drug of interest**

Salamon, A., Simon, L., and Nemesanszky, E. First experiences with infliximab therapy in Crohn's disease - Results of a Hungarian multicentre study: Elso tapasztalatok a Crohn-betegseg infliximabkezelese vel - Magyarorszagi multicentrikus tanulmany eredmenyei. Lege Artis Med. 2004; 14 (7): 483-487. **Not written in English**

Salmon-Ceron, D., Tubach, F., Lortholary, O., Chosidow, O., Bretagne, S., Nicolas, N., et al. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann. Rheum. Dis. 2011; 70 (4): 616-623. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; case report or case series**

Sample, C., Bailey, R. J., Todoruk, D., Sadowski, D., Gramlich, L., Milan, M., et al. Clinical experience with infliximab for Crohn's disease: the first 100 patients in Edmonton, Alberta. Can J Gastroenterol. 2002; 16 (3): 165-70. **Other observational study without a comparison group**

San Jose Bermejo, F., San Roman, A. L., Algaba, A., Van Domselaar, M., Carneros, J. A., Rivero, M., et al. Efficacy of premedication with intravenous corticosteroids and antihistaminics in preventing infusion reactions to infliximab: Eficacia de la premedicacion con un esteroide y un antihistaminico en la prevencion de reacciones infusionales por infliximab. Gastroenterol. Hepatol. 2008; 31 (10): 629-632. **Not written in English**

Sanchez Cano, D., Ruiz-Villaverde, R., Olvera Porcel, M. C., Callejas Rubio, J. L., Perez, C. C., Garcia, M. G., et al. [Evaluation of bone mineral density, bone turnover markers, the OPG/RANKL system and sTNF-RI in Crohn's disease]. Gastroenterol. Hepatol. 2011; 34 (1): 3-9. **Not written in English**

Sanchez, J. M., Maldonado, J. C., Torres, E. A., and Rivera, C. Infliximab in Hispanics: characterization of response to infliximab in an ethnic minority with Crohn's disease. P R Health Sci J. 2005; 24 (1): 11-7. **Other observational study without a comparison group; does not report side effects by medication class**

Sandborn WJ, Schreiber S, Hanauer SB, Colombel JF, Bloomfield R, Lichtenstein GR, and PRECiSE 4 Study Investigators Reinduction with certolizumab pegol in patients with relapsed Crohn's disease: results from the PRECiSE 4 Study. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2010; 8 (8): 696-702.e1. **Does not evaluate a drug of interest**

Sandborn, W. J. A controlled trial of anti-tumor necrosis factor alpha antibody for Crohn's disease. Gastroenterology. 97; 113 (3): 1042-3. **No original data**

Sandborn, W. J. Certolizumab pegol for moderate-to-severe Crohn's disease. Gastroenterol. Hepatol. 2008; 4 (7): 467-468. **No original data**

Sandborn, W. J. Initial combination therapy in early Crohn's disease. Lancet. 2008; 371 (9613): 635-636. **No original data**

Sandborn, W. J., Abreu, M. T., D'Haens, G., Colombel, J. F., Vermeire, S., Mitchev, K., et al. Certolizumab Pegol in Patients With Moderate to Severe Crohn's Disease and Secondary Failure to Infliximab. Clin Gastroenterol Hepatol. 2010. **Does not evaluate a drug of interest**

Sandborn, W. J., Feagan, B. G., Fedorak, R. N., Scherl, E., Fleisher, M. R., Katz, S., et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. Gastroenterology. 2008; 135 (4): 1130-41. **Does not evaluate a drug of interest**

Sandborn, W. J., Hanauer, S., Loftus, E. V. Jr, Tremaine, W. J., Kane, S., Cohen, R., et al. An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. Am J Gastroenterol. 2004; 99 (10): 1984-9. **Does not report side effects by medication class**

Sandborn, W. J., Schreiber, S., Hanauer, S. B., Colombel, J. F., Bloomfield, R., and Lichtenstein, G. R. Reinduction With Certolizumab Pegol in Patients With Relapsed Crohn's Disease: Results From the PRECiSE 4 Study. Clin Gastroenterol Hepatol. 2010. **Does not report side effects by medication class**

Sandborn, W. J., Tremaine, W. J., Wolf, D. C., Targan, S. R., Sninsky, C. A., Sutherland, L. R., et al. Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. Gastroenterology. 99; 117 (3): 527-535. **Other reason**

Sandborn, W. J., Van, O. EC, Zins, B. J., Tremaine, W. J., Mays, D. C., and Lipsky, J. J. An intravenous loading dose of azathioprine decreases the time to response in patients with Crohn's disease. Gastroenterology. 95; 109 (6): 1808-17. **Does not evaluate a drug of interest**

Sanderson, J. Incidence of adverse reactions to azathioprine in patients with Crohn's disease. Nat Clin Pract Gastroenterol Hepatol. 2005; 2 (11): 510-1. **No original data; does not evaluate a drug of interest**

Santos, J. V., Baudet, J. A., Casellas, F. J., Guarner, L. A., Vilaseca, J. M., and Malagelada, J. R. Intravenous cyclosporine for steroid-refractory attacks of Crohn's disease. Short- and long-term results. J Clin Gastroenterol. 95; 20 (3): 207-10. **Does not evaluate a drug of interest; other observational study without a comparison group**

Savilahti, E. Sulphasalazine induced immunodeficiency. Br Med J (Clin Res Ed). 83; 287 (6394): 759. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; case report or case series**

Savoye-Collet, C., Savoye, G., Koning, E., Dacher, J. N., and Lerebours, E. Fistulizing perianal Crohn's disease: Contrast-enhanced magnetic resonance imaging assessment at 1 year on maintenance anti-TNF-alpha therapy. Inflamm Bowel Dis. 2010. **Does not evaluate a drug of interest; does not apply to key questions**

Sayani, F. A., Prosser, C., Bailey, R. J., Jacobs, P., and Fedorak, R. N. Thiopurine methyltransferase enzyme activity determination before treatment of inflammatory bowel disease with azathioprine: effect on cost and adverse events. Can J Gastroenterol. 2005; 19 (3): 147-51. **Does not evaluate a drug of interest; does not report side effects by medication class**

Scheurlen, C. and Kruis, W. 5-Aminosalicylic acid preparations in the therapy of chronic bowel disease: 5-Aminosalicylsaure-Praparate In Der Therapie Chronisch-Entzundlicher Darmerkrankungen. INN. MED. 92; 19 (3): 88-93. **Not written in English**

Schmidt, C., Wittig, B. M., Moser, C., Zeitz, M., and Stallmach, A. Cyclophosphamide pulse therapy followed by azathioprine or methotrexate induces long-term remission in patients with steroid-refractory Crohn's disease. Aliment Pharmacol Ther. 2006; 24 (2): 343-50. **Does not evaluate a drug of interest; other observational study without a comparison group**

Schmidt, S., Mellstrom, D., Norjavaara, E., Sundh, S. V., and Saalman, R. Low bone mineral density in children and adolescents with inflammatory bowel disease: A population-based study from Western Sweden. Inflamm Bowel Dis. 2009; 15 (12): 1844-1850. **Does not apply to key questions; other observational study without a comparison group**

Schnitzler, F., Fidder, H., Ferrante, M., Noman, M., Arijs, I., Van Assche, G., et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut. 2009; 58 (4): 492-500. **Does not report side effects by medication class**

Schoepfer, A. M., Vavricka, S. R., Binek, J., Felley, C., Geyer, M., Manz, M., et al. Efficacy and safety of certolizumab pegol induction therapy in an unselected Crohn's disease population: results of the FACTS survey. Inflamm Bowel Dis. 2010; 16 (6): 933-8. **Other observational study without a comparison group**

Schreiber, S., Hamling, J., Zehnter, E., Howaldt, S., Daerr, W., Raedler, A., et al. Renal tubular dysfunction in patients with inflammatory bowel disease treated with aminosalicylate. Gut. 97; 40 (6): 761-6. **Does not report side effects by medication class**

Schroder, O., Blumenstein, I., Schulte-Bockholt, A., and Stein, J. Combining infliximab and methotrexate in fistulizing Crohn's disease resistant or intolerant to azathioprine. Aliment Pharmacol Ther. 2004; 19 (3): 295-301. **Other observational study without a comparison group**

Schroder, O., Naumann, M., and Stein, J. Anti-Saccharomyces cerevisiae antibodies and response to infliximab in refractory Crohn's disease. Aliment Pharmacol Ther. 2004; 20 (7): 823-4. **Does not apply to key questions; does not report side effects by medication class**

Schulte, C., Dignass, A. U., Mann, K., and Goebell, H. Reduced bone mineral density and unbalanced bone metabolism in patients with inflammatory bowel disease. Inflamm Bowel Dis. 98; 4 (4): 268-75. **Does not apply to key questions**

Schwartz, D. A. What is the optimal maintenance treatment for perianal Crohn's disease?. Inflamm Bowel Dis. 2008; 14 Suppl 2 S269-70. **No original data**

Sciaudone, G., Di Stazio, C., Limongelli, P., Guadagni, I., Pellino, G., Riegler, G., et al. Treatment of complex perianal fistulas in Crohn disease: infliximab, surgery or combined approach. Can J Surg. 2010; 53 (5): 299-304. **Other observational study without a comparison group; other reason**

Sciaudone, G., Pellino, G., Riegler, G., and Selvaggi, F. Infliximab in drug-naive patients with failed ileorectal anastomosis for crohn's disease: A new chance for sparing the rectum? Eur. Surg. Res. 2011; 46 (4): 163-168. **Does not evaluate a drug of interest; does not apply to key questions**

Scribano, M. L. Adverse events of IBD therapies. Inflamm Bowel Dis. 2008; 14 Suppl 2 S210-1. **No original data**

Scribano, M. L. and Marmo, R. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease: Azatioprina e mesalazina nella prevenzione della riaccensione dopo intervento chirurgico conservativo per malattia di Crohn. G. Ital. Endosc. Dig. 2006; 29 (1): 61-67. **Not written in English**

Segarra Canton, O., Infante Pina, D., and Tormo Carnice, R. [Infliximab therapy for inflammatory bowel disease: seven years on]. An Pediatr (Barc). 2007; 67 (4): 344-51. **Not written in English**

Seiderer, J., Brand, S., Dambacher, J., Pfennig, S., Jurgens, M., Goke, B., et al. Adalimumab in patients with Crohn's disease--safety and efficacy in an open-label single centre study. Aliment Pharmacol Ther. 2007; 25 (7): 787-96. **Does not evaluate a drug of interest**

Selby, L. A., Hess, D., Shashidar, H., de Villiers, W. J., and Selby, L. A. Crohn's disease, infliximab and idiopathic thrombocytopenic purpura. Inflamm Bowel Dis. 2004; 10 (5): 698-700. **Case report or case series**

Semeao, E. J., Jawad, A. F., Stouffer, N. O., Zemel, B. S., Piccoli, D. A., and Stallings, V. A. Risk factors for low bone mineral density in children and young adults with Crohn's disease. J Pediatr. 99; 135 (5): 593-600. **Does not report side effects by medication class**

Seo, J. K., Yeon, K. M., and Chi, J. G. Inflammatory bowel disease in children--clinical, endoscopic, radiologic and histopathologic investigation. J Korean Med Sci. 92; 7 (3): 221-35. **Does not evaluate a drug of interest**

Serra, I., Oller, B., Manosa, M., Naves, J. E., Zabana, Y., Cabre, E., et al. Systemic amyloidosis in inflammatory bowel disease: Retrospective study on its prevalence, clinical presentation, and outcome. J. Crohn's Colitis. 2010; 4 (3): 269-274. **Case report or case series**

Serrano, M. S., Schmidt-Sommerfeld, E., Kilbaugh, T. J., Brown, R. F., Udall, J. N. Jr, and Mannick, E. E. Use of infliximab in pediatric patients with inflammatory bowel disease. Ann Pharmacother. 2001; 35 (7-8): 823-8. **Other observational study without a comparison group**

Serrate, C., Silva-Moreno, M., Dartigues, P., Poujol-Robert, A., Sokol, H., Gorin, N. C., et al. Epstein-Barr virus-associated lymphoproliferation awareness in hemophagocytic syndrome complicating thiopurine treatment for Crohn's disease. Inflamm Bowel Dis. 2009; 15 (10): 1449-51. **Case report or case series**

Sesin, G. P., Mucciardi, N., and Almeida, S. Mesalamine-associated pleural effusion with pulmonary infiltration. Am J Health Syst Pharm. 98; 55 (21): 2304-5. **Case report or case series**

Seydtaghia, F., De Saussure, P., and Hadengue, A. High frequency of cutaneous adverse effects under Infliximab. Geneva experience, 1999-2008: Frequence elevee d'Effets secondaires cutanes sous infliximab Experience aGeneve, 1999-2008. Rev. Med. Suisse. 2011; 7 (286): 619-623. **Not written in English**

Shale, M., Kanfer, E., Panaccione, R., and Ghosh, S. Hepatosplenic T cell lymphoma in inflammatory bowel disease. Gut. 2008; 57 (12): 1639-41. **No original data**

Shanahan, F. and Bernstein, C. N. Safety of low-dose purine analogues in inflammatory bowel disease. Gastroenterology. 94; 107 (6): 1905-6. **No original data**

Shaye, O. A., Yadegari, M., Abreu, M. T., Poordad, F., Simon, K., Martin, P., et al. Hepatotoxicity of 6-mercaptopurine (6-MP) and Azathioprine (AZA) in adult IBD patients. Am J Gastroenterol. 2007; 102 (11): 2488-94. **Does not report side effects by medication class**

Sheehan, T., Tansey, P., Cochran, K. M., and O'Donnell, J. R. Inflammatory bowel disease, anaemia and sulphasalazine. Clin Lab Haematol. 85; 7 (3): 275-8. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; case report or case series**

Sheffield, L. J., Irving, P., Gupta, A., Byron, K., Macrae, F. A., Phillimore, H., et al. Thiopurine methyltransferase and thiopurine metabolite testing in patients with inflammatory bowel disease who are taking thiopurine drugs. Pharmacogenomics. 2009; 10 (7): 1091-9. **Does not report side effects by medication class**

Shen, B., Remzi, F. H., Lavery, I. C., Lopez, R., Queener, E., Shen, L., et al. Administration of adalimumab in the treatment of Crohn's disease of the ileal pouch. Aliment Pharmacol Ther. 2009; 29 (5): 519-26. **Does not report side effects by medication class**

Shergill, A. K. and Terdiman, J. P. The Early Use of Immunosuppression Reduces Morbidity in Patients With Moderately Severe or Severe Crohn's Disease. Gastroenterology. 2008; 135 (4): 1417-1420. **No original data**

Shipkova, M., Franz, J., Abe, M., Klett, C., Wieland, E., and Andus, T. Association between adverse effects under azathioprine therapy and inosine triphosphate pyrophosphatase activity in patients with chronic inflammatory bowel disease. Ther. Drug Monit. 2011. **Does not evaluate a drug of interest; does not apply to key questions**

Siegel, C. A., Hur, C., Korzenik, J. R., Gazelle, G. S., and Sands, B. E. Risks and benefits of infliximab for the treatment of Crohn's disease. Clin Gastroenterol Hepatol. 2006; 4 (8): 1017-24; quiz 976. **No original data**

Siemanowski, B. and Regueiro, M. Management of perianal fistula in Crohn's disease. Inflamm Bowel Dis. 2008; 14 Suppl 2 S266-8. **No original data**

Silvennoinen, J. A., Karttunen, T. J., Niemela, S. E., Manelius, J. J., and Lehtola, J. K. A controlled study of bone mineral density in patients with inflammatory bowel disease. Gut. 95; 37 (1): 71-6. **Does not apply to key questions**

Singh, H., Demers, A. A., Nugent, Z., Mahmud, S. M., Kliewer, E. V., and Bernstein, C. N. Risk of cervical abnormalities in women with inflammatory bowel disease: a population-based nested case-control study. Gastroenterology. 2009; 136 (2): 451-8. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD**

Singleton, J. W. Azathioprine has a very limited role in the treatment of Crohn's disease. Dig Dis Sci. 81; 26 (4): 368-71. **No original data; does not report side effects by medication class**

Singleton, J. W., Hanauer, S. B., Gitnick, G. L., Peppercorn, M. A., Robinson, M. G., Wruble, L. D., et al. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. Gastroenterology. 93; 104 (5): 1293-301. **Other reason**

Skacel, M., Petras, R. E., Gramlich, T. L., Sigel, J. E., Richter, J. E., and Goldblum, J. R. Infliximab in Crohn's disease: First anniversary clinical experience. Am. J. Gastroenterol. 2000; 95 (12): 3469-3477. **Does not evaluate a drug of interest; does observational study without a comparison group**

Skelly, M. M., Logan, R. F., Jenkins, D., Mahida, Y. R., and Hawkey, C. J. Toxicity of mycophenolate mofetil in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2002; 8 (2): 93-7. **Does not evaluate a drug of interest**

Slattery, E., Keegan, D., Hyland, J., O'Donoghue, D., and Mulcahy, H. E. Surgery, Crohn's disease, and the biological era: Has there been an impact?. J. Clin. Gastroenterol. 2010. **Other observational study without a comparison group; does not report side effects by medication class**

Socha, P., Wawer, Z., Ryzko, J., Orlowska, E., Szczepanski, M., Kierkus, J., et al. [Efficacy and safety of cyclosporine in the treatment of inflammatory bowel disease in children - a retrospective study]. Med Wieku Rozwoj. 2006; 10 (2): 429-35. **Not written in English**

Sokol, H., Seksik, P., Nion-Larmurier, I., Vienne, A., Beaugerie, L., and Cosnes, J. Current smoking, not duration of remission, delays Crohn's disease relapse following azathioprine withdrawal. Inflamm Bowel Dis. 2010; 16 (3): 362-3. **Other observational study without a comparison group**

Soon, S. Y., Ansari, A., Yaneza, M., Raoof, S., Hirst, J., and Sanderson, J. D. Experience with the use of low-dose methotrexate for inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2004; 16 (9): 921-6. **Does not evaluate a drug of interest; does not report side effects by medication class**

Sorrentino, D., Paviotti, A., Terrosu, G., Avellini, C., Geraci, M., and Zarifi, D. Low-Dose Maintenance Therapy With Infliximab Prevents Postsurgical Recurrence of Crohn's Disease. Clin Gastroenterol Hepatol. 2010. **Does not apply to key questions; other observational study without a comparison group**

Sorrentino, D., Terrosu, G., Avellini, C., and Maiero, S. Infliximab with low-dose methotrexate for prevention of postsurgical recurrence of ileocolonic Crohn disease. Arch Intern Med. 2007; 167 (16): 1804-7. **Does not evaluate a drug of interest; does not apply to key questions**

Sorrentino, D., Terrosu, G., Vadala, S., and Avellini, C. Fibrotic strictures and anti-TNF-alpha therapy in Crohn's disease. Digestion. 2007; 75 (1): 22-4. **Case report or case series**

Sou, S., Matsui, T., Yao, T., Yorioka, M., Tsuda, S., Kikuchi, Y., et al. Clinical and endoscopic healing after infliximab treatment in patients with Crohn's disease. Dig. Endosc. 2006; 18 (1): 29-33. **Other observational study without a comparison group**

Sousa, H., Portela, F., and Cipriano, M. A. Posttransplant lymphoproliferative disorders in patients with IBD on immunosuppressive treatment. Inflamm Bowel Dis. 2009; 15 (3): 481-3. **Case report or case series**

Sparberg, M. and Kirsner, J. B. Long-term corticosteroid therapy for regional enteritis: an analysis of 58 courses in 54 patients. Am J Dig Dis. 66; 11 (11): 865-80. **Does not evaluate a drug of interest; other observational study without a comparison group**

Sparrow, M. P., Hande, S. A., Friedman, S., Cao, D., and Hanauer, S. B. Effect of allopurinol on clinical outcomes in inflammatory bowel disease nonresponders to azathioprine or 6-mercaptopurine. Clin Gastroenterol Hepatol. 2007; 5 (2): 209-14. **Other observational study without a comparison group; does not report side effects by medication class**

Spector, R. The use of sulfasalazine in the treatment of inflammatory bowel disease. J Iowa Med Soc. 83; 73 (6): 230-4. **No original data**

Stange EF, Modigliani R, Pena, AS, Wood AJ, Feutren G, and Smith PR. European trial of cyclosporine in chronic active Crohn's disease: a 12-month study. The European Study Group. Gastroenterology. 95; 109 (3): 774-82. **Does not evaluate a drug of interest**

Stange, E. F. In the case of nonresponse, what is the second-level treatment for induction of remission in Crohn's disease?. Inflamm Bowel Dis. 2008; 14 Suppl 2 S251-2. **No original data**

Steenholdt, C., Svenson, M., Bendtzen, K., Thomsen, O. O., Brynskov, J., and Ainsworth, M. A. Severe infusion reactions to infliximab: Aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. Aliment. Pharmacol. Ther. 2011. **Case report or case seriesOther reason**

Steiner, S. J., Pfefferkorn, M. D., Fitzgerald, J. F., and Denne, S. C. Effects of infliximab and parenteral nutrition on albumin and fibrinogen synthesis rates in pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2008; 47 (5): 579-84. **Does not evaluate a drug of interest; does not apply to key questions**

Steinwurz, F. [Clinical experience with the use of infliximab in 44 patients with Crohn's disease]. Arq Gastroenterol. 2003; 40 (3): 198-200. **Not written in English**

Stepanas, A. V., Grant, A. K., and Alp, M. H. Corticosteroid therapy in Crohn's colitis. Aust N Z J Med. 71; 1 (1): 30-4. **Case report or case seriesOther observational study without a comparison group**

Stephens, M. C., Shepanski, M. A., Mamula, P., Markowitz, J. E., Brown, K. A., and Baldassano, R. N. Safety and steroid-sparing experience using infliximab for Crohn's disease at a pediatric inflammatory bowel disease center. Am J Gastroenterol. 2003; 98 (1): 104-11. **Other observational study without a comparison group; does not report side effects by medication class**

Sternthal, M. B., Murphy, S. J., George, J., Kornbluth, A., Lichtiger, S., and Present, D. H. Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. Am J Gastroenterol. 2008; 103 (4): 937-43. **Does not evaluate a drug of interestDoes not report side effects by medication class**

Stocco, G., Martelossi, S., Barabino, A., Decorti, G., Bartoli, F., Montico, M., et al. Glutathione-S-transferase genotypes and the adverse effects of azathioprine in young patients with inflammatory bowel disease. Inflamm Bowel Dis. 2007; 13 (1): 57-64. **Other observational study without a comparison group; does not report side effects by medication class**

Stocco, G., Martelossi, S., Barabino, A., Fontana, M., Lionetti, P., Decorti, G., et al. TPMT genotype and the use of thiopurines in paediatric inflammatory bowel disease. Dig Liver Dis. 2005; 37 (12): 940-5. **Does not evaluate a drug of interest; other observational study without a comparison group**

Stockbrugger, R. W., Schoon, E. J., Bollani, S., Mills, P. R., Israeli, E., Landgraf, L., et al. Discordance between the degree of osteopenia and the prevalence of spontaneous vertebral fractures in Crohn's disease. Aliment Pharmacol Ther. 2002; 16 (8): 1519-27. **Does not apply to key questions**

Stokkers, P. C., Camoglio, L., and van Deventer, S. J. Tumor necrosis factor (TNF) in inflammatory bowel disease: gene polymorphisms, animal models, and potential for anti-TNF therapy. J Inflamm. 95-96; 47 (1-2): 97-103. **No original data; does not apply to key questions**

Stricker, T. and Braegger, C. P. Antibody to tumor necrosis factor in the treatment of Crohn's disease. J Pediatr Gastroenterol Nutr. 98; 27 (3): 369-70. **No original dataAbstract only**

Stuby, U., Biesenbach, G., and Pieringer, H. Administration of infliximab in general practitioners' offices is safe. Clin Rheumatol. 2007; 26 (11): 1863-6. **Does not evaluate a drug of interest; does not report side effects by medication class**

Sturdevant, R. A., Singleton, J. W., Deren, J. L., Law, D. H., and McCleery, J. L. Azathioprine-related pancreatitis in patients with Crohn's disease. Gastroenterology. 79; 77 (4 Pt 2): 883-6. **Other reason**

Sutherland, L. R., Martin, F., Bailey, R. J., Fedorak, R. N., Poleski, M., Dallaire, C., et al. A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. GASTROENTEROLOGY. 97; 112 (4): 1069-1077. **Other reason**

Suwannalai, P., Auethavekiat, P., Udomsubpayakul, U., and Janvitayanujit, S. The infectious profiles of anti-tumor necrosis factor agents in a Thai population: A retrospective study a the university-based hospital. Int. J. Rheum. Dis. 2009; 12 (2): 118-124. **Does not apply to key questions; other observational study without a comparison group**

Swaminath, A., Lebwohl, B., Capiak, K. M., and Present, D. H. Practice patterns in the use of anti-tumor necrosis factor alpha agents in the management of Crohn's disease: A US national practice survey comparing experts and non-experts. Dig. Dis. Sci. 2011; 56 (4): 1160-1164. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD; other reason**

Swaminath, A., Ullman, T., Rosen, M., Mayer, L., Lichtiger, S., and Abreu, M. T. Early clinical experience with adalimumab in treatment of inflammatory bowel disease with infliximab-treated and naive patients. Aliment Pharmacol Ther. 2009; 29 (3): 273-8. **Does not report side effects by medication class**

Szamosi, T., Banai, J., Lakatos, L., Czegledi, Z., David, G., Zsigmond, F., et al. Early azathioprine/biological therapy is associated with decreased risk for first surgery and delays time to surgery but not reoperation in both smokers and nonsmokers with Crohn's disease, while smoking decreases the risk of colectomy in ulcerative colitis. Eur J Gastroenterol Hepatol. 2010; 22 (7): 872-9. **Other observational study without a comparison group; does not report side effects by medication class**

Takahashi, S., Takagi, S., Shiga, H., Umemura, K., Endo, K., Kakuta, Y., et al. Scheduled maintenance therapy with infliximab improves the prognosis of Crohn's disease: a single center prospective cohort study in Japan. Tohoku J Exp Med. 2010; 220 (3): 207-15. **Other observational study without a comparison group; does not report side effects by medication class**

Takatsu, N., Matsui, T., Murakami, Y., Ishihara, H., Hisabe, T., Nagahama, T., et al. Adverse reactions to azathioprine cannot be predicted by thiopurine S-methyltransferase genotype in Japanese patients with inflammatory bowel disease. J Gastroenterol Hepatol. 2009; 24 (7): 1258-64. **Other observational study without a comparison group; does not report side effects by medication class**

Talbot, C., Sagar, P. M., Johnston, M. J., Finan, P. J., and Burke, D. Infliximab in the surgical management of complex fistulating anal Crohn's disease. Colorectal Dis. 2005; 7 (2): 164-8. **Other observational study without a comparison group; does not report side effects by medication class**

Tanaka, S., Matsuo, K., Sasaki, T., Nakano, M., Sakai, K., Beppu, R., et al. Clinical advantages of combined seton placement and infliximab maintenance therapy for perianal fistulizing Crohn's disease: when and how were the seton drains removed?. Hepatogastroenterology. 2010; 57 (97): 3-7. **Does not apply to key questions; other observational study without a comparison group**

Tankova, L., Mendizova, A., Penchev, P., and Muhtarov, M. Therapeutical effect of remicade in Crohn's disease. Gen. Med. 2002; 4 (1): 20-24. **Other reason**

Tao, Q. S., Ren, J. A., Ji, Z. L., Li, J. S., Wang, X. B., and Jiang, X. H. [Maintenance effect of polyglycosides of Tripterygium wilfordii on remission in postoperative Crohn disease]. Zhonghua Wei Chang Wai Ke Za Zhi. 2009; 12 (5): 491-3. **Not written in English**

Te, H. S., Schiano, T. D., Kuan, S. F., Hanauer, S. B., Conjeevaram, H. S., and Baker, A. L. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. Am J Gastroenterol. 2000; 95 (11): 3150-6. **Other observational study without a comparison group; does not report side effects by medication class**

Teitelbaum, J. E., Saeed, S., Triantafyllopoulou, M., and Daum, F. Infliximab in pediatric Crohn disease patients with enterovesicular fistulas. J Pediatr Gastroenterol Nutr. 2007; 44 (2): 279-82. **Case report or case series**

Teml, A., Schwab, M., Hommes, D. W., Almer, S., Lukas, M., Feichtenschlager, T., et al. A systematic survey evaluating 6-thioguanine-related hepatotoxicity in patients with inflammatory bowel disease. Wien. Klin. Wochenschr. 2007; 119 (17-18): 519-526. **Does not evaluate a drug of interest; other observational study without a comparison group**

Tenore, A., Berman, W. F., Parks, J. S., and Bongiovanni, A. M. Basal and stimulated serum growth hormone concentrations in inflammatory bowel disease. J Clin Endocrinol Metab. 77; 44 (4): 622-8. **Does not apply to key questions; does not report side effects by medication class**

Terdiman, J. P. Prevention of postoperative recurrence in Crohn's disease. Clin Gastroenterol Hepatol. 2008; 6 (6): 616-20. **No original data**

Terranova M, Leonello G, Macri A, Versaci A, Scuderi G, Crisafulli C, et al. Enteral nutrition in the short-term treatment of active inflammatory bowel diseases: A single-centre experience. Rivista Italiana di Nutrizione Parenterale Ed Enterale. 2001; 19 (1): 12-17. **Not written in English**

Teshima, C. and Fedorak, R. N. Are there differences in type, dosage, and method of administration for the systemic steroids in IBD treatment?. Inflamm Bowel Dis. 2008; 14 Suppl 2 S216-8. **No original data**

Teshima, C. W., Thompson, A., Dhanoa, L., Dieleman, L. A., and Fedorak, R. N. Long-term response rates to infliximab therapy for Crohn's disease in an outpatient cohort. Can J Gastroenterol. 2009; 23 (5): 348-52. **Other observational study without a comparison group**

Thayu, M., Leonard, M. B., Hyams, J. S., Crandall, W. V., Kugathasan, S., Otley, A. R., et al. Improvement in biomarkers of bone formation during infliximab therapy in pediatric Crohn's disease: results of the REACH study. Clin Gastroenterol Hepatol. 2008; 6 (12): 1378-84. **Does not evaluate a drug of interest**

Thia, K. T., Li, M., Ling, K.-L., Kong, S.-C., and Ooi, C.-J. Azathioprine is effective in corticosteroid-dependent Asian inflammatory bowel disease patients. Inflammatory Bowel Dis. 2011; 17 (3): 809-815. **Other observational study without a comparison group**

Thodis, E., Rossos, P., Habal, F., and Oreopoulos, D. Negative impact of Crohn's disease on bone mineral mass. J Musculoskelet Neuronal Interact. 2003; 3 (3): 246-50. **Does not report side effects by medication class**

Thomas, M. C. and Schlup, M. M. Budesonide substitution in Crohn's disease relieves CNS toxicity of systemic steroids. Med J Aust. 98; 169 (10): 560. **Case report or case series**

Thomas, P., Seaton, A., and Edwards, J. Respiratory disease due to sulphasalazine. Clin Allergy. 74; 4 (1): 41-7. **Case report or case series**

Thomsen O, Cortot A, Jewell D, Wright JP, Winter T, Veloso FT, et al. Budesonide CIR is more effective than mesalazine in active Crohn's disease. A 16 week, international randomized, double-blind multicentre trial [abstract]. Gut. 97; 41 Suppl 3 A70. **Abstract only**

Thomsen O, Cortot A, Jewell D, Wright JP, Winther T, Veloso FT, et al. Budesonide CIR improved quality of life more than mesalazine measured by psychological general well-being index in active Crohn's disease. A 16-week international, randomized, double-blind multicentre trial [abstract]. Gut. 97; 41 Suppl 3 A223. **Abstract only**

Tiemi, J., Komati, S., and Sdepanian, V. L. Effectiveness of infliximab in Brazilian children and adolescents with Crohn disease and ulcerative colitis according to clinical manifestations, activity indices of inflammatory bowel disease, and corticosteroid use. J Pediatr Gastroenterol Nutr. 2010; 50 (6): 628-33. **Other observational study without a comparison group; does not report side effects by medication class**

Tietjen, K., Behrens, R., and Weimann, E. Growth failure in children and adolescents with Crohn's disease. Turk J Gastroenterol. 2009; 20 (1): 13-9. **Does not apply to key questionsOther observational study without a comparison groupDoes not report side effects by medication class**

Tillinger, W., Gasche, C., Reinisch, W., Lichtenberger, C., Bakos, S., Dejaco, C., et al. Influence of topically and systemically active steroids on circulating leukocytes in Crohn's disease. Am J Gastroenterol. 98; 93 (10): 1848-53. **Other reason**

Tobias, J. H., Sasi, M. R., Greenwood, R., and Probert, C. S. Rapid hip bone loss in active Crohn's disease patients receiving short-term corticosteroid therapy. Aliment Pharmacol Ther. 2004; 20 (9): 951-7. **Does not apply to key questions**

Tolia, V. Sulfasalazine desensitization in children and adolescents with chronic inflammatory bowel disease. Am J Gastroenterol. 92; 87 (8): 1029-32. **Does not evaluate a drug of interest; does not apply to key questions**

Tomecki, R., Bartnik, W., Butruk, E., Kosciuczyk, A., Kozlowska, A., Marlicz, K., et al. Assessment of the efficacy, tolerance and safety of infliximab (Remicade) in the treatment of Crohn's disease - Results of an open, multicentre clinical trial. Gastroenterol. Pol. 2004; 11 (6): 537-542. **Does not evaluate a drug of interest; other observational study without a comparison group**

Toovey, S., Hudson, E., Hendry, W. F., and Levi, A. J. Sulphasalazine and male infertility: reversibility and possible mechanism. Gut. 81; 22 (6): 445-51. **Other reason**

Topstad, D. R., Panaccione, R., Heine, J. A., Johnson, D. R., MacLean, A. R., and Buie, W. D. Combined seton placement, infliximab infusion, and maintenance immunosuppressives improve healing rate in fistulizing anorectal Crohn's disease: a single center experience. Dis Colon Rectum. 2003; 46 (5): 577-83. **Other observational study without a comparison group**

Tougeron, D., Savoye, G., Savoye-Collet, C., Koning, E., Michot, F., and Lerebours, E. Predicting factors of fistula healing and clinical remission after infliximab-based combined therapy for perianal fistulizing Crohn's disease. Dig Dis Sci. 2009; 54 (8): 1746-52. **Does not apply to key questions; other observational study without a comparison group**

Treton, X., Bouhnik, Y., Mary, J. Y., Colombel, J. F., Duclos, B., Soule, J. C., et al. Azathioprine withdrawal in patients with Crohn's disease maintained on prolonged remission: a high risk of relapse. Clin Gastroenterol Hepatol. 2009; 7 (1): 80-5. **Does not evaluate a drug of interest**

Triantafillidis, J. K., Fouskas, J., Malgarinos, G., Malli, Ch., Gikas, A., Mylonaki, M., et al. Short and long-term results of adalimumab treatment of patients with active Crohn's disease: Experience of a Greek single center for inflammatory bowel disease. Ann. Gastroenterol. 2009; 22 (3): 168-172. **Other observational study without a comparison group; does not report side effects by medication class**

Triantafillidis, J. K., Mantzaris, G., Karagiannis, J., Papavasilliou, E., Papatheodoridis, G., Fouskas, J., et al. Similar response to adalimumab in patients with active Crohn's disease either naive to biologic agents or with prior loss of response or intolerance to infliximab. Rev Med Chir Soc Med Nat Iasi. 2010; 114 (1): 85-90. **Other observational study without a comparison group**

Trinder, M. W. and Lawrance, I. C. Efficacy of adalimumab for the management of inflammatory bowel disease in the clinical setting. J Gastroenterol Hepatol. 2009; 24 (7): 1252-7. **Does not evaluate a drug of interest; does not report side effects by medication class**

Tripathi, R. C., Kipp, M. A., Tripathi, B. J., Kirschner, B. S., Borisuth, N. S., Shevell, S. K., et al. Ocular toxicity of prednisone in pediatric patients with inflammatory bowel disease. Lens Eye Toxic Res. 92; 9 (3-4): 469-82. **Other reason**

Tripathi, R. C., Kirschner, B. S., Kipp, M., Tripathi, B. J., Slotwiner, D., Borisuth, N. S., et al. Corticosteroid treatment for inflammatory bowel disease in pediatric patients increases intraocular pressure. Gastroenterology. 92; 102 (6): 1957-61. **Does not evaluate a drug of interest**

Tsujikawa, T., Andoh, A., Inatomi, O., Bamba, S., Nakahara, T., Sasaki, M., et al. Alendronate improves low bone mineral density induced by steroid therapy in Crohn's disease. Intern Med. 2009; 48 (12): 933-7. **Does not report side effects by medication class**

Turner, D., Grossman, A. B., Rosh, J., Kugathasan, S., Gilman, A. R., Baldassano, R., et al. Methotrexate following unsuccessful thiopurine therapy in pediatric Crohn's disease. Am J Gastroenterol. 2007; 102 (12): 2804-12; quiz 2803, 2813. **Other observational study without a comparison group; does not report side effects by medication class**

Tursi, A., Elisei, W., Brandimarte, G., Giorgetti, G., Penna, A., and Castrignano, V. Safety and effectiveness of infliximab for inflammatory bowel diseases in clinical practice. Eur Rev Med Pharmacol Sci. 2010; 14 (1): 47-55. **No original dataDoes not report side effects by medication class**

Tursi, A., Giorgetti, G. M., Brandimarte, G., and Elisei, W. Safety and effectiveness of long-term budesonide treatment in maintaining remission in patients with mild-to-moderate Crohn's disease. Inflamm Bowel Dis. 2007; 13 (9): 1184-6. **Other observational study without a comparison group**

Tursi, A., Giorgetti, G. M., Brandimarte, G., Elisei, W., and Aiello, F. Beclomethasone dipropionate for the treatment of mild-to-moderate Crohn's disease: an open-label, budesonide-controlled, randomized study. Med Sci Monit. 2006; 12 (6): PI29-32. **Does not evaluate a drug of interest; does not apply to key questions**

Uchino, M., Ikeuchi, H., Bando, T., Matsuoka, H., Takesue, Y., Takahashi, Y., et al. Long-term efficacy of infliximab maintenance therapy for perianal Crohn's disease. World J. Gastroenterol. 2011; 17 (9): 1174-1179. **Does not evaluate a drug of interest**

Uhlen, S., Belbouab, R., Narebski, K., Goulet, O., Schmitz, J., Cezard, J. P., et al. Efficacy of methotrexate in pediatric Crohn's disease: a French multicenter study. Inflamm Bowel Dis. 2006; 12 (11): 1053-7. **Other observational study without a comparison group; does not report side effects by medication class**

Umeno, J., Matsumoto, T., Jo, Y., Ichikawa, M., Urabe, K., and Iida, M. Psoriasis during anti-tumor necrosis factor-alpha therapy for Crohn's disease. Inflamm Bowel Dis. 2007; 13 (9): 1188-9. **Case report or case series**

Usta, Y., Ozen, H., Gurakan, F., Uslu, N., Saltik-Temizel, I. N., Demir, H., et al. Hypereosinophilia due to mesalazine treatment. J Clin Gastroenterol. 2009; 43 (4): 382. **Case report or case series**

Vadan, R., Gheorghe, L. S., Constantinescu, A., and Gheorghe, C. The prevalence of malnutrition and the evolution of nutritional status in patients with moderate to severe forms of Crohn's disease treated with Infliximab. Clin. Nutr. 2011; 30 (1): 86-91. **Does not apply to key questions**

Vadan, R., Gheorghe, L., Gheorghe, C., Badea, M., Cotruta, B., Angelescu, C., et al. The long term efficacy of Infliximab therapy in Crohn's disease: The experience of a tertiary referral center from Romania. Arch. Balk. Med. Union. 2007; 42 (1): 5-10. **Other reason**

Vahedi, H., Momtahen, S., Olfati, G., Abtahi, A., Hosseini, S., Kazzazi, A. S., et al. A case-control study on risk factors of osteoporosisin patients with Crohn's disease. Arch Iran Med. 2009; 12 (6): 570-5. **Does not evaluate a drug of interest**

Van Assche, G. Optimizing the benefit to risk ratio of medical therapy of inflammatory bowel diseases. Verh K Acad Geneeskd Belg. 2008; 70 (5-6): 339-46. **No original data**

Van Assche, G., Vermeire, S., Noman, M., Amant, C., Weyts, E., Vleminckx, A., et al. Infliximab administered with shortened infusion times in a specialized IBD infusion unit: A prospective cohort study. J. Crohn's Colitis. 2010; 4 (3): 329-333. **Does not evaluate a drug of interest; does not report side effects by medication class**

van Balkom, B. P., Schoon, E. J., Stockbrugger, R. W., Wolters, F. L., van Hogezand, R. A., van Deventer, S. J., et al. Effects of anti-tumour necrosis factor-alpha therapy on the quality of life in Crohn's disease. Aliment Pharmacol Ther. 2002; 16 (6): 1101-7. **Other observational study without a comparison group**

van Bodegraven, A. A., Sloots, C. E., Felt-Bersma, R. J., and Meuwissen, S. G. Endosonographic evidence of persistence of Crohn's disease-associated fistulas after infliximab treatment, irrespective of clinical response. Dis Colon Rectum. 2002; 45 (1): 39-45; discussion 45-6. **Case report or case series; does not report side effects by medication class**

van der Valk, M. E., van Oijen, M. G., Ammerlaan, M., Siersema, P. D., and Oldenburg, B. Crohn's disease patients treated with adalimumab benefit from co-treatment with immunomodulators. Gut. 2011. **Does not evaluate a drug of interest; does not report side effects by medication class**

van Deventer SJH, Rutgeerts P, Targan SR, Hanauer SB, Mayer L, Present D, et al. Anti-tumor necrosis factor antibody cA2 treatment induces clinical remissions in patients with active Crohn's disease [abstract]. Gut. 96; 39 (Suppl 3): A188. **Abstract only**

van Deventer SJH, van Hogezand R, Present D, Hanauer S, Targan S, D'haens G, et al. Controlled study of anti-TNF-alfa treatment for enterocutaneous fistulae complicating Crohn's disease [abstract]. Gut. 97; 41 Suppl 3 A2. **Abstract only**

van Deventer, S. J. Anti-TNF antibody treatment of Crohn's disease. Ann Rheum Dis. 99; 58 Suppl 1 I114-20. **No original data**

Van Domselaar, M., Lopez San Roman, A., Bastos Oreiro, M., and Garrido Gomez, E. Lymphoproliferative disorders in an inflammatory bowel disease unit: Trastornos linfoproliferativos en una unidad de enfermedad inflamatoria intestinal. Gastroenterol. Hepatol. 2010; 33 (1): 12-16. **Not written in English**

van Dullemen, H. M., van Deventer, S. J., Hommes, D. W., Bijl, H. A., Jansen, J., Tytgat, G. N., et al. Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). Gastroenterology. 95; 109 (1): 129-35. **Does not evaluate a drug of interest; does not report side effects by medication class**

Van Hees P, Ten Velde G, Van Hogezand R, et al. Effect of sulphasalazine in patients with Crohn's disease. A controlled double-blind trial. Hepato-Gastroenterology. 80; 27 (SUPPL.): E38.5. **Abstract only**

Van Hees P, Van Hogezand R, Ten Velde G, and et al. Effect of sulphasalazine in patients with active Crohn's disease. A controlled double-blind trial. Netherlands Journal of Medicine. 81; 24 (4): 157. **Other reason**

Van Hees, P. A., Van Lier, H. J., Van Elteren, P. H., Driessen, M., Van Hogezand, R. A., Ten Velde, G. P., et al. Effect of sulphasalazine in patients with active Crohn's disease: a controlled double-blind study. Gut. 81; 22 (5): 404-9. **Other reason**

Van Staa, T. P., Travis, S., Leufkens, H. G., and Logan, R. F. 5-aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. Gastroenterology. 2004; 126 (7): 1733-9. **Does not report side effects by medication class**

Vandeputte, L., D'Haens, G., Baert, F., and Rutgeerts, P. Methotrexate in refractory Crohn's disease. Inflamm Bowel Dis. 99; 5 (1): 11-5. **Other observational study without a comparison group; does not report side effects by medication class**

Vecchi, M., Spina, L., Pastorelli, L., Cavallaro, F., and Ciscato, C. The relevance of mucosal healing. Dig. Liver Dis. Suppl. 2008; 2 (1): 9-10. **No original data**

Veres, G., Szabo, D., Varkonyi, A., Tari, B., Polgar, M., B. Kovacs, J., et al. Analysis of infl iximab treated pediatric patients with Crohn disease in Hungary: Crohn-beteg gyermekek infliximabkezelesenek kezdeti tapasztalatai hazankban. Orvosi Hetil. 2010; 151 (5): 179-183. **Not written in English**

Vernier-Massouille, G., Cosnes, J., Lemann, M., Marteau, P., Reinisch, W., Laharie, D., et al. Nodular regenerative hyperplasia in patients with inflammatory bowel disease treated with azathioprine. Gut. 2007; 56 (10): 1404-9. **Other observational study without a comparison group; does not report side effects by medication class**

Vestergaard, P., Krogh, K., Rejnmark, L., Laurberg, S., and Mosekilde, L. Fracture risk is increased in Crohn's disease, but not in ulcerative colitis. Gut. 2000; 46 (2): 176-81. **Does not apply to key questions**

Viazis, N., Vlachogiannakos, J., Georgiadis, D., Keyoglou, A., Vasianopoulou, P., Markoutsaki, Th., et al. Azathioprine use in patients with inflammatory bowel disease. Adherence to treatment and adverse events. A single center experience. Ann. Gastroenterol. 2009; 22 (3): 173-177. **Other observational study without a comparison group; does not report side effects by medication class**

Vihinen, M. K., Kolho, K. L., Janne, O. A., Andersson, S., and Raivio, T. Circulating adiponectin as a marker for glucocorticoid-related side effects in children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2009; 48 (4): 504-6. **Does not apply to key questions; does not report side effects by medication class**

Vihinen, M. K., Raivio, T., Verkasalo, M., Janne, O. A., and Kolho, K. L. Circulating glucocorticoid bioactivity during peroral glucocorticoid treatment in children and adolescents with inflammatory bowel disease. J Clin Gastroenterol. 2008; 42 (9): 1017-24. **Does not evaluate a drug of interest; does not apply to key questions**

Vinklerova, I., Prochazka, M., Prochazka, V., and Urbanek, K. Incidence, Severity, and Etiology of Drug-Induced Acute Pancreatitis. Dig Dis Sci. 2010. **Does not apply to key questions**

Viola, F., Civitelli, F., Di Nardo, G., Barbato, M. B., Borrelli, O., Oliva, S., et al. Efficacy of adalimumab in moderate-to-severe pediatric Crohn's disease. Am J Gastroenterol. 2009; 104 (10): 2566-71. **Other observational study without a comparison group; does not report side effects by medication class**

von Ahsen, N., Armstrong, V. W., Behrens, C., von Tirpitz, C., Stallmach, A., Herfarth, H., et al. Association of inosine triphosphatase 94C>A and thiopurine S-methyltransferase deficiency with adverse events and study drop-outs under azathioprine therapy in a prospective Crohn disease study. Clin Chem. 2005; 51 (12): 2282-8. **Does not evaluate a drug of interest**

von Scheven, E., Gordon, C. M., Wypij, D., Wertz, M., Gallagher, K. T., and Bachrach, L. Variable deficits of bone mineral despite chronic glucocorticoid therapy in pediatric patients with inflammatory diseases: a Glaser Pediatric Research Network study. J Pediatr Endocrinol Metab. 2006; 19 (6): 821-30. **Other observational study without a comparison group**

von Tirpitz, C., Epp, S., Klaus, J., Mason, R., Hawa, G., Brinskelle-Schmal, N., et al. Effect of systemic glucocorticoid therapy on bone metabolism and the osteoprotegerin system in patients with active Crohn's disease. Eur J Gastroenterol Hepatol. 2003; 15 (11): 1165-70. **Other observational study without a comparison group; does not report side effects by medication class**

Vos, A. C., Bakkal, N., Minnee, R. C., Casparie, M. K., de Jong, D. J., Dijkstra, G., et al. Risk of malignant lymphoma in patients with inflammatory bowel diseases: A Dutch nationwide study. Inflamm Bowel Dis. 2010. **Other observational study without a comparison group; does not report side effects by medication class**

Wahed, M., Louis-Auguste, J. R., Baxter, L. M., Limdi, J. K., McCartney, S. A., Lindsay, J. O., et al. Efficacy of methotrexate in Crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine /mercaptopurine. Aliment Pharmacol Ther. 2009; 30 (6): 614-20. **Other observational study without a comparison group; does not report side effects by medication class**

Wallensten, S. and Persson, S. Azathioprine therapy for Crohn's disease. Acta Chir Scand. 72; 138 (5): 521-6. **Case report or case series**

Warman, J. I., Korelitz, B. I., Fleisher, M. R., and Janardhanam, R. Cumulative experience with short- and long-term toxicity to 6-mercaptopurine in the treatment of Crohn's disease and ulcerative colitis. J Clin Gastroenterol. 2003; 37 (3): 220-5. **Other observational study without a comparison group**

Waugh, A. W., Garg, S., Matic, K., Gramlich, L., Wong, C., Sadowski, D. C., et al. Maintenance of clinical benefit in Crohn's disease patients after discontinuation of infliximab: long-term follow-up of a single centre cohort. Aliment Pharmacol Ther. 2010; 32 (9): 1129-34. **Does not report side effects by medication class**

Weersma, R. K., Batstra, M. R., Kleibeuker, J. H., and van Dullemen, H. M. Are pancreatic autoantibodies associated with azathioprine-induced pancreatitis in Crohn's disease?. JOP. 2008; 9 (3): 283-9. **Does not apply to key questions**

Wenckert, A., Kristensen, M., Eklund, A. E., Barany, F., Jarnum, S., Worning, H., et al. The long-term prophylactic effect of salazosulphapyridine (Salazopyrin) in primarily resected patients with Crohn's disease. A controlled double-blind trial. Scand J Gastroenterol. 78; 13 (2): 161-7. **Other reason**

Wenzl, H. H., Reinisch, W., Jahnel, J., Stockenhuber, F., Tilg, H., Kirchgatterer, A., et al. Austrian infliximab experience in Crohn's disease: a nationwide cooperative study with long-term follow-up. Eur J Gastroenterol Hepatol. 2004; 16 (8): 767-73. **Does not evaluate a drug of interest; other observational study without a comparison group**

Werlin, S. L. and Grand, R. J. Bloody diarrhea--a new complication of sulfasalazine. J Pediatr. 78; 92 (3): 450-1. **Case report or case series**

West, R. L., Zelinkova, Z., Wolbink, G. J., Kuipers, E. J., Stokkers, P. C., and van der Woude, C. J. Immunogenicity negatively influences the outcome of adalimumab treatment in Crohn's disease. Aliment Pharmacol Ther. 2008; 28 (9): 1122-6. **Other observational study without a comparison group; does not report side effects by medication class**

Wewer, V., Riis, L., Vind, I., Husby, S., Munkholm, P., and Paerregaard, A. Infliximab dependency in a national cohort of children with Crohn's disease. J Pediatr Gastroenterol Nutr. 2006; 42 (1): 40-5. **Does not apply to key questions; does not report side effects by medication class**

Wiese, D., Lashner, B., and Seidner, D. Measurement of nutrition status in Crohn's disease patients receiving infliximab therapy. Nutr Clin Pract. 2008; 23 (5): 551-6. **Does not evaluate a drug of interest; does not report side effects by medication class**

Williams, C. N. Is the incidence of cancer increased in patients with Crohn's disease or after its complications or treatment?. Can J Gastroenterol. 97; 11 (5): 397-8. **No original data**

Williams, C. N., Haber, G., and Aquino, J. A. Double-blind, placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using 99mTc-labeled 5-ASA suppositories. Dig Dis Sci. 87; 32 (12 Suppl): 71S-75S. **RCT patient population not exclusively Crohn's or observational study not exclusively IBD**

Willot, S., Noble, A., and Deslandres, C. Methotrexate in the treatment of inflammatory bowel disease: An 8-year retrospective study in a Canadian pediatric IBD center. Inflamm Bowel Dis. 2011. O**ther observational study without a comparison group**

Willoughby, J. M., Kumar, P., Beckett, J., and Dawson, A. M. A double-blind trial of azathioprine in Crohn's disease. Gut. 71; 12 (10): 864. **Other observational study without a comparison group; other reason**

Winship, D. H., Summers, R. W., Singleton, J. W., Best, W. R., Becktel, J. M., Lenk, L. F., et al. National Cooperative Crohn's Disease Study: study design and conduct of the study. Gastroenterology. 79; 77 (4 Pt 2): 829-42. **Other reason**

Winter, H. Initial maintenance therapy (relapse prevention) and therapy of steroid resistance and dependence. Inflamm Bowel Dis. 98; 4 (3): 209-13. **No original data**

Winter, J. W., Gaffney, D., Shapiro, D., Spooner, R. J., Marinaki, A. M., Sanderson, J. D., et al. Assessment of thiopurine methyltransferase enzyme activity is superior to genotype in predicting myelosuppression following azathioprine therapy in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2007; 25 (9): 1069-77. **Does not apply to key questions; other observational study without a comparison group**

Witthoft, T. and Ludwig, D. Effectiveness and tolerability of repeated treatment with infliximab in patients with Crohn's disease: a retrospective data analysis in Germany. Int J Colorectal Dis. 2005; 20 (1): 18-23. **Does not report side effects by medication class**

Wong, D. R., De Boer, N. K. H., Jharap, B., De Graaf, P., Van Bodegraven, A. A., Mulder, C. J. J., et al. [Influence of mesalazine on thiopurine metabolism in inflammatory bowel disease patients. Prospective multicenter pharmacokinetic study]. Pharm. Weekbl. 2008; 143 (12): 62-65. **Not written in English**

Wong, J. M. and Wei, S. C. Efficacy of Pentasa tablets for the treatment of inflammatory bowel disease. J Formos Med Assoc. 2003; 102 (9): 613-9. **Does not evaluate a drug of interest**

Wusk, B., Kullak-Ublick, G. A., Rammert, C., von Eckardstein, A., Fried, M., and Rentsch, K. M. Therapeutic drug monitoring of thiopurine drugs in patients with inflammatory bowel disease or autoimmune hepatitis. Eur J Gastroenterol Hepatol. 2004; 16 (12): 1407-13. **Does not apply to key questions; does not report side effects by medication class**

Wyneski, M. J., Green, A., Kay, M., Wyllie, R., and Mahajan, L. Safety and efficacy of adalimumab in pediatric patients with Crohn disease. J Pediatr Gastroenterol Nutr. 2008; 47 (1): 19-25. **Other observational study without a comparison group; does not report side effects by medication class**

Yamagata, S., Baba, S., and Hosoda, S. Salazopyrin in the management of Crohn's disease. GASTROENTEROL. JPN. 85; 20 (1): 71-81. **Does not evaluate a drug of interest; other observational study without a comparison group**

Yang, Y. X. and Lichtenstein, G. R. Methotrexate for the maintenance of remission in Crohn's disease. Gastroenterology. 2001; 120 (6): 1553-5. **No original data**

Yeckes, A. R. and Hoffenberg, E. J. Rapid infliximab infusions in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2009; 49 (1): 151-4. **Other observational study without a comparison group; does not report side effects by medication class**

Yu, A. P., Johnson, S., Wang, S. T., Atanasov, P., Tang, J., Wu, E., et al. Cost utility of adalimumab versus infliximab maintenance therapies in the United States for moderately to severely active Crohn's disease. Pharmacoeconomics. 2009; 27 (7): 609-21. **Does not apply to key questions**

Zabana, Y., Domenech, E., Manosa, M., Garcia-Planella, E., Bernal, I., Cabre, E., et al. Infliximab safety profile and long-term applicability in inflammatory bowel disease: 9-year experience in clinical practice. Aliment Pharmacol Ther. 2010; 31 (5): 553-60. **Does not evaluate a drug of interest; does not report side effects by medication class**

Zali, M., Bahari, A., Firouzi, F., Daryani, N. E., Aghazadeh, R., Emam, M. M., et al. Bone mineral density in Iranian patients with inflammatory bowel disease. Int J Colorectal Dis. 2006; 21 (8): 758-66. **Does not apply to key questions**

Zboril, V., Prokopova, L., and Abbe, M. L. [Anti-TNF Alfa in Combination with Immunosuppresive Agents in the Management of Aggressive Perforating Type of Crohn's Disease]. Ceska Slov. Gastroenterol. Hepatol. 2003; 57 (4): 140-145. **Not written in English**

Zheng, J. J., Chu, X. Q., Shi, X. H., Zhou, C. L., and Seng, B. W. Efficacy and safety of azathioprine maintenance therapy in a group of Crohn's disease patients in China. J Dig Dis. 2008; 9 (2): 84-8. **Does not evaluate a drug of interest; does not report side effects by medication class**

Zheng, J. J., Zhi, P., Wang, Y. M., Zhu, F., Gu, W., Xing, Y. C., et al. Short-term study of infliximab treatment for Crohn's disease in China. J. Dig. Dis. 2011; 12 (2): 105-109. **Does not evaluate a drug of interest**

Adalimumab: Hepatosplenic T-cell lymphoma. WHO Drug Inf. 2008; 22 (3): 198. **No original data**

Azathioprine in Crohn's disease. Drug Ther Bull. 73; 11 (18): 71-2. **No original data**

Betamethasone 17-valerate and prednisolone 21-phosphate retention enemata in proctocolitis. A multicentre trial. Br Med J. 71; 3 (5766): 84-6. **Does not evaluate a drug of interest**

Certolizumab (Cimzia) for Crohn's disease. Med Lett Drugs Ther. 2008; 50 (1297): 81-2. **No original data**

Coated oral 5-aminosalicylic acid versus placebo in maintaining remission of inactive Crohn's disease. International Mesalazine Study Group. Aliment Pharmacol Ther. 90; 4 (1): 55-64. **Other reason**

Evaluating the safety and efficacy of biologic agents in Crohn's disease. Gastroenterol. Hepatol. 2007; 3 (8 SUPPL. 23): 5-12. **No original data**

Heart failure on infliximab. Prescrire Int. 2002; 11 (59): 86-7. **No original data**

Infliximab (Remicade) for Crohn's disease. Med Lett Drugs Ther. 99; 41 (1047): 19-20. **No original data**

Infliximab provides short-term relief in Crohn's disease. Drugs Ther. Perspect. 99; 13 (8): 1-5. **No original data**

Quality of life and chronic inflammatory bowel diseases: Chronisch entzundliche darmerkrankungen: Im visier die lebensqualitat. Coloproctology. 2000; 22 (6): 246-247. **Not written in English**

Salazopyrin in the management of Crohn's disease. The Japanese Research Committee for Crohn's disease. Gastroenterol Jpn. 85; 20 (1): 71-81. **Does not evaluate a drug of interest; other observational study without a comparison group**

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Natalizumab vs. placebo – wks 2-4	Disease activity measures	3 (1444)[32-34]	Medium	Consistent	Direct	Precise	Favors natalizumab Pooled RR, 1.5; 95% CI 1.1 to 2.0; placebo rate, 8% to 16% SOE: Moderate
Natalizumab vs. placebo–wk 12	Disease activity measures	3 (1444)[32-34]	Medium	Consistent	Direct	Imprecise	Favors natalizumab RD range, 9% to 13%; placebo rate, 0% to 31% SOE: Low
Natalizumab vs. placebo–wk 12	Patient-reported outcomes	2 (539)[32 34]	Medium	Consistent	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 12 pts; placebo change in IBDQ, 15 pts SOE: Moderate
Natalizumab + infliximab vs. infliximab–wks 2 and 10	Disease activity measures	1 (79)[35]	Low	Unknown (single trial)	Indirect Combination no longer used in clinical practice	Imprecise	Favors neither RD across time points, 7% to 8%; infliximab rate, 7% to 30% SOE: Low
Natalizumab + infliximab vs. infliximab–wk 10	Patient-reported outcomes	1 (79)[35]	Low	Unknown (single trial)	Indirect Combination no longer used in clinical practice	Imprecise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 2 pts; infliximab change in IBDQ, 17 pts SOE: Low
TNF vs. placebo–wk 2	Disease activity measures	7 (2208)[37-43]	Medium	Consistent	Direct	Precise	Favors TNF Pooled RR, 1.8; 95% CI, 1.4 to 2.4; placebo rate, 4 to 16% SOE: Moderate

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Adalimumab vs. placebo (160 mg x 1) –wk 2	Disease activity measures	2 (475)[37 38]	Low	Consistent	Direct	Precise	Favors adalimumab RD, 10% to 15%; placebo rate, 6% to 14% SOE: High
Adalimumab vs. placebo (≦ 80 mg x 1) –wk 2	Disease activity measures	2 (223)[37]	Low	Unknown (single trial)	Direct	Imprecise	Favors neither RD, 0% to 6%; placebo rate, 14% SOE: Moderate
Adalimumab vs. placebo–wk 4	Fistula response	1 (32)[37]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD, -17% to 58%; placebo rate, 17% SOE: Low
Adalimumab vs. placebo–wk 4	Patient-reported outcomes	2 (624)[37 38]	Low	Consistent	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 2 to 15 pts; placebo change in IBDQ, 15 pts SOE: High
Certolizumab pegol vs. placebo–wk 2, 12-16	Disease activity measures	4 (1478)[39-42]	Medium	Inconsistent	Indirect IV formulation not presently approved[41]	Imprecise	Favors neither RD, -19% to 31%; placebo rate, 8% to 32% SOE: Low
Certolizumab pegol vs. placebo–wk 26	Disease activity measures	1 (331)[39]	High	Unknown (single trial)	Direct	Precise	Favors certolizumab pegol RD, 11%; placebo rate, 18% SOE: Low
Certolizumab pegol vs. placebo–wk 26	Fistula response	1 (107)[39]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD, -1%; placebo rate, 31% SOE: Low

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect
			Risk of bias	Consistency	Directness	Precision	Strength of evidence
Certolizumab pegol vs. placebo–wks 12, 26	Patient-reported outcomes	2 (954)[39 40]	High	Consistent	Indirect Single dose for induction not presently used in practice[40]	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline across time points, 5 to 11 pts; placebo change in IBDQ, 18 to 21 pts SOE: Low
Infliximab vs. placebo–wk 2	Disease activity measures	1 (106)[43]	Medium	Unknown (single trial)	Direct	Precise	Favors infliximab RD, 16% to 34%; placebo rate, 4% SOE: Moderate
Infliximab vs. placebo–wk 12	Disease activity measures	1 (106)[43]	High	Unknown (single trial)	Indirect Single dose for induction not presently used in practice	Imprecise	Favors infliximab RD, 10% to 22%; placebo rate, 8% SOE: Low
Infliximab vs. placebo–wk 4	Mucosal healing	1 (30)[49]	High	Unknown (single trial)	Direct	Precise	Favors infliximab Absolute between-group difference in the change from baseline in CDEIS, 7.7; placebo difference, 0.9 SOE: Low
Infliximab vs. placebo–wk 6	Fistula response	1 (94)[44]	Low	Unknown (single trial)	Direct	Precise	Favors infliximab RD, 25% to 42%; placebo rate, 13% SOE: High

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Infliximab vs. placebo–wk 4	Patient-reported outcomes	1 (83)[43]	Medium	Unknown (single trial)	Direct	Precise	Favors infliximab Absolute between-group difference in change in mean IBDQ from baseline, 31 pts; placebo change in IBDQ, 5 pts SOE: Moderate
Infliximab vs. azathioprine–wks 10, 26	Disease activity measures	1 (339)[45]	Medium	Unknown (single trial)	Direct	Precise	Favors infliximab RD across time points, 13% to 14%; azathioprine rate, 24% to 30% SOE: Moderate
Infliximab vs. azathioprine–wk 26	Mucosal healing	1 (202)[45]	High	Unknown (single trial)	Direct	Precise	Favors infliximab RD in percentage of patients who achieved absence of mucosal ulcers, 13%; azathioprine rate, 17% SOE: Low
Infliximab vs. azathioprine–wk 26	Patient-reported outcomes	1 (339)[45]	Medium	Unknown (single trial)	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 9 pts; azathioprine change in IBDQ, 31 pts SOE: Moderate
Infliximab + azathioprine vs. infliximab–wks 10, 26	Disease activity measures	1 (338)[45]	Medium	Unknown (single trial)	Direct	Precise	Favors infliximab + azathioprine RD across time points, 10% to 13%; infliximab alone rate, 37% to 44% SOE: Moderate

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect
			Risk of bias	Consistency	Directness	Precision	Strength of evidence
Infliximab + azathioprine vs. infliximab–wk 26	Mucosal healing	1 (200)[45]	High	Unknown (single trial)	Direct	Precise	Favors infliximab + azathioprine RD in percentage of patients who achieved absence of mucosal ulcers, 14%; infliximab rate, 30% SOE: Low
Infliximab + azathioprine vs. infliximab–wk 26	Patient-reported outcomes	1 (338)[45]	Medium	Unknown (single trial)	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 5 pts; infliximab change in IBDQ, 40 pts SOE: Moderate
Infliximab + azathioprine vs. azathioprine–wks 10-12, 24-26	Disease activity measures	2 (393)[45 46]	Medium	Consistent	Direct	Precise	Favors infliximab + azathioprine RD across time points, 12% to 30%; azathioprine rate, 24% to 44% SOE: Moderate
Infliximab + azathioprine vs. azathioprine–wk 26	Mucosal healing	1 (216)[45]	High	Unknown (single trial)	Direct	Precise	Favors infliximab + azathioprine RD in percentage of patients who achieved absence of mucosal ulcers, 27%; azathioprine rate, 17% SOE: Low
Infliximab + azathioprine vs. azathioprine–wk 26	Patient-reported outcomes	1 (508)[45]	Medium	Unknown (single trial)	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 14 pts; azathioprine change in IBDQ, 31 pts SOE: Moderate

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Infliximab + azathioprine vs. steroids–wk 104	Disease activity measures	1 (129)[48]	High	Unknown (single trial)	Indirect Single dose for induction not presently used in practice	Imprecise	Favors neither RD, 6%; corticosteroid rate, 49% SOE: Low
Infliximab+ azathioprine vs. steroids–wk 104	Mucosal healing	1 (49)[48]	High	Unknown (single trial)	Indirect Single dose for induction not presently used in practice	Precise	Favors infliximab + azathioprine RD in percentage of patients with no ulcers, 43%; steroid rate, 30% SOE: Low
Infliximab + azathioprine vs. steroids–wk 10	Patient-reported outcomes	1 (129)[48]	High	Unknown (single trial)	Indirect Single dose for induction not presently used in practice	Precise	Favors infliximab + azathioprine Absolute between-group difference in change in mean IBDQ from baseline, 22 pts; steroids change in IBDQ, 37 pts SOE: Low
Infliximab + methotrexate vs. infliximab–wks 2, 12, 48	Disease activity measures	1 (19)[47]	High	Unknown (single trial)	Direct	Imprecise	Favors infliximab + methotrexate RD across time points, 17% to 39%; infliximab rate, 25% to 50% SOE: Low
Infliximab + methotrexate vs. infliximab–wk 48	Reduction of steroids	1 (13)[47]	High	Unknown (single trial)	Direct	Imprecise	Favors infliximab + methotrexate Reduction in prednisolone dose from baseline, 17 mg vs. 6 mg SOE: Low

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Infliximab + methotrexate vs. infliximab–wk 4 and 8	Patient-reported outcomes	1 (19)[47]	High	Unknown (single trial)	Direct	Imprecise	Favors infliximab + methotrexate Absolute between-group difference in change in mean IBDQ from baseline, 22 pts; infliximab change in IBDQ, 28 pts SOE: Low
Thiopurine vs. placebo–wks 3-4, 17-38	Disease activity measures	2 (158)[56 57]	High	Inconsistent	Indirect	Imprecise	Favors neither RD across time points, -5% to 13%; placebo rate, 5% to 48% SOE: Low
Thiopurine vs. placebo–wk 104	Disease activity measures	1 (33)[60]	High	Unknown (single trial)	Indirect	Imprecise	Favors 6-MP RD, 33%; placebo rate, 14% SOE: Low
Thiopurines vs. placebo–wk 16	Reduction of steroids	1 (26)[62]	Medium	Unknown (single trial)	Direct	Imprecise	Favors neither Reduction in steroid dose from baseline, 7 mg vs. 12 mg SOE: Low
Thiopurine vs. placebo–wk 17	Fistula response	1 (17)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD in perianal fistula closure, 2%; placebo rate, 11% SOE: Low
Thiopurine vs. placebo– wk 104	Fistula response	1 (46)[60]	High	Unknown (single trial)	Direct	Imprecise	Favors 6-MP RD in perianal fistula closure, 25%; placebo rate, 6% SOE: Low
Thiopurines vs. placebo–wk 8 and 16	Patient-reported outcomes	3 (116)[57 61 62]	Medium	Inconsistent	Direct	Imprecise	Favors neither Multiple measures; see text SOE: Low

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Thiopurines vs. methotrexate (oral)–wks 4, 12, 30-38	Disease activity measures	2 (89)[52 57]	Medium	Inconsistent	Indirect	Imprecise	Favors neither RD across time points, -1% to 21%; placebo rate, 9% to 80% SOE: Low
Azathioprine vs. prednisone–wks 2, 13, 17	Disease activity measures	1 (144)[56]	High	Unknown (single trial)	Direct	Imprecise	Favors prednisone RD across time points, -24 to -12%; prednisone rate, 27-77% SOE: Low
Azathioprine vs. prednisone–wk 17	Fistula response	1 (18)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors prednisone RD, -17%; prednisone rate, 30% SOE: Low
Azathioprine vs. sulfasalazine–wk 2	Disease activity measures	1 (133)[56]	High	Unknown (single trial)	Direct	Precise	Favors sulfasalazine RD, -14%; sulfasalazine rate, 20% SOE: Low
Azathioprine vs. sulfasalazine–wks 13, 17	Disease activity measures	1 (133)[56]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD across time points, 0% to 6%; sulfasalazine rate, 32% to 53% SOE: Low
Azathioprine vs. sulfasalazine–wk 17	Fistula response	1 (17)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD, -9%; sulfasalazine rate, 22% SOE: Low
6-MP vs. ASA–wks 12, 30	Disease activity measures	1 (23)[52]	High	Unknown (single trial)	Direct	Precise	Favors 6-MP RD across time points, 67% to 80%; ASA rate, 14% SOE: Low

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Azathioprine (IV and oral) vs. thiopurine (oral)–wk 8, 16	Disease activity measures	1 (96)[59]	Medium	Unknown (single trial)	Indirect IV AZA is not presently used as a treatment	Imprecise	Favors neither RD across time points, 1% to 4%; oral azathioprine alone rate, 24% to 27% SOE: Low
Azathioprine + steroid vs. steroid–wks 12, 28	Disease activity measures	3 (186)[51 53 54]	Medium	Inconsistent	Direct	Imprecise	Favors azathioprine + steroid RD across time points, 10%; steroid rate, 28% to 63% SOE: Low
Azathioprine + prednisone vs. methotrexate (IV followed by oral) + prednisone–wk 13, 26	Disease activity measures	1 (54)[58]	Medium	Unknown (single trial)	Direct	Imprecise	Favors neither RD across time points, -11% to 7%; methotrexate + prednisone rate, 44% to 56% SOE: Low
Azathioprine + prednisone vs. methotrexate (IV followed by oral) + prednisone–wk 26	Fistula response	1 (10)[58]	High	Unknown (single trial)	Direct	Imprecise	Favors methotrexate + prednisone RD in fistula closure, -42%; methotrexate + prednisone rate, 67% SOE: Low
Methotrexate (oral) vs. placebo–wks 4, 12, 38	Disease activity measures	1 (52)[57]	Medium	Unknown (single trial)	Direct	Imprecise	Favors neither RD across time points, -8% to 3%; placebo rate, 5% to 46% SOE: Low
Methotrexate (oral) vs. ASA–wks 12, 30	Disease activity measures	1 (22)[52]	Medium	Unknown (single trial)	Direct	Precise	Favors methotrexate RD, 46% to 66%; ASA rate, 14% SOE: Moderate

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Methotrexate (IM) + prednisone vs. placebo + prednisone–wk 16	Disease activity measures	1 (141)[63]	Medium	Unknown (single trial)	Direct	Precise	Favors methotrexate + prednisone RD, 20%; prednisone only rate, 19% SOE: Moderate
Methotrexate (IM) + prednisone vs. placebo + prednisone–wk 16	Patient-reported outcomes	1 (141)[63]	Medium	Unknown (single trial)	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 15; prednisone only change in IBDQ, -8 SOE: Moderate
Budesonide (≥ 9 mg) vs. placebo–wk 2	Disease activity measures	2 (391)[65 66]	Medium	Consistent	Direct	Precise	Favors budesonide RD, 17% to 27%; placebo rate, 11% to 13% SOE: Moderate
Budesonide (< 9 mg) vs. placebo–wk 2	Disease activity measures	1 (128)[66]	Medium	Unknown (single trial)	Direct	Imprecise	Favors neither RD, -1%; placebo rate, 11% SOE: Low
Budesonide vs. placebo–wk 8	Disease activity measures	2 (458)[65 66]	Medium	Consistent	Direct	Precise	Favors budesonide RD across time points, 13% to 31%; placebo rate, 20% to 33% SOE: Moderate
Budesonide vs. placebo–wk 8	Patient-reported outcomes	2 (458)[65 66]	High	Consistent	Direct	Imprecise	Favors neither Absolute between-group difference in change in IBDQ from baseline, 7 to 30; placebo change in IBDQ, 10 to 29 SOE: Low
Prednisone vs. placebo – wk 2	Disease activity measures	1 (162)[56]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD, 5%; placebo rate, 15% SOE: Low

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
6-methylprednisolone vs. placebo–wk 3	Disease activity measures	1 (105)[64]	High	Unknown (single study)	Direct	Precise	Favors 6-methylprednisolone RD, 14%; placebo rate, 79% SOE: Low
Steroid (6-methyl-prednisolone, prednisone) vs. placebo–wks 16-17, 104	Disease activity measures	2 (267)[56 64]	High	Consistent	Direct	Precise	Favors steroids RD across time points, 25% to 47%; placebo rate, 8% to 42% SOE: Low
Prednisone vs. placebo–wk 17	Fistula response	1 (19)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors prednisone RD in fistula closure, 19%; placebo rate, 11% SOE: Low
Budesonide vs. other steroid (prednisolone, prednisone)–wks 2, 8	Disease activity measures	3 (557)[67-69]	Medium	Consistent	Direct	Precise	Favors neither Pooled RR at wk 8, 0.9; CI, 0.8 to 1.0; steroid rate, 55% to 65% SOE: Moderate
Budesonide vs. prednisone–wk 8	Patient-reported outcomes	1 (201)[67]	Low	Unknown (single trial)	Direct	Imprecise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, -8; prednisone change in IBDQ, 34 SOE: Moderate
Steroid vs. ASA–wks 2-3, 12-17, 54-104	Disease activity measures	7 (919)[56 64 70-74]	Medium	Inconsistent	Direct	Imprecise	Favors steroids RD across time points, -18% to 30%; ASA rate, 6% to 87% SOE: Low

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Prednisone vs. sulfasalazine	Fistula healing	2 (19)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors neither RD in fistula closure, 9%; sulfasalazine rate, 22% SOE: Low
Prednisone vs. ASA – wk 2	Patient-reported outcomes	1 (50)[73]	Low	Unknown (single trial)	Direct	Precise	Favors prednisone Absolute between-group difference in Quality of Life Index from baseline, 16%; ASA improvement in Quality of Life Index, 7% SOE: High
Prednisone vs. ASA – wk 12	Patient-reported outcomes	1 (50)[73]	Low	Unknown (single trial)	Direct	Imprecise	Favors neither Absolute between-group difference in Quality of Life Index from baseline, 4%; ASA improvement in Quality of Life Index, 33% SOE: Moderate
Prednisolone + sulfasalazine vs. placebo–wks 3,16, 104	Disease activity measures	1 (114)[64]	High	Unknown (single trial)	Direct	Precise	Favors prednisolone + sulfasalazine RD across time points, 19% to 47%; placebo rate, 8% to 79% SOE: Low
Steroid + sulfasalazine vs. steroid–wks 3, 8-16, 104	Disease activity measures	2 (192)[64 75]	Medium	Consistent	Direct	Imprecise	Favors neither RD across time points, 2% to 19%; steroid rate, 33% to 93% SOE: Low

Appendix D. Evidence Tables

(reference list located in full report)

Evidence Table 1. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for induction of remission (KQ1)

Comparison	Outcome	Number of trials (participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Steroid + sulfasalazine vs. sulfasalazine–wks 3, 16, 104	Disease activity measures	1 (110)[64]	High	Consistent	Direct	Precise	Favors steroids + sulfasalazine RD across time points, 11% to 26%; sulfasalazine rate, 22% to 87% SOE: Low
ASA vs. placebo-wks 2-3	Disease activity measures	5 (330)[56 64 78]	Medium	Inconsistent	Direct	Imprecise	Favors neither RD, -8 to 9%; placebo rate, 8 to 79% SOE: Low
ASA (mesalamine ≥ 3.2 g daily or sulfasalazine) vs. placebo-wks 16-17	Disease activity measures	5 (456)[56 64 77 79]	Medium	Consistent	Direct	Imprecise	Favors ASA RD, 12 to 25%; placebo rate, 18 to 36% SOE: Low
ASA (mesalamine < 3.2 g daily) vs. placebo-wk 16	Disease activity measures	5 (302)[78 79]	Medium	Consistent	Direct	Imprecise	Favors neither RD, 2 to 6%; placebo rate, 18 to 25% SOE: Low
Sulfasalazine vs. placebo – wk 104	Disease activity measures	1 (112)[64]	High	Unknown (single trial)	Direct	Precise	Favors sulfasalazine RD, 14%; placebo rate, 8% SOE: Low
Sulfasalazine vs. placebo-wk 17	Fistula response	1 (18)[55]	High	Unknown (single trial)	Direct	Imprecise	Favors sulfasalazine RD in fistula closure, 11%; placebo rate, 11% SOE: Low

6-MP = 6-mercaptopurine; ASA = aminosalicylates; CDEIS = Crohn's Disease Endoscopic Index of Severity; CI = 95% confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IM = intramuscular; IV = intravenous; mg = milligrams; pts = points; RD = absolute risk difference; RR = relative risk; SOE = strength of evidence; steroid = corticosteroids; TNF = tumor necrosis factor-alpha inhibitor; TPMT = thiopurine methyltransferase; vs. = versus; wk = week

Evidence Table 2. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Randomized controlled trials evaluating biologics					
Colombel, 2010[45]	RCT, parallel arms	Start year: 2005 Duration of assigned treatment: 50 weeks	US, North America, Europe, Asia Multicenter	No	Adults, CD only, no previous surgery (abdominal surgery in past 6 months), CDAI (219-451), previous use of corticosteroids, mesalamine or budesonide, no use of TNF-alpha inhibitors, methotrexate, 6-mercaptopurine, azathioprine, moderate-severe disease, no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, no history of TB, no cancer, other criteria
D'Haens, 2008[48]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 2 years	Europe Multicenter	Yes Yes	Pediatrics, adults, CD only, CDAI (>200), no use of corticosteroids, antimetabolites, biological agents, active disease, not pregnant, no obstructive symptoms with strictures, no history of TB, no cancer, other criteria
Gordon, 2001[34]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 weeks	Location: NR Number of centers NR	No	Adults, CD only, CDAI (150-451), no use of methotrexate, cyclosporin, tacrolimus, not pregnant, not nursing, using adequate contraception, no ostomy, no cancer, other criteria
Hanauer, 2006[37]	RCT, parallel arms	Start year: 2002 Duration of assigned treatment: 4 weeks	US, North America, Europe Multicenter	No	Adults, CD only, no previous surgery (extensive bowel resection (>100 cm)), CDAI (220-450), no use of TNF-alpha inhibitors, moderate-severe disease, not pregnant, not nursing, using adequate contraception, no short bowel syndrome, no ostomy, no obstructive symptoms with strictures, no history of TB, no cancer, other criteria
Lemann, 2006[46]	RCT, parallel arms	Start year: 2000 Duration of assigned treatment: 24 weeks	Europe Multicenter	No	Adults, CD only, previous use of corticosteroids, prednisone, no use of 5-aminosalicylate acids, TNF-alpha inhibitors, topical steroids, budesonide, active disease, not pregnant, not nursing, using adequate contraception, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Present, 1999[44]	RCT, parallel arms	Start year: 1996 Duration of assigned treatment: 6 weeks	US, Europe Multicenter	Yes Yes	Adults, CD only, not pregnant, using adequate contraception, no abscess, other criteria

Evidence Table 2. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Sandborn, 2005[33]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 8 weeks	US, North America, Europe, Australia, Africa Multicenter	Yes Yes	Adults, CD only, CDAI (220-450), no use of TNF-alpha inhibitors in past 3 months, no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, other criteria
Sandborn, 2007[39]	RCT, parallel arms	Start year: 2003 Duration of assigned treatment: 26 weeks	Worldwide Multicenter	No	Adults, CD only, CDAI (220-450), active disease, no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, no cancer, other criteria
Sandborn, 2007[38]	RCT, parallel arms	Start year: 2004 Duration of assigned treatment: 4 weeks	US, North America, Europe Multicenter	No	Adults, CD only, no previous surgery (bowel resection in past 6 months), CDAI (220-450), no use of adalimumab, active disease, not pregnant, not nursing, no short bowel syndrome, no ostomy, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, other criteria
Sandborn, 2011[42]	RCT, parallel arms	Start year: 2008 Duration of assigned treatment: 6 weeks	US, North America, Europe, Asia, 20 countries all over Multicenter	NR	Adults, CD only, CDAI (220-450), previous use of TNF-alpha inhibitors, intravenous corticosteroids, other biological agent, no short bowel syndrome, no ostomy, no abscess, no history of TB, no demyelinating disease, no cancer, other criteria
Sands, 2007[35]	RCT, parallel arms	Start year: 2002 Duration of assigned treatment: NR	US Multicenter	No	Adults, CD only, previous use of TNF-alpha inhibitors, no abscess, no obstructive symptoms with strictures, other criteria
Schreiber, 2005[40]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 8 weeks	North America, Europe, Africa, Russia Multicenter	No	Adults, CD only, CDAI (220-450), no use of TNF-alpha inhibitors, certolizumab pegol, sodium cromoglycate, mycophenolate, cyclosporin in past 4 weeks, TNF-alpha inhibitor with a biologic agent in past 12 weeks, moderate-severe disease, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria

Evidence Table 2. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Schroder, 2006[47]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 48 weeks	Europe Single center	No	Adults, CD only, no use of TNF-alpha inhibitors, infliximab, active disease, other criteria
Targan, 1997[43]	RCT, parallel arms	Start year: 1995 Duration of assigned treatment: 12 weeks	US, North America, Europe Multicenter	Yes Yes	Adults, CD only, no previous surgery (proctocolectomy), CDAI (220-400), no use of cyclosporine, methotrexate or experimental agents in past 3 months, no ostomy, no obstructive symptoms with strictures, other criteria
Targan, 2007[32]	RCT, parallel arms with a 2-week run-in period	Start year: 2004 Duration of assigned treatment: 8 weeks	US, North America, Europe, Australia, Africa Multicenter	Yes Yes	Adults, CD only, no previous surgery (total colectomy), CDAI (220-450), no use of TNF-alpha inhibitors, natalizumab, active disease (moderate-severe), no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, other criteria
Winter, 2004[41]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 12 weeks	Europe, Africa, Israel Multicenter	No	Adults, CD only, no previous surgery (extended bowel resection), CDAI (220-450), moderate-severe disease, no ostomy, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Randomized controlled trials evaluating thiopurines					
Ardizzone, 2003[58]	RCT, parallel arms	Start year: 1997 Duration of assigned treatment: 6 months	Europe Single center	No	Adults, CD only, CDAI (>200), active disease, not pregnant, no abscess, no obstructive symptoms with strictures, no cancer, other criteria
Candy, 1995[53]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 weeks	Africa Single center	No	Pediatrics, adults, CD only, no previous surgery (extensive surgery for CD), CDAI (>200), not pregnant, not nursing, other criteria

Evidence Table 2. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Ewe, 1993[54]	RCT, parallel arms	Start year: 1987 Duration of assigned treatment: 4 months	Europe Single center	No	Adults, CD only, CDAI (>150), no use of thiopurines, perianal fistulizing, not pregnant, no abscess
Klein, 1974[62]	RCT, crossover	Start year: NR Duration of assigned treatment: 4 months	US Single center	Yes Yes	Adults, CD only, other criteria
Markowitz, 2000[192]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 18 months	US Multicenter	No	Pediatrics, CD only, moderate-severe disease, other criteria
Mate-Jimenez, 2000[52]	RCT, parallel arms	Start year: 1994 Duration of assigned treatment: 26.5 months	Europe Single center	No	Pediatrics, adults, IBD, no previous surgery (extensive surgery), previous use of corticosteroids, not pregnant, not nursing, using adequate contraception, no abscess, other criteria
Oren, 1997[57]	RCT, parallel arms	Start year: 1992 Duration of assigned treatment: 9 months	Israel Multicenter	No	Adults, CD only, HBI (<7), previous use of corticosteroids, no use of immunomodulators in past 3 months, not pregnant, not nursing, using adequate contraception, no abscess, no obstructive symptoms with strictures, other criteria
Present, 1980[60]	RCT, parallel arms, crossover	Start year: NR Duration of assigned treatment: 1 year	US Single center	Yes No	Pediatrics, adults, CD only, active disease, other criteria

Evidence Table 2. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Reinisch, 2008[51]	RCT, parallel arms	Start year: 2004 Duration of assigned treatment: 12 months	North America, Europe, Africa, Russia Multicenter	No	Adults, CD only, no previous surgery (resection of >100 cm of small bowel), CDAI (220-450), previous use of corticosteroids, no use of 5-aminosalicylate acids, TNF-alpha inhibitors, corticosteroids, methotrexate, corticosteroids for current flare >21 days prior to randomization, active disease, perianal fistulizing, no obstructive symptoms with strictures, other criteria
Rhodes, 1971[61]	RCT, crossover	Start year: NR Duration of assigned treatment: 2 months	Location: NR Number of centers NR	Yes No	Pediatrics, adults, CD only
Sandborn, 1999[59]	RCT, parallel arms with a 2-week run-in period	Start year: 1996 Duration of assigned treatment: 16 weeks	US, North America Multicenter	Yes Yes	Adults, CD only, no previous surgery (> 100 cm ileum), CDAI (150-450), previous use of corticosteroids, no use of antibiotics, thiopurines, infliximab, adalimumab, certolizumab pegol, active disease (mild-moderate), perianal fistulizing, no abscess, no obstructive symptoms with strictures, no cancer
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 17 weeks	US Multicenter	No	Adults, CD only, CDAI (>150), active disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Randomized controlled trials evaluating methotrexate					
Feagan, 1995[63]	RCT, parallel arms with a 2-week run-in period	Start year: 1992 Duration of assigned treatment: 16 weeks	US, North America Multicenter	No	CD only, previous use of prednisone, no use of prednisone > 10 mg/day, active disease, not pregnant, no cancer, other criteria
Mate-Jimenez, 2000[52]	RCT, parallel arms	Start year: 1994 Duration of assigned treatment: 26.5 months	Europe Single center	No	Pediatrics, adults, IBD, no previous surgery (extensive surgery), previous use of corticosteroids, not pregnant, not nursing, using adequate contraception, no abscess, other criteria

Evidence Table 2. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Oren, 1997[57]	RCT, parallel arms	Start year: 1992 Duration of assigned treatment: 9 months	Israel Multicenter	No	Adults, CD only, HBI (<7), previous use of corticosteroids, no use of immunomodulators in past 3 months, not pregnant, not nursing, using adequate contraception, no abscess, no obstructive symptoms with strictures, other criteria
Randomized controlled trials evaluating corticosteroids					
Bar-Meir, 1998[67]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 8 weeks	Israel Multicenter	Yes Yes	Adults, CD only, CDAI (150-350), no use of immunomodulators or corticosteroids in past 3 months, NSAIDs, no obstructive symptoms with strictures, other criteria
Campieri, 1997[68]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 weeks	Europe, Australia Multicenter	Yes	Adults, CD only, no previous surgery (ileostomy or more extensive resection of the ileum (>100 cm)), CDAI (>200), active disease, no abscess, other criteria
Escher, 2004[190]	RCT, parallel arms	Start year: 1998 Duration of assigned treatment: 12 weeks	Europe Multicenter	No	Pediatrics, CD only, CDAI (>200), no use of corticosteroids, thiopurines, active disease, other criteria
Greenberg, 1994[66]	RCT, parallel arms	Start year: 1991 Duration of assigned treatment: 8 weeks	North America Multicenter	Yes Yes	Adults, CD only, CDAI (>200), not pregnant, not nursing, no cancer, other criteria
Gross, 1995[72]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 8 weeks	Europe Multicenter	Yes No	CD only, CDAI (150-350), other criteria

Evidence Table 2. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Levine, 2003[191]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 weeks	Israel Multicenter	No	Pediatrics, CD only, no previous surgery (in past 6 weeks), PCDAI (12.5-40), no use of corticosteroids, thiopurines, active disease, other criteria
Malchow, 1984[64]	RCT, parallel arms	Start year: 1975 Duration of assigned treatment: 6 weeks	Europe Multicenter	Yes Yes	Adults, CD only, not pregnant, no abscess, no obstructive symptoms with strictures, other criteria
Martin F, 1990[73]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 weeks	North America Multicenter	Yes Yes	Adults, CD only, CDAI (200-450), previous use of corticosteroids, prednisone, no use of any medication taken for treatment for active CD in past month, active disease, not pregnant, not nursing, other criteria
Prantera, 1999[71]	RCT, parallel arms	Start year: 1994 Duration of assigned treatment: 12 weeks	Europe Multicenter	Yes Yes	Adults, CD only, no previous surgery (small bowel resection of >100 cm or colectomy or proctocolectomy), CDAI (180-350), no use of corticosteroids or other immunomodulators in past 3 months, mild-moderate disease, not pregnant, no short bowel syndrome, no obstructive symptoms with strictures, other criteria
Rutgeerts, 1994[69]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 10 weeks	Europe Multicenter	Yes Yes	Adults, CD only, no previous surgery (ileostomy or small bowel resection >100 cm), CDAI (>200), no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, other criteria
Schoon, 2005[185]	RCT, parallel arms	Start year: 1996 Duration of assigned treatment: 2 years	Europe, Israel Multicenter	 No	Adults, CD only, no previous surgery (gastric surgery or resection of >100 cm of small bowel or of tissues distal to the mid-transverse colon), no use of hormone replacement therapy in past 6 months, bisphosphonates in past 6 months, androgens/anabolic steroids in past 6 months, no abscess, no obstructive symptoms with strictures, other criteria
Singleton, 1979[75]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 8 weeks	US Multicenter	Yes Yes	CD only, CDAI (>150), active disease

Evidence Table 2. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 17 weeks	US Multicenter	No	Adults, CD only, CDAI (>150), active disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Thomsen, 1998[70]	RCT, parallel arms	Start year: 1994 Duration of assigned treatment: 16 weeks	Europe, Australia, Africa Multicenter	Yes No	Adults, CD only, no previous surgery (resection of >100 cm of ileum or if need immediate surgery), CDAI (200-400), not pregnant, not nursing, no abscess, other criteria
Tremaine, 2002[65]	RCT, parallel arms with a 2-week run-in period	Start year: 1995 Duration of assigned treatment: 8 weeks	US Multicenter	Yes Yes	Adults, CD only, CDAI (200-450), mild-moderate disease, not pregnant, not nursing, no ostomy, other criteria
Tromm, 2011[74]	RCT, parallel arms	Start year: 2004 Duration of assigned treatment: 8 weeks	Europe, Israel Multicenter		Adults, CD only, CDAI (200-400), no use of methotrexate, within 3 monthsperianal fistulizing, no short bowel syndrome, no ostomy, no obstructive symptoms with strictures, other criteria
Randomized controlled trials evaluating aminosalicylate acids					
Griffiths, 1993[221]	RCT, crossover	Start year: 1988 Duration of assigned treatment: 8 weeks	North America Single center	No	Pediatrics, CD only, HBI (>4), other criteria
Malchow, 1984[64]	RCT, parallel arms	Start year: 1975 Duration of assigned treatment: 6 weeks	Europe Multicenter	Yes Yes	Adults, CD only, not pregnant, no abscess, no obstructive symptoms with strictures, other criteria
Singleton, 1993[79]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 16 weeks	US Multicenter	Yes Yes	Adults, CD only, CDAI (151-400), mild-moderate disease, using adequate contraception, no ostomy, other criteria

Evidence Table 2. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Singleton, 1995[222]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 16 weeks	US Multicenter	No	Adults, CD only, no previous surgery (ileostomies or colostomies), CDAI (150-400), not pregnant, using adequate contraception, other criteria
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 17 weeks	US Multicenter	No	Adults, CD only, CDAI (>150), active disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Tremaine, 1994[77]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 16 weeks	US Single center	No	Adults, CD only, no previous surgery (extensive small bowel resection with more than one half of the length of the small intestine removed), CDAI (150-450.9), mild-moderate disease, other criteria

Abbreviations: CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; HBI= Harvey-Bradshaw Index; NR = not reported; RCT = randomized controlled trial; TB = tuberculosis; US = United States

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Randomized controlled trials evaluating biologics								
Colombel, 2010[45]	Infliximab + Placebo, 169 Route: IV + Oral Dose: 5 mg/kg every 8 weeks + NA every day	Male, %: 49.7 Race, % W: 86.4 Smoking, % Smoker, 42 CD NR	Age at diagnosis NR Disease duration Median: 2.2 Age at enrollment Median: 35	Severity NR Location, % Ileal: 32 Ileo-colonic: 37.9 Colonic: 26.6 Behavior NR CRP Median: 1.1	CDAI Mean: 284.8	5ASA: 51.5 Corticosteroids: 30.8 Budesonide: 16.6	NR	NR
Colombel, 2010[45]	Azathioprine + Infliximab, 169 Route: Oral + IV Dose: 2.5 mg/kg every day + 5 mg/kg every 8 weeks	Male, %: 52.1 Race, % W: 84 Smoking, % Smoker, 38.5 CD NR	Age at diagnosis NR Disease duration Median: 2.2 Age at enrollment Median: 34	Severity NR Location, % Ileal: 32 Ileo-colonic: 43.2 Colonic: 23.7 Behavior NR CRP Median: 1	CDAI Mean: 289.9	5ASA: 50.3 Corticosteroids: 27.8 Budesonide: 11.2	NR	NR
Colombel, 2010[45]	Azathioprine + Placebo, 170 Route: Oral + IV Dose: 2.5 mg/kg every day + NA every 8 weeks	Male, %: 52.9 Race, % W: 86.5 Smoking, % Smoker, 35.3 CD NR	Age at diagnosis NR Disease duration Median: 2.4 Age at enrollment Median: 35	Severity NR Location, % Ileal: 40 Ileo-colonic: 40.6 Colonic: 19.4 Behavior NR CRP Median: 1	CDAI Mean: 287.2	5ASA: 61.2 Corticosteroids: 23.5 Budesonide: 14.7	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone, 64 Route: Oral + Oral Dose: 9 mg every day + 32 mg every day	Male, %: 42.2 Race, % W: 95.3 Smoking, % Current smoker, 35.9 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 28.7	Severity NR Location, % Ileo-colonic: 43.8 Colonic: 32.8 Behavior NR CRP Median: 25	CDAI Mean: 306 IBDQ Mean: 136	TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines Budesonide	5ASA: 3.1	NR
D'Haens, 2008[48]	Infliximab + Azathioprine, 65 Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Male, %: 33.8 Race, % W: 98.5 Smoking, % Current smoker, 43.1 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30	Severity NR Location, % Ileo-colonic: 47.7 Colonic: 30.8 Behavior NR CRP Median: 19	CDAI Mean: 330 IBDQ Mean: 122	TNF-alpha inhibitors: 100 Methotrexate Azathioprine: 100 Methylprednisolone	5ASA: 4.6	NR
Gordon, 2001[34]	Natalizumab, 18 Route: IV Dose: 3 mg/kg	Male, %: 38.9 Race, % W: 94.4 A: 5.6 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.5 Age at enrollment Mean: 36	Severity NR Location, % Ileo-colonic: 27.8 Colonic: 27.8 Perianal: 27.8 Behavior NR CRP Mean: 14	CDAI Mean: 258 Min: 122 Max: 436 IBDQ Mean: 121 Min: 74 Max: 167	Corticosteroids: 55.6 Thiopurines: 33.3 Mesalamine: 72.2 Mesalamine alone: 16.7	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Gordon, 2001[34]	Placebo, 12 Route: IV Dose: NA	Male, %: 41.7 Race, % W: 91.7 A: 8.3 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.4 Age at enrollment Mean: 34.4	Severity NR Location, % Ileo-colonic: 33.3 Colonic: 25 Perianal: 33.3 Behavior NR CRP Mean: 35	CDAI Mean: 273 Min: 191 Max: 420 IBDQ Mean: 118 Min: 78 Max: 144	Corticosteroids: 75 Thiopurines: 16.7 Mesalamine: 75 Mesalamine alone: 16.7	NR	NR
Hanauer, 2006[37]	Placebo, 74 Route: SC Dose: NA every 2 weeks	Male, %: 50 Race NR Smoking, % Current smoker, 38 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 37	Severity NR Location, % Ileal: 68 Ileo-colonic: 9 Colonic: 19 Perianal: 0 Behavior NR CRP Mean: 1.8 Median: 0.9 Min: 0 Max: 17.3	CDAI Mean: 296 IBDQ Median: 131 Min: 52 Max: 200	5ASA: 50 Antibiotics: 7 Corticosteroids: 34 Methotrexate: 1 Thiopurines: 28.4 Immunomodulators: 30	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hanauer, 2006[37]	Adalimumab, 75 Route: SC Dose: 80 mg then 40 mg every 2 weeks	Male, %: 33 Race NR Smoking, % Current smoker, 43 CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 38	Severity NR Location, % Ileal: 63 Ileo-colonic: 9 Colonic: 23 Perianal: 1 Behavior NR CRP Mean: 2 Median: 0.9 Min: 0 Max: 14.9	CDAI Mean: 301 IBDQ Median: 128 Min: 63 Max: 200	5ASA: 53 Antibiotics: 9 Corticosteroids: 43 Methotrexate: 4 Thiopurines: 25.3 Immunomodulators: 28	NR	NR
Hanauer, 2006[37]	Adalimumab, 76 Route: SC Dose: 160 mg then 80 mg every 2 weeks	Male, %: 47 Race NR Smoking, % Current smoker, 42 CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 39	Severity NR Location, % Ileal: 53 Ileo-colonic: 11 Colonic: 29 Perianal: 1 Behavior NR CRP Mean: 1.4 Median: 0.7 Min: 0 Max: 9.3	CDAI Mean: 295 IBDQ Median: 127 Min: 37 Max: 192	5ASA: 51 Antibiotics: 5 Corticosteroids: 32 Methotrexate: 1 Thiopurines: 27.6 Immunomodulators: 29	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hanauer, 2006[37]	Adalimumab, 74 Route: SC Dose: 40 mg then 20 mg every 2 weeks	Male, %: 53 Race NR Smoking, % Current smoker, 34 CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 39	Severity NR Location, % Ileal: 61 Ileo-colonic: 5 Colonic: 31 Perianal: 0 Behavior NR CRP Mean: 1.6 Median: 0.9 Min: 0 Max: 11.3	CDAI Mean: 299 IBDQ Median: 129 Min: 81 Max: 218	5ASA: 50 Antibiotics: 14 Corticosteroids: 23 Methotrexate: 5 Thiopurines: 25.7 Immunomodulators: 31	NR	NR
Lemann, 2006[46]	Infliximab + Azathioprine or 6-MP, 57 Route: IV Dose: 5 mg/kg + stable	Male, %: 47.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Min: 1 Max: 10 Age at enrollment Min: 22 Max: 38	Severity NR Location, % Ileal: 28.1 Ileo-colonic: 50.9 Colonic: 21.1 Perianal: 33.3 Behavior NR CRP Min: 4 Max: 47	CDAI Min: 90 Max: 281	NR	Thiopurines: 100	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lemann, 2006[46]	Placebo + Azathioprine or 6-MP, 56 Route: IV + Oral Dose: NA + stable mg/kg every day	Male, %: 42.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Min: 1 Max: 11 Age at enrollment Min: 22 Max: 36	Severity NR Location, % Ileal: 12.5 Ileo-colonic: 48.2 Colonic: 39.3 Perianal: 10.7 Behavior NR CRP Min: 4 Max: 35	CDAI Min: 42 Max: 262	NR	Thiopurines: 100	NR
Present, 1999[44]	Infliximab, 31 Route: IV Dose: 5 mg/kg	Male, %: 48.4 Race, % W: 90.3 B: 9.7 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 13.6 Age at enrollment Mean: 41.2	Severity NR Location, % Ileal: 22.6 Ileo-colonic: 54.8 Colonic: 22.6 Behavior NR CRP NR	CDAI Mean: 184.4 Median: 163 Perianal DAI Median: 8	5ASA: 54.8 Antibiotics: 19.4 Corticosteroids: 38.7 Thiopurines: 38.7	NR	NR
Present, 1999[44]	Placebo, 31 Route: IV	Male, %: 54.8 Race, % W: 93.5 B: 6.5 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 12 Age at enrollment Mean: 35.4	Severity NR Location, % Ileal: 9.7 Ileo-colonic: 61.3 Colonic: 29 Behavior NR CRP NR	CDAI Mean: 192.9 Median: 162 Perianal DAI Median: 9	5ASA: 61.3 Antibiotics: 35.5 Corticosteroids: 35.5 Thiopurines: 29	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Present, 1999[44]	Infliximab, 32 Route: IV Dose: 10 mg/kg	Male, %: 37.5 Race, % W: 90.6 B: 9.4 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 11.5 Age at enrollment Mean: 35	Severity NR Location, % Ileal: 12.5 Ileo-colonic: 56.2 Colonic: 31.2 Behavior NR CRP NR	CDAI Mean: 184.9 Median: 203 Perianal DAI Median: 10	5ASA: 50 Antibiotics: 34.4 Corticosteroids: 31.2 Thiopurines: 53.1	NR	NR
Sandborn, 2005[33]	Natalizumab, 724 Route: IV Dose: 300 mg every 4 weeks	Male, %: 43 Race NR Smoking, % >10 cigarettes/day, 22.7 CD NR	Age at diagnosis NR Disease duration Mean: 10.1 Age at enrollment Mean: 38	Severity NR Location, % Ileal: 26.8 Ileo-colonic: 51.5 Colonic: 21.7 Behavior NR CRP Mean: 20 Median: 9 Min: 0 Max: 370	CDAI Mean: 302	5ASA: 47.4 Antibiotics: 5.9 Corticosteroids: 37.4 Methotrexate: 4.3 Thiopurines: 29.8 Prednisone: 27.2 Budesonide: 10.9 >/= 1 corticosteroids or immunomodulators: 56.2 Corticosteroids and immunomodulators: 15.3	TNF-alpha inhibitors: 40.2	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 2005[33]	Placebo, 181 Route: IV Dose: NA every 4 weeks	Male, %: 40.3 Race NR Smoking, % >10 cigarettes/day, 24.3 CD NR	Age at diagnosis NR Disease duration Mean: 9.16 Age at enrollment Mean: 39	Severity NR Location, % Ileal: 26 Ileo-colonic: 46.4 Colonic: 27.1 Behavior NR CRP Mean: 23 Median: 12 Min: 0 Max: 127	CDAI Mean: 303	5ASA: 44.2 Antibiotics: 6.6 Corticosteroids: 38.7 Methotrexate: 3.3 Thiopurines: 25.4 Prednisone: 29.3 Budesonide: 11 >/= 1 corticosteroid or immunomodulators: 55.2 Corticosteroids and immunomodulators: 12.2	TNF-alpha inhibitors: 38.1	NR
Sandborn, 2007[39]	Placebo, 328 Route: SC Dose: NA every 4 weeks	Male, %: 40 Race NR Smoking, % Current smoker, 33 CD NR	Age at diagnosis NR Disease duration Mean: 8 Median: 5 Min: 1 Max: 40 Age at enrollment Mean: 38 Min: 18 Max: 77	Severity NR Location, % Ileal: 27 Ileo-colonic: 51 Colonic: 23 Behavior NR CRP Mean: 9 Min: 2 Max: 244	CDAI Mean: 297 Min: 161 Max: 513	Corticosteroids: 23 Immunomodulators: 20 Glucocorticoids + immunomodulators: 17 Neither glucocorticoids nor immunomodulators: 40	infliximab: 26	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 2007[39]	Certolizumab pegol, 331 Route: SC Dose: 400 mg every 4 weeks	Male, %: 47 Race NR Smoking, % Current smoker, 31 CD NR	Age at diagnosis NR Disease duration Mean: 7 Median: 5 Min: 1 Max: 44 Age at enrollment Mean: 37 Min: 18 Max: 73	Severity NR Location, % Ileal: 29 Ileo-colonic: 45 Colonic: 26 Behavior NR CRP Mean: 8 Min: 2 Max: 205	CDAI Mean: 300 Min: 149 Max: 491	Corticosteroids: 22 Immunomodulators: 21 Glucocorticoids + immunomodulators: 17 Neither glucocorticoids nor immunomodulators: 40	infliximab: 30	NR
Sandborn, 2007[38]	Adalimumab, 159 Route: SC	Male, %: 31.4 Race NR Smoking, % Smoker, 34.6 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 39	Severity NR Location, % Ileal: 70.4 Colonic: 66 Perianal: 17 Behavior NR CRP Mean: 19	CDAI Mean: 313 IBDQ Mean: 120	5ASA: 28.3 Corticosteroids: 34.6 Immonomodulator: 45.9	NR	NR
Sandborn, 2007[38]	Placebo, 166 Route: SC Dose: NA	Male, %: 39.2 Race NR Smoking, % Smoker, 33.7 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 37	Severity NR Location, % Ileal: 74.7 Colonic: 68.1 Perianal: 18.7 Behavior NR CRP Mean: 20	CDAI Mean: 313 IBDQ Mean: 124	5ASA: 36.1 Corticosteroids: 44 Immunomodulators: 51.2	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 2011[42]	Certolizumab pegol, 223 Route: SC Dose: 400 mg every 2 weeks	Male, %: 47.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.5 Age at enrollment NR	Severity NR Location, % Ileal: 28.3 Ileo-colonic: 40.4 Colonic: 29.1 Behavior, % Inflammatory: 75.3 Stricturing: 14.8 Penetrating: 9 CRP Mean: 9.41	CDAI Mean: 262.1 HBI Mean: 9.8 IBDQ Mean: 126.5	Corticosteroids: 43.5 Immunomodulators: 34.5 corticosteroid or IMM: 62.3 corticosteroid and IMM: 15.7 neither corticosteroid nor IMM: 37.7	NR	NR
Sandborn, 2011[42]	Placebo, 215 Route: SC Dose: 400 mg every 2 weeks	Male, %: 41.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7 Age at enrollment Min: 18 Max: 70	Severity NR Location, % Ileal: 26.5 Ileo-colonic: 41.4 Colonic: 28.4 Behavior, % Inflammatory: 76.7 Stricturing: 15.8 Penetrating: 7.4 CRP Mean: 9.02	CDAI Mean: 292.7 HBI Mean: 9.7 IBDQ Mean: 122.1	Corticosteroids: 45.6 Immunomodulators: 31.2 corticosteroid or IMM: 62.3 corticosteroid and IMM: 14.4 neither corticosteroid nor IMM: 37.7	NR	NR
Sands, 2007[35]	Placebo + Infliximab, 27 Route: IV + IV Dose: NA every 4 weeks + 5 mg/kg every 8 weeks	Male, %: 63 Race, % W: 85.2 B: 7.4 Other: 7.4 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10 Min: 0 Max: 36 Age at enrollment Mean: 38.9 Min: 19 Max: 72	Severity NR Location, % Ileal: 14.8 Ileo-colonic: 55.6 Colonic: 29.6 Behavior NR CRP Mean: 5.9 Min: 0 Max: 49	CDAI Mean: 243.6 Min: 150 Max: 366	5ASA: 37 Antibiotics: 18.5 Corticosteroids: 29.6 Azathioprine, 6-mercaptopurine, or methotrexate: 55.6	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sands, 2007[35]	Natalizumab + Infliximab, 52 Route: IV + IV Dose: 300 mg every 4 weeks + 5 mg/kg every 8 weeks	Male, %: 46.2 Race, % W: 94.2 B: 3.8 Other: 1.9 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 12.5 Age at enrollment Mean: 39.9 Min: 20 Max: 69	Severity NR Location, % Ileal: 21.2 Ileo-colonic: 53.8 Colonic: 25 Behavior NR CRP Mean: 6.5 Min: 0 Max: 71	CDAI Mean: 263.8 Min: 129 Max: 545	5ASA: 46.2 Antibiotics: 19.2 Corticosteroids: 26.9 Azathioprine, 6-mercaptopurine, or methotrexate: 50	NR	NR
Schreiber, 2005[40]	Certolizumab pegol, 72 Route: SC Dose: 200 mg every 4 weeks	Male, %: 30.6 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.84 Min: 0 Max: 30.7 Age at enrollment Mean: 40.1 Min: 19 Max: 71	Severity NR Location, % Ileal: 70.8 Perianal: 31.9 Behavior NR CRP Mean: 6.5 Min: 0.2 Max: 127	IBDQ Mean: 122.9	5ASA: 44.4 Antibiotics: 9.7 Corticosteroids: 40.3 Methotrexate: 5.6 Thiopurines: 34.7 Immunomodulators: 40.3 Anti-diarrheals: 22.2 Codeine and derivatives: 6.9 Azathioprine: 31.9 6-MP: 2.8	TNF-alpha inhibitors: 23.6	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schreiber, 2005[40]	Certolizumab pegol, 74 Route: SC Dose: 100 mg every 4 weeks	Male, %: 47.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.73 Min: 0 Max: 31.8 Age at enrollment Mean: 33.5 Min: 18 Max: 56	Severity NR Location, % Ileal: 77 Perianal: 27 Behavior NR CRP Mean: 6.2 Min: 0.2 Max: 141	IBDQ Mean: 132.2	5ASA: 50 Antibiotics: 8.1 Corticosteroids: 32.4 Methotrexate: 5.4 Immunomodulators: 35.1 Anti-diarrheals: 25.7 Codeine and derivatives: 6.8 Azathioprine: 17.6 6-MP: 12.2	TNF-alpha inhibitors: 24.3	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schreiber, 2005[40]	Placebo, 73 Route: SC Dose: NA every 4 weeks	Male, %: 32.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.95 Min: 0.1 Max: 27.6 Age at enrollment Mean: 35.8 Min: 19 Max: 64	Severity NR Location, % Ileal: 74 Perianal: 31.5 Behavior NR CRP Mean: 7.3 Min: 0.3 Max: 86.1	IBDQ Mean: 122.9	5ASA: 39.7 Antibiotics: 9.6 Corticosteroids: 39.7 Methotrexate: 6.8 Immunomodulators: 35.6 Anti-diarrheals: 13.7 Codeine and derivatives: 8.2 Azathioprine: 23.3 6-MP: 5.5	TNF-alpha inhibitors: 21.9	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schreiber, 2005[40]	Certolizumab pegol, 72 Route: SC Dose: 400 mg every 4 weeks	Male, %: 44.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.43 Min: 0.2 Max: 26.5 Age at enrollment Mean: 35.9 Min: 18 Max: 67	Severity NR Location, % Ileal: 77.8 Perianal: 29.2 Behavior NR CRP Mean: 7.7 Min: 0.4 Max: 128.2	IBDQ Mean: 126.5	5ASA: 38.9 Antibiotics: 8.3 Corticosteroids: 30.6 Methotrexate: 4.2 Immunomodulators: 37.5 Anti-diarrheals: 16.7 Codeine and derivatives: 2.8 Azathioprine: 30.6 6-MP: 2.8	TNF-alpha inhibitors: 16.7	NR
Schroder, 2006[47]	Infliximab, 8 Route: IV Dose: 5 mg/kg every 2 weeks	Male, %: 25 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 9.6 Age at enrollment Mean: 36.5	Severity NR Location, % Ileal: 12.5 Ileo-colonic: 62.5 Colonic: 12.5 Behavior NR CRP NR	CDAI Mean: 293 IBDQ Mean: 106	5ASA: 37.5 Corticosteroids: 87.5	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schroder, 2006[47]	Methotrexate + Infliximab, 11 Route: IV + IV Dose: 20 mg every 1 week + 5 mg/kg every 2 weeks	Male, %: 54.5 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.2 Age at enrollment Mean: 31.6	Severity NR Location, % Ileal: 9.1 Ileo-colonic: 63.6 Colonic: 9.1 Behavior NR CRP NR	CDAI Mean: 251 IBDQ Mean: 113	5ASA: 18.2 Corticosteroids: 72.7	NR	NR
Targan, 1997[43]	Infliximab, 28 Route: IV Dose: 10 mg/kg	Male, %: 46 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 11.5 Age at enrollment Mean: 39.3	Severity NR Location, % Ileal: 14 Ileo-colonic: 50 Colonic: 36 Behavior NR CRP Mean: 23.2	CDAI Mean: 318 IBDQ Mean: 116	5ASA: 64 Corticosteroids: 57.1 Thiopurines: 28 Prednisolone < 20 mg/day: 29 Prednisolone >/= 20 mg/day: 29	NR	NR
Targan, 1997[43]	Placebo, 25 Route: IV Dose: NA	Male, %: 60 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10.4 Age at enrollment Mean: 38.5	Severity, % Mod-sev disease: 100 Location, % Ileal: 32 Ileo-colonic: 40 Colonic: 28 Behavior NR CRP Mean: 12.8	CDAI Mean: 288 IBDQ Mean: 128	5ASA: 68 Corticosteroids: 64 Thiopurines: 44 Prednisolone < 20mg/day: 40 Prednisolone >/= 20 mg/day: 24	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Targan, 1997[43]	Infliximab, 27 Route: IV Dose: 5 mg/kg	Male, %: 52 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 12.5 Age at enrollment Mean: 37	Severity NR Location, % Ileal: 11 Ileo-colonic: 56 Colonic: 33 Behavior NR CRP Mean: 22.1	CDAI Mean: 312 IBDQ Mean: 122	5ASA: 59 Corticosteroids: 56 Thiopurines: 34 Prednisolone < 20mg/day: 30 Prednisolone >/= 20 mg: 26	NR	NR
Targan, 1997[43]	Infliximab, 28 Route: IV Dose: 20 mg/kg	Male, %: 46 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 13.5 Age at enrollment Mean: 36	Severity NR Location, % Ileal: 7 Ileo-colonic: 68 Colonic: 25 Behavior NR CRP Mean: 22.4	CDAI Mean: 307 IBDQ Mean: 118	5ASA: 46 Corticosteroids: 60.7 Thiopurines: 43 Prednisolone < 20mg/day: 36 Prednisolone >/= 20 mg /day: 25	NR	NR
Targan, 2007[32]	Natalizumab, 259 Route: IV Dose: 300 mg every 4 weeks	Male, %: 41 Race, % W: 95 H: 1 B: 1 A: 1 not specified: 3 Smoking, % >10 cigarettes/day, 22 CD NR	Age at diagnosis NR Disease duration Mean: 10.1 Age at enrollment Mean: 38.1	Severity, % Severe disease: 32 Location, % Ileal: 22 Ileo-colonic: 52 Colonic: 27 Behavior NR CRP Mean: 23	CDAI Mean: 303.9 IBDQ Mean: 123.6	5ASA: 49 Antibiotics: 7 Corticosteroids: 42 Immunomodulators: 37	TNF-alpha inhibitors: 50	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Targan, 2007[32]	Placebo, 250 Route: IV Dose: NR every 4 weeks	Male, %: 41 Race, % W: 94 H: 1 B: 2 A: 1 not specified: 2 Smoking, % >10 cigarettes/day, 19 CD NR	Age at diagnosis NR Disease duration Mean: 10 Age at enrollment Mean: 37.7	Severity, % Severe disease: 28 Location, % Ileal: 26 Ileo-colonic: 48 Colonic: 26 Behavior NR CRP Mean: 23.4	CDAI Mean: 299.5 IBDQ Mean: 122.5	5ASA: 48 Antibiotics: 5 Corticosteroids: 38 Immunomodulators: 38	TNF-alpha inhibitors: 45	NR
Winter, 2004[41]	Certolizumab pegol, 25 Route: IV Dose: 5 mg/kg	Male, %: 48 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.52 Min: 0.69 Max: 17.0 Age at enrollment Mean: 36.4 Min: 21 Max: 61	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 48 Corticosteroids: 24 Immunomodulators: 44	TNF-alpha inhibitors: 23	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Winter, 2004[41]	Placebo, 25 Route: IV Dose: NA	Male, %: 24 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.74 Min: 0.1 Max: 21.9 Age at enrollment Mean: 32.1 Min: 18 Max: 56	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 40 Corticosteroids: 28 Immunomodulators: 44	TNF-alpha inhibitors: 13	NR
Winter, 2004[41]	Certolizumab pegol, 2 Route: IV Dose: 1.25 mg/kg	Male, %: 0 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 9.28 Min: 7.7 Max: 10.9 Age at enrollment Mean: 36.5 Min: 31 Max: 42	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 0 Corticosteroids: 50 Immunomodulators: 0	TNF-alpha inhibitors: 50	NR
Winter, 2004[41]	Certolizumab pegol, 23 Route: IV Dose: 20 mg/kg	Male, %: 44 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.94 Min: 1.3 Max: 18.9 Age at enrollment Mean: 33.3 Min: 19 Max: 60	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 39 Corticosteroids: 26 Immunomodulators: 44	TNF-alpha inhibitors: 30	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Winter, 2004[41]	Certolizumab pegol, 17 Route: IV Dose: 10 mg/kg	Male, %: 35 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10.20 Min: 0.9 Max: 26.0 Age at enrollment Mean: 40.3 Min: 18 Max: 64	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 53 Corticosteroids: 35 Immunomodulators: 53	TNF-alpha inhibitors: 29	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Randomized controlled trials evaluating thiopurines								
Ardizzone, 2003[58]	Methotrexate, 27 Route: IV for first 3 months, then oral Dose: 25 mg every 1 week	Male, %: 48.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 6.38 Min: 0.25 Max: 7.08 Age at enrollment Mean: 37 Min: 25 Max: 54	Severity NR Location, % Colonic: 15 Behavior NR CRP Mean: 8.03 Min: 4 Max: 54	CDAI Mean: 213.36 Min: 210 Max: 390	Corticosteroids: 100	5ASA: 100 Antibiotics: 7.4 Corticosteroids: 100 Immunomodulators (AZA/6-MP, CyA): 14.8	NR
Ardizzone, 2003[58]	Azathioprine, 27 Route: Oral Dose: 2 mg/kg every day	Male, %: 55.6 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 4.77 Min: 0.67 Max: 17 Age at enrollment Mean: 31 Min: 18 Max: 60	Severity NR Location, % Colonic: 22 Behavior NR CRP Mean: 8.75 Min: 5 Max: 73	CDAI Mean: 225.96 Min: 205 Max: 408	Corticosteroids: 100	5ASA: 100 Antibiotics: 7.4 Corticosteroids: 100 Immunomodulators (AZA/6-MP, CyA): 7.4	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Candy, 1995[53]	Placebo + Prednisolone, 30 Route: Oral + Oral Dose: NA + 1 mg/kg every day	Male, %: 37 Race NR Smoking, % Smoker, 67 CD NR	Age at diagnosis NR Disease duration Median: 3.7 Min: 0.1 Max: 18.7 Age at enrollment Median: 31.8 Min: 21 Max: 62	Severity, % Severe disease: 43 Location, % Ileal: 20 Ileo-colonic: 63.3 Colonic: 16.7 Behavior NR CRP Median: 3.9 Min: 2.8 Max: 5.3	CDAI Median: 282 Min: 240 Max: 356	Corticosteroids: 100	Corticosteroids corticosteroids in the last 6 months: 63 no previous corticosteroids: 7	NR
Candy, 1995[53]	Azathioprine + Prednisolone, 33 Route: Oral + Oral Dose: 2.5 mg/kg every day + 1 mg/kg every day	Male, %: 21 Race NR Smoking, % Smoker, 67 CD NR	Age at diagnosis NR Disease duration Median: 2.6 Min: 0.1 Max: 19.3 Age at enrollment Median: 33.9 Min: 15 Max: 60	Severity, % Severe disease: 52 Location, % Ileal: 24.2 Ileo-colonic: 60.6 Colonic: 15.2 Behavior NR CRP Median: 5.4 Min: 2.9 Max: 7.3	CDAI Median: 301 Min: 264 Max: 358	Corticosteroids: 100 Thiopurines: 100	corticosteroids in previous 6-12 mo: 67 no previous corticosteroids: 15	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Ewe, 1993[54]	Placebo + Prednisolone, 21 Dose: 60 mg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.3 Min: 18 Max: 48	Severity NR Location, % Ileal: 23.8 Ileo-colonic: 52.4 Colonic: 23.8 Behavior NR CRP NR	CDAI Mean: 285	NR	5ASA: 28.6 5-ASA + GCs: 38.1	NR
Ewe, 1993[54]	Azathioprine + Prednisolone, 21 Dose: 2.5 mg/kg every day + 60 mg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.4 Age at enrollment Mean: 27.3 Min: 18 Max: 43	Severity NR Location, % Ileal: 4.8 Ileo-colonic: 66.7 Colonic: 28.6 Behavior NR CRP NR	CDAI Mean: 290	NR	5ASA: 33.3 5-ASA + GCs: 57.1	NR
Klein, 1974[62]	Azathioprine, 13 Route: Oral Dose: 3 mg/kg every 24 hours	Male, %: 61.5 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.8 Age at enrollment Mean: 29	Severity NR Location, % Ileal: 30.8 Ileo-colonic: 53.8 Colonic: 15.4 Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Klein, 1974[62]	Placebo, 13 Route: Oral Dose: NA	Male, %: 69.2 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.2 Age at enrollment Mean: 31	Severity NR Location, % Ileal: 46.2 Ileo-colonic: 46.2 Colonic: 7.7 Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Markowitz, 2000[192]	Placebo + Prednisone, 28 Dose: 40 mg every day	Male, %: 64.3 Race, % W: 93 Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13.4	Severity NR Location, % Ileal: 3.6 Ileo-colonic: 78.6 Colonic: 17.9 Behavior NR CRP NR	PCDAI Mean: 44.7 HBI Mean: 7.4 partial HB Mean: 6.5	NR	NR	NR
Markowitz, 2000[192]	6-MP + Prednisone, 27 Dose: 1.5 mg/kg every day + 40 mg every day	Male, %: 55.6 Race, % W: 93 Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13	Severity NR Location, % Ileal: 14.8 Ileo-colonic: 70.4 Colonic: 14.8 Behavior NR CRP NR	PCDAI Mean: 46.7 HBI Mean: 7.7 partial HB Mean: 6.6	NR	NR	NR
Mate-Jimenez, 2000[52]	5-ASA, 7 Route: Oral Dose: 3 g every day	Gender NR Race NR Smoking, % Smoker, 85.7 CD NR	Age at diagnosis NR Disease duration Mean: 3.5 Age at enrollment NR	Severity NR Location, % Colonic: 14.3 Perianal: 14.3 Behavior NR CRP NR	CDAI Mean: 215	Corticosteroids: 100	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Mate-Jimenez, 2000[52]	6-MP, 16 Route: Oral Dose: 1.5 mg/kg every day	Gender NR Race NR Smoking, % Smoker, 75 CD NR	Age at diagnosis NR Disease duration Mean: 4.5 Age at enrollment NR	Severity NR Location, % Colonic: 37.5 Perianal: 25 Behavior NR CRP NR	CDAI Mean: 191	Corticosteroids: 100	NR	NR
Mate-Jimenez, 2000[52]	Methotrexate, 15 Route: Oral Dose: 15 mg every 1 week	Gender NR Race NR Smoking, % Smoker, 66.7 CD NR	Age at diagnosis NR Disease duration Mean: 4.3 Age at enrollment NR	Severity NR Location, % Colonic: 40 Perianal: 20 Behavior NR CRP NR	CDAI Mean: 200	Corticosteroids: 100	NR	NR
Oren, 1997[57]	Methotrexate + Placebo, 26 Route: Oral + Oral Dose: 12.5 mg every 1 week + NA every 24 hours	Male, %: 53.8 Race NR Smoking, % Present smoker, 24 CD NR	Age at diagnosis NR Disease duration Mean: 7.5 Age at enrollment Mean: 38.2	Severity NR Location, % Ileal: 33.3 Ileo-colonic: 29.2 Colonic: 37.5 Behavior NR CRP NR	HBI Mean: 9	5ASA: 72 Corticosteroids: 80	Corticosteroids: 100 Immunomodulators: 12	NR
Oren, 1997[57]	Placebo + Placebo, 26 Route: Oral + Oral Dose: NA every 24 hours + NA every 1 week	Male, %: 46.2 Race NR Smoking, % Present smoker, 32 CD NR	Age at diagnosis NR Disease duration Mean: 4.77 Age at enrollment Mean: 33.43	Severity NR Location, % Ileal: 50 Ileo-colonic: 25 Colonic: 25 Behavior NR CRP NR	HBI Mean: 7.8	5ASA: 69 Corticosteroids: 73	Corticosteroids: 100 Immunomodulators: 15	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Oren, 1997[57]	6-MP + Placebo, 32 Route: Oral + Oral Dose: 50 mg every 24 hours + NA every 1 week	Male, %: 54.8 Race NR Smoking, % Present smoker, 33.3 CD NR	Age at diagnosis NR Disease duration Mean: 8.43 Age at enrollment Mean: 34.03	Severity NR Location, % Ileal: 46.7 Ileo-colonic: 40 Colonic: 13.3 Behavior NR CRP NR	HBI Mean: 8.7	5ASA: 63 Corticosteroids: 79	Corticosteroids: 100 Immunomodulators: 27	NR
Present, 1980[60]	Placebo Route: Oral Dose: NA	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Present, 1980[60]	6-MP Route: Unknown Dose: 1.5 mg/kg every 24 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Reinisch, 2008[51]	Placebo + Prednisone, 29 Route: Oral + Oral Dose: NA every day + 1mg/kg or >/= 40mg every day	Male, %: 55.2 Race NR Smoking, % Smoker, 34.5 CD NR	Age at diagnosis NR Disease duration Median: 0.6 Min: 0 Max: 14.9 Age at enrollment Median: 39.5 Min: 18 Max: 64	Severity NR Location, % Ileal: 82.8 Colonic: 58.6 Behavior NR CRP NR	CDAI Median: 280 Min: 230 Max: 432 IBDQ Median: 120 Min: 70 Max: 147	NR	NR	Corticosteroids: 96.6

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Reinisch, 2008[51]	Azathioprine + Prednisone, 52 Route: Oral + Oral Dose: 2.5 mg/kg every day + 1 mg/kg or >/= 40 mg every day	Male, %: 50 Race NR Smoking, % Smoker, 30.8 CD NR	Age at diagnosis NR Disease duration Median: 1.2 Min: 0 Max: 20.3 Age at enrollment Median: 38.5 Min: 19 Max: 74	Severity NR Location, % Ileal: 71.2 Colonic: 73.1 Behavior NR CRP NR	CDAI Median: 282 Min: 225 Max: 435 IBDQ Median: 126 Min: 46 Max: 198	NR	NR	Corticosteroids: 96.2
Rhodes, 1971[61]	Placebo, 16 Route: Oral Dose: NA	Male, %: 75 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Min: 1 Max: 16 Age at enrollment Min: 14 Max: 69	Severity NR Location, % Ileal: 50 Ileo-colonic: 37.5 Colonic: 12.5 Behavior NR CRP NR	Disease activity index NR	Corticosteroids: 18.8 Sulfasalazine: 18.8	NR	NR
Rhodes, 1971[61]	Azathioprine, 16 Route: Oral Dose: 4 mg/kg every 24 hours	Male, %: 75 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Min: 1 Max: 14 Age at enrollment Min: 14 Max: 69	Severity NR Location, % Ileal: 50 Ileo-colonic: 37.5 Colonic: 12.5 Behavior NR CRP NR	Disease activity index NR	Sulfasalazine: 18.8 Prednisolone: 18.8	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 1999[59]	Azathioprine + Azathioprine, 51 Route: IV + Oral Dose: 40 mg/kg + 2 mg/kg every day	Male, %: 47.1 Race NR Smoking, % Smoker, 43.1 CD NR	Age at diagnosis NR Disease duration Median: 7.1 Min: 0 Max: 28 Age at enrollment Median: 33 Min: 19 Max: 63	Severity NR Location, % Ileal: 33.3 Ileo-colonic: 52.9 Colonic: 13.7 Behavior NR CRP NR	CDAI Median: 244 Min: 89 Max: 424 IBDQ Median: 127 Min: 73 Max: 183	NR	NR	NR
Sandborn, 1999[59]	Placebo + Azathioprine, 45 Route: Oral Dose: 2 mg/kg every day	Male, %: 55.6 Race NR Smoking, % Smoker, 35.6 CD NR	Age at diagnosis NR Disease duration Median: 6.6 Min: 0 Max: 35 Age at enrollment Median: 35 Min: 19 Max: 65	Severity NR Location, % Ileal: 17.8 Ileo-colonic: 60 Colonic: 22.2 Behavior NR CRP NR	CDAI Median: 245 Min: 142 Max: 476 IBDQ Median: 123 Min: 77 Max: 182	NR	NR	NR
Summers, 1979[56]	Sulfasalazine, 74 Route: Oral Dose: 1g/15kgs every 24 hours	Male, %: 65.7 Race, % W: 93.2 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.42 Age at enrollment Mean: 29.6	Severity NR Location, % Ileal: 23 Ileo-colonic: 66.2 Colonic: 10.8 Behavior NR CRP NR	CDAI Mean: 256.2	NR	Corticosteroids: 38.4 sulfasalazine: 51.1	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Placebo, 77 Route: Oral Dose: NA	Male, %: 45.5 Race, % W: 93.5 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.97 Age at enrollment Mean: 33.7	Severity NR Location, % Ileal: 32.5 Ileo-colonic: 55.8 Colonic: 11.7 Behavior NR CRP NR	CDAI Mean: 241.9	NR	Corticosteroids: 37.7 sulfasalazine: 35.1	NR
Summers, 1979[56]	Prednisone, 85 Route: Oral Dose: If CDAI<150 then dose of prednisone is 1/4mg/kg, if CDAI = 150-300 then prednisone was dosed at 1/2mg/kg, if CDAI >300 then prednisone is 3/4mg/kg. every 24 hours	Male, %: 52.9 Race, % W: 92.9 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.48 Age at enrollment Mean: 31.8	Severity NR Location, % Ileal: 30.6 Ileo-colonic: 60 Colonic: 9.4 Behavior NR CRP NR	CDAI Mean: 243.4	NR	Corticosteroids: 24.7 Sulfasalazine: 30.6	NR
Summers, 1979[56]	Azathioprine, 59 Route: Oral Dose: 2.5 mg/kg every 24 hours	Male, %: 52.5 Race, % W: 89.8 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.25 Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 40.7 Ileo-colonic: 44.1 Colonic: 15.3 Behavior NR CRP NR	CDAI Mean: 240.7	NR	Corticosteroids: 37.3 Sulfasalazine: 30.5	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Randomized controlled trials evaluating methotrexate								
Feagan, 1995[63]	Placebo + Prednisone, 47 Route: IM + Oral Dose: NA every 1 week + every day	Male, %: 55 Race NR Smoking, % Cigarette smoker, 47 CD NR	Age at diagnosis NR Disease duration Mean: 98 Age at enrollment Mean: 36	Severity NR Location, % Ileal: 17 Ileo-colonic: 64 Colonic: 19 Behavior NR CRP NR	CDAI Mean: 190 IBDQ Mean: 159	Hydrocortisone ointment	NR	NR
Feagan, 1995[63]	Methotrexate + Prednisone, 94 Route: IM + Oral Dose: 25 mg every 1 week	Male, %: 54 Race NR Smoking, % Cigarette smoker, 49 CD NR	Age at diagnosis NR Disease duration Mean: 93 Age at enrollment Mean: 34	Severity NR Location, % Ileal: 32 Ileo-colonic: 52 Colonic: 16 Behavior NR CRP NR	CDAI Mean: 181 IBDQ Mean: 162	NR	NR	NR
Mate-Jimenez, 2000[52]	5-ASA, 7 Route: Oral Dose: 3 g every day	Gender NR Race NR Smoking, % Smoker, 85.7 CD NR	Age at diagnosis NR Disease duration Mean: 3.5 Age at enrollment NR	Severity NR Location, % Colonic: 14.3 Perianal: 14.3 Behavior NR CRP NR	CDAI Mean: 215	Corticosteroids: 100	NR	NR
Mate-Jimenez, 2000[52]	Methotrexate, 15 Route: Oral Dose: 15 mg every 1 week	Gender NR Race NR Smoking, % Smoker, 66.7 CD NR	Age at diagnosis NR Disease duration Mean: 4.3 Age at enrollment NR	Severity NR Location, % Colonic: 40 Perianal: 20 Behavior NR CRP NR	CDAI Mean: 200	Corticosteroids: 100	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Mate-Jimenez, 2000[52]	6-MP, 16 Route: Oral Dose: 1.5 mg/kg every day	Gender NR Race NR Smoking, % Smoker, 75 CD NR	Age at diagnosis NR Disease duration Mean: 4.5 Age at enrollment NR	Severity NR Location, % Colonic: 37.5 Perianal: 25 Behavior NR CRP NR	CDAI Mean: 191	Corticosteroids: 100	NR	NR
Oren, 1997[57]	Placebo + Placebo, 26 Route: Oral + Oral Dose: NA every 24 hours + NA every week	Male, %: 46.2 Race NR Smoking, % Present smoker, 32 CD NR	Age at diagnosis NR Disease duration Mean: 4.77 Age at enrollment Mean: 33.43	Severity NR Location, % Ileal: 50 Ileo-colonic: 25 Colonic: 25 Behavior NR CRP NR	HBI Mean: 7.8	5ASA: 69 Corticosteroids: 73	Corticosteroids: 100 Immunomodulators: 15	NR
Oren, 1997[57]	6-MP + Placebo, 32 Route: Oral + Oral Dose: 50 mg every 24 hours + NA every 1 week	Male, %: 54.8 Race NR Smoking, % Present smoker, 33.3 CD NR	Age at diagnosis NR Disease duration Mean: 8.43 Age at enrollment Mean: 34.03	Severity NR Location, % Ileal: 46.7 Ileo-colonic: 40 Colonic: 13.3 Behavior NR CRP NR	HBI Mean: 8.7	5ASA: 63 Corticosteroids: 79	Corticosteroids: 100 Immunomodulators: 27	NR
Oren, 1997[57]	Methotrexate + Placebo, 26 Route: Oral + Oral Dose: 12.5 mg every 1 week + NA every 24 hours	Male, %: 53.8 Race NR Smoking, % Present smoker, 24 CD NR	Age at diagnosis NR Disease duration Mean: 7.5 Age at enrollment Mean: 38.2	Severity NR Location, % Ileal: 33.3 Ileo-colonic: 29.2 Colonic: 37.5 Behavior NR CRP NR	HBI Mean: 9	5ASA: 72 Corticosteroids: 80	Corticosteroids: 100 Immunomodulators: 12	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Randomized controlled trials evaluating corticosteroids								
Bar-Meir, 1998[67]	Prednisone + Placebo, 101 Route: Oral + Oral Dose: 40mg every 24 hours + NA every 8 hours	Male, %: 50.5 Race NR Smoking, % Smoker, 30.7 CD NR	Age at diagnosis NR Disease duration Mean: 5 Age at enrollment Mean: 32.8	Severity NR Location, % Colonic: 16.6 Behavior NR CRP NR	CDAI Mean: 265 IBDQ Mean: 131.2	NR	5ASA: 81.2 Antibiotics: 34.7 Corticosteroids: 37.6	NR
Bar-Meir, 1998[67]	Budesonide + Placebo, 100 Route: Oral Dose: 3 mg every 8 hours + NA every day	Male, %: 53 Race NR Smoking, % Smoker, 30 CD NR	Age at diagnosis NR Disease duration Mean: 5 Age at enrollment Mean: 32.7	Severity NR Location, % Colonic: 10 Behavior NR CRP NR	CDAI Mean: 264 IBDQ Mean: 136.8	NR	5ASA: 80 Antibiotics: 28 Corticosteroids: 33	NR
Campieri, 1997[68]	Budesonide + Placebo, 58 Route: Oral + Oral Dose: 9 mg every day + NA every 24 hours	Male, %: 36.2 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.3 Min: 0 Max: 30 Age at enrollment Mean: 36 Min: 17 Max: 71	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 277 Min: 121 Max: 476	Corticosteroids: 100	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Campieri, 1997[68]	Prednisolone + Placebo, 58 Route: Oral + Oral Dose: 40 mg every day + NA every 12 hours	Male, %: 39.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 6.7 Min: 0 Max: 27 Age at enrollment Mean: 36 Min: 19 Max: 70	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 279 Min: 202 Max: 458	Corticosteroids: 100	NR	NR
Campieri, 1997[68]	Budesonide + Placebo, 61 Route: Oral + Oral Dose: 4.5 mg every 12 hours + NA every 24 hours	Male, %: 45.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.9 Min: 0 Max: 37 Age at enrollment Mean: 38 Min: 20 Max: 71	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 274 Min: 107 Max: 465	Corticosteroids: 100	NR	NR
Escher, 2004[190]	Prednisolone, 26 Dose: 1 mg/kg every day	Male, %: 69.2 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 0.8 Age at enrollment Mean: 13	Severity NR Location, % Ileal: 26.9 Ileo-colonic: 65.4 Colonic: 3.8 Behavior NR CRP NR	CDAI Mean: 268 PCDAI Mean: 45	NR	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Escher, 2004[190]	Budesonide, 22 Dose: 9 mg every day	Male, %: 31.8 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 0.6 Age at enrollment Mean: 13	Severity NR Location, % Ileal: 59.1 Ileo-colonic: 31.8 Colonic: 9.1 Behavior NR CRP NR	CDAI Mean: 239 PCDAI Mean: 39	NR	NR	NR
Greenberg, 1994[66]	Placebo, 66 Route: Oral Dose: NA every 12 hours	Male, %: 37.9 Race NR Smoking, % Smoker, 57.6 CD NR	Age at diagnosis NR Disease duration Median: 6.3 Age at enrollment Median: 32 Min: 19 Max: 62	Severity NR Location, % Ileal: 84.8 Ileo-colonic: 15.2 Colonic: 0 Behavior NR CRP Median: 4	CDAI Median: 287 IBDQ Median: 130	Loperamide	Corticosteroids: 38	NR
Greenberg, 1994[66]	Budesonide, 67 Route: Oral Dose: 1.5 mg every 12 hours	Male, %: 29.9 Race NR Smoking, % Smoker, 49 CD NR	Age at diagnosis NR Disease duration Median: 5.3 Age at enrollment Median: 30	Severity NR Location, % Ileal: 81 Ileo-colonic: 19 Colonic: 0 Behavior NR CRP Median: 10	CDAI Median: 293 IBDQ Median: 131	Loperamide	Corticosteroids: 45	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Greenberg, 1994[66]	Budesonide, 61 Route: Oral Dose: 4.5 mg every 12 hours	Male, %: 38 Race NR Smoking, % Smoker, 46 CD NR	Age at diagnosis NR Disease duration Median: 5.9 Age at enrollment Median: 37	Severity NR Location, % Ileal: 84 Ileo-colonic: 16 Colonic: 0 Behavior NR CRP Median: 4	CDAI Median: 296 IBDQ Median: 125	Loperamide	Corticosteroids: 43	NR
Greenberg, 1994[66]	Budesonide, 64 Route: Oral Dose: 7.5 mg every 12 hours	Male, %: 45.3 Race NR Smoking, % Smoker, 47 CD NR	Age at diagnosis NR Disease duration Median: 6.1 Age at enrollment Median: 31	Severity NR Location, % Ileal: 88 Ileo-colonic: 12 Behavior NR CRP Median: 4	CDAI Median: 285 IBDQ Median: 130	Loperamide	Corticosteroids: 47	NR
Gross, 1995[72]	(6)-Methylprednisolone, 16 Route: Oral Dose: 48 mg/day every 24 hours	Male, %: 31.2 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.6 Age at enrollment Mean: 31.9	Severity NR Location, % Ileal: 75 Colonic: 93.8 Behavior NR CRP Mean: 3.9	CDAI Mean: 236.2	Corticosteroids: 100	Previous therapy (not specified): 62.5	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Gross, 1995[72]	5-ASA (Salofalk), 15 Route: Oral Dose: 1.5 g every 8 hours	Male, %: 40 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.4 Age at enrollment Mean: 26.4	Severity NR Location, % Ileal: 86.7 Colonic: 73.3 Behavior NR CRP Mean: 5.3	CDAI Mean: 251.5	5ASA: 100	Previous therapy (not specified): 26.7	NR
Levine, 2003[191]	Budesonide + Mesalamine, 19 Dose: 3 mg every 8 hours + 3-4 g every day	Male, %: 68.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13.8	Severity NR Location NR Behavior NR CRP NR	PCDAI Mean: 29.3	NR	NR	NR
Levine, 2003[191]	Prednisone + Mesalamine, 14 Dose: 40 mg every day + 3-4 g every day	Male, %: 50 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 14.15	Severity NR Location NR Behavior NR CRP NR	PCDAI Mean: 28.9	NR	NR	NR
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 74 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 41.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 32.4 Ileo-colonic: 46 Colonic: 21.6 Behavior NR CRP NR	CDAI Mean: 148.2	NR	Sulfasalazine: 83.8 Prednisolone: 59.5 Azathioprine: 6.8	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	(6)-Methylprednisolone, 38 Route: IV Dose: 48 mg every 24 hours	Male, %: 47.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 26.1	Severity NR Location, % Ileal: 31.6 Ileo-colonic: 57.9 Colonic: 10.5 Behavior NR CRP NR	CDAI Mean: 147.4	NR	NR	NR
Malchow, 1984[64]	(6)-Methylprednisolone, 75 Route: Unknown Dose: 48 mg every 24 hours	Male, %: 50.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 32.5	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 159.9	NR	Sulfasalazine: 81.3 Prednisolone: 55.4 Azathioprine: 4	NR
Malchow, 1984[64]	Sulfasalazine, 75 Route: Oral Dose: 3 g every 24 hours	Male, %: 48 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 31.2	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 165.2	NR	sulfasalazine: 88 Prednisolone: 54.7 Azathioprine: 5.3	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Sulfasalazine, 42 Route: Oral Dose: 3 g every 24 hours	Male, %: 50 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 33.1	Severity NR Location, % Ileal: 62.4 Ileo-colonic: 113.3 Colonic: 62.4 Behavior NR CRP NR	CDAI Mean: 181.9	NR	NR	NR
Malchow, 1984[64]	Placebo, 68 Route: Oral Dose: NA	Male, %: 44.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.1	Severity NR Location, % Ileal: 33.8 Ileo-colonic: 45.6 Colonic: 20.6 Behavior NR CRP NR	CDAI Mean: 161.4	NR	sulfasalazine: 92.6 Prednisolone: 47.8 Azathioprine: 4.4	NR
Malchow, 1984[64]	Placebo, 42 Route: Oral Dose: NA	Male, %: 35.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.1	Severity NR Location, % Ileal: 23.8 Ileo-colonic: 52.4 Colonic: 23.8 Behavior NR CRP NR	CDAI Mean: 178.2	NR	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 38 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 42.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.2	Severity NR Location, % Ileal: 23.7 Ileo-colonic: 52.6 Colonic: 23.7 Behavior NR CRP NR	CDAI Mean: 185.3	NR	NR	NR
Martin F, 1990[73]	Prednisone, 28 Route: Oral Dose: 40 mg every 24 hours	Male, %: 35.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.4 Age at enrollment Mean: 30.6	Severity NR Location, % Ileal: 64.3 Ileo-colonic: 35.7 Behavior, % Inflammatory: 100 CRP NR	CDAI Mean: 291 QOLI Mean: 129	NR	Prednisone: 21.4	NR
Martin F, 1990[73]	5-ASA (Salofalk), 22 Route: Oral Dose: 250 mg every 8 hours	Male, %: 40.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 5.3 Age at enrollment Mean: 29.2 Min: 19 Max: 60	Severity NR Location, % Ileal: 54.5 Ileo-colonic: 45.5 Behavior NR CRP NR	CDAI Mean: 295 QOLI Mean: 134	NR	Corticosteroids: 31.8	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Prantera, 1999[71]	Mesalamine (Asacol), 28 Route: Oral Dose: 4 g every day	Male, %: 53.5 Race NR Smoking, % Smoker, 42.85 CD NR	Age at diagnosis NR Disease duration Mean: 3.3 Age at enrollment Mean: 32.4	Severity NR Location, % Ileal: 75 Ileo-colonic: 25 Behavior NR CRP NR	CDAI Median: 222 Min: 204 Max: 241	NR	5ASA: 57.14	NR
Prantera, 1999[71]	Mesalamine (Asacol), 35 Route: Oral Dose: 4 g every day	Male, %: 57.14 Race NR Smoking, % Smoker, 48.6 CD NR	Age at diagnosis NR Disease duration Mean: 4.1 Age at enrollment Mean: 36.8	Severity NR Location, % Ileal: 71.4 Ileo-colonic: 28.6 Behavior NR CRP NR	CDAI Median: 220 Min: 205 Max: 244	NR	5ASA: 60	NR
Prantera, 1999[71]	(6)-Methylprednisolone, 31 Route: Oral Dose: 40 mg	Male, %: 58.06 Race NR Smoking, % Smoker, 41.9 CD NR	Age at diagnosis NR Disease duration Mean: 4.3 Age at enrollment Mean: 38.3	Severity NR Location, % Ileal: 74.2 Ileo-colonic: 25.8 Behavior NR CRP NR	CDAI Median: 233 Min: 216 Max: 257	NR	5ASA: 58.06	NR
Rutgeerts, 1994[69]	Prednisolone + Placebo, 88 Route: Oral + Oral Dose: 40 mg every 24 hours + NA every day	Male, %: 42 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7 Age at enrollment Mean: 36	Severity NR Location NR Behavior NR CRP Mean: 23	CDAI Mean: 279 HBI Mean: 9.3	NR	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Rutgeerts, 1994[69]	Budesonide + Placebo, 88 Route: Oral + Oral Dose: 9 mg every 24 hours	Male, %: 34.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7 Age at enrollment Mean: 35	Severity NR Location NR Behavior NR CRP Mean: 25	CDAI Mean: 275 HBI Mean: 9.3	NR	NR	NR
Schoon, 2005[185]	Prednisolone, 134 Route: Oral Dose: 40 mg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Vitamin D: 15 Calcium: 51	NR	NR
Schoon, 2005[185]	Budesonide, 137 Route: Oral Dose: 9 mg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Vitamin D: 12 Calcium: 46	NR	NR
Singleton, 1979[75]	Sulfasalazine + Prednisone, 43 Route: Oral + Unknown Dose: 1g per 15kg body weight to 5g max every day + every day	Male, %: 47 Race, % W: 86 Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30	Severity NR Location, % Ileo-colonic: 56 Colonic: 9 Behavior NR CRP NR	CDAI Mean: 239	NR	5ASA: 51 Corticosteroids: 47	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Singleton, 1979[75]	Placebo + Prednisone, 46 Route: Unknown + Oral Dose: NA + every day	Male, %: 46 Race, % W: 89 Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 31.9	Severity NR Location, % Ileo-colonic: 55 Colonic: 11 Behavior NR CRP NR	CDAI Mean: 236.3	NR	5ASA: 54 Corticosteroids: 52	NR
Summers, 1979[56]	Azathioprine, 59 Route: Oral Dose: 2.5 mg/kg every 24 hours	Male, %: 52.5 Race, % W: 89.8 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.25 Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 40.7 Ileo-colonic: 44.1 Colonic: 15.3 Behavior NR CRP NR	CDAI Mean: 240.7	NR	Corticosteroids: 37.3 Sulfasalazine: 30.5	NR
Summers, 1979[56]	Sulfasalazine, 74 Route: Oral Dose: 1g/15kgs every 24 hours	Male, %: 65.7 Race, % W: 93.2 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.42 Age at enrollment Mean: 29.6	Severity NR Location, % Ileal: 23 Ileo-colonic: 66.2 Colonic: 10.8 Behavior NR CRP NR	CDAI Mean: 256.2	NR	Corticosteroids: 38.4 sulfasalazine: 51.1	NR
Summers, 1979[56]	Placebo, 77 Route: Oral Dose: NA	Male, %: 45.5 Race, % W: 93.5 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.97 Age at enrollment Mean: 33.7	Severity NR Location, % Ileal: 32.5 Ileo-colonic: 55.8 Colonic: 11.7 Behavior NR CRP NR	CDAI Mean: 241.9	NR	Corticosteroids: 37.7 sulfasalazine: 35.1	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Prednisone, 85 Route: Oral Dose: If CDAI<150 then dose of prednisone is 1/4mg/kg, if CDAI = 150-300 then prednisone was dosed at 1/2mg/kg, if CDAI >300 then prednisone is 3/4mg/kg every 24 hours	Male, %: 52.9 Race, % W: 92.9 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.48 Age at enrollment Mean: 31.8	Severity NR Location, % Ileal: 30.6 Ileo-colonic: 60 Colonic: 9.4 Behavior NR CRP NR	CDAI Mean: 243.4	NR	Corticosteroids: 24.7 Sulfasalazine: 30.6	NR
Thomsen, 1998[70]	Mesalamine (Pentasa), 89 Route: Oral Dose: 2 g every 12 hours	Male, %: 31.5 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 4.6 Age at enrollment Median: 31	Severity NR Location, % Ileal: 56.2 Ileo-colonic: 39.3 Colonic: 4.5 Behavior NR CRP NR	CDAI Median: 278 Min: 193 Max: 394	Opiates & loperamide	5ASA Corticosteroids Immunomodulators	NR
Thomsen, 1998[70]	Budesonide + Placebo, 93 Route: Oral + Oral Dose: 9 mg every day + NA every day	Male, %: 32.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 6.1 Age at enrollment Median: 34	Severity NR Location, % Ileal: 60.2 Ileo-colonic: 38.7 Colonic: 1.1 Behavior NR CRP NR	CDAI Median: 266 Min: 166 Max: 398	Opiates & loperamide	5ASA Corticosteroids Immunomodulators	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Tremaine, 2002[65]	Budesonide, 79 Route: Oral Dose: 4.5 mg every 12 hours	Male, %: 44.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10 Median: 7.1 Age at enrollment Mean: 39 Median: 38	Severity, % Mild-mod disease: 100 Location NR Behavior NR CRP NR	CDAI Mean: 279 Median: 270 Min: 166 Max: 437	NR	NR	NR
Tremaine, 2002[65]	Placebo, 41 Route: Oral Dose: NA every day	Male, %: 43.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10 Median: 8.2 Age at enrollment Mean: 37 Median: 36	Severity, % Mild-mod disease: 100 Location NR Behavior NR CRP NR	CDAI Mean: 271 Median: 253 Min: 197 Max: 425	NR	NR	NR
Tremaine, 2002[65]	Budesonide, 80 Route: Oral Dose: 9 mg every day	Male, %: 23.8 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 11.9 Median: 9.2 Age at enrollment Mean: 41 Median: 36	Severity, % Mild-mod disease: 100 Location NR Behavior NR CRP NR	CDAI Mean: 280 Median: 268 Min: 199 Max: 484	NR	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Tromm, 2011[74]	Budesonide, 154 Route: Oral Dose: two administrations of 9mg total every 1 days	Male, %: 53.2 Race, % W: 99.4 Smoking, % No smoking defintion abstracted, 30.5 CD NR	Age at diagnosis NR Disease duration Mean: 6.1 Age at enrollment Mean: 36.8	Severity NR Location NR Behavior NR CRP Mean: 15.4	CDAI Mean: 265.6	Thiopurines: 3.2	NR	NR
Tromm, 2011[74]	Mesalamine (Salofalk), 153 Route: Oral Dose: 3 x 1.5 g/day	Male, %: 50.3 Race, % W: 99.3 Smoking, % No smoking defintion abstracted, 25.5 CD NR	Age at diagnosis NR Disease duration Mean: 5.9 Age at enrollment Mean: 37.8	Severity NR Location NR Behavior NR CRP Mean: 16.6	CDAI Mean: 267.2	Thiopurines: 3.3	NR	NR
Randomized controlled trials evaluating aminosalicylate acids								
Griffiths, 1993[221]	Mesalamine (Pentasa), 7 Route: Oral Dose: 50 mg/kg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 188.3 HBI Mean: 3.71	NR	NR	NR
Griffiths, 1993[221]	Placebo, 6 Route: Oral Dose: NA every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 182.5 HBI Mean: 3.5	NR	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Sulfasalazine, 75 Route: Oral Dose: 3 g every 24 hours	Male, %: 48 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 31.2	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 165.2	NR	Sulfasalazine: 88.0 Prednisolone: 54.7 Azathioprine: 5.3	NR
Malchow, 1984[64]	(6)-Methylprednisolone, 38 Route: IV Dose: 48 mg every 24 hours	Male, %: 47.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 26.1	Severity NR Location, % Ileal: 31.6 Ileo-colonic: 57.9 Colonic: 10.5 Behavior NR CRP NR	CDAI Mean: 147.4	NR	NR	NR
Malchow, 1984[64]	(6)-Methylprednisolone, 75 Route: Unknown Dose: 48 mg every 24 hours	Male, %: 50.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 32.5	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 159.9	NR	Sulfasalazine: 81.3 Prednisolone: 55.4 Azathioprine: 4	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Sulfasalazine, 42 Route: Oral Dose: 3 g every 24 hours	Male, %: 50 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 33.1	Severity NR Location, % Ileal: 62.4 Ileo-colonic: 113.3 Colonic: 62.4 Behavior NR CRP NR	CDAI Mean: 181.9	NR	NR	NR
Malchow, 1984[64]	Placebo, 68 Route: Oral Dose: NA	Male, %: 44.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.1	Severity NR Location, % Ileal: 33.8 Ileo-colonic: 45.6 Colonic: 20.6 Behavior NR CRP NR	CDAI Mean: 161.4	NR	Sulfasalazine: 92.6 Prednisolone: 47.8 Azathioprine: 4.4	NR
Malchow, 1984[64]	Placebo, 42 Route: Oral Dose: NA	Male, %: 35.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.1	Severity NR Location, % Ileal: 23.8 Ileo-colonic: 52.4 Colonic: 23.8 Behavior NR CRP NR	CDAI Mean: 178.2	NR	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 74 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 41.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 32.4 Ileo-colonic: 46 Colonic: 21.6 Behavior NR CRP NR	CDAI Mean: 148.2	NR	Sulfasalazine: 83.8 Prednisolone: 59.5 Azathioprine: 6.8	NR
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 38 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 42.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.2	Severity NR Location, % Ileal: 23.7 Ileo-colonic: 52.6 Colonic: 23.7 Behavior NR CRP NR	CDAI Mean: 185.3	NR	NR	NR
Singleton, 1993[79]	Mesalamine (Pentasa), 75 Route: Oral Dose: 2 g every day	Male, %: 39 Race NR Smoking, % Smoker, 41 CD NR	Age at diagnosis NR Disease duration Mean: 8.6 Min: 0 Max: 33 Age at enrollment Mean: 36 Min: 20 Max: 70	Severity NR Location, % Ileal: 40 Ileo-colonic: 35 Colonic: 25 Behavior NR CRP NR	CDAI Mean: 265 Min: 133 Max: 409 HBI Mean: 8.8 Min: 3 Max: 18 Van Hees index Mean: 155 Min: 97 Max: 249	NR	5ASA: 15 Corticosteroids: 21	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Singleton, 1993[79]	Mesalamine (Pentasa), 80 Route: Oral Dose: 1 g every day	Male, %: 36 Race NR Smoking, % Smoker, 40 CD NR	Age at diagnosis NR Disease duration Mean: 8.4 Min: 0 Max: 28 Age at enrollment Mean: 36 Min: 18 Max: 67	Severity NR Location, % Ileal: 38 Ileo-colonic: 38 Colonic: 23 Behavior NR CRP NR	CDAI Mean: 271 Min: 168 Max: 388 HBI Mean: 9 Min: 3 Max: 17 Van Hees index Mean: 158 Min: 72 Max: 224	NR	5ASA: 18 Corticosteroids: 16	NR
Singleton, 1993[79]	Placebo, 80 Route: Oral Dose: NA every day	Male, %: 41 Race NR Smoking, % Smoker, 50 CD NR	Age at diagnosis NR Disease duration Mean: 9.5 Min: 0 Max: 38 Age at enrollment Mean: 37 Min: 16 Max: 75	Severity NR Location, % Ileal: 45 Ileo-colonic: 36 Colonic: 19 Behavior NR CRP NR	CDAI Mean: 277 Min: 112 Max: 460 HBI Mean: 9.8 Min: 4 Max: 20 Van Hees index Mean: 154 Min: 91 Max: 279	NR	5ASA: 25 Corticosteroids: 26	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Singleton, 1993[79]	Mesalamine (Pentasa), 75 Route: Oral Dose: 4 g every day	Male, %: 27 Race NR Smoking, % Smoker, 29 CD NR	Age at diagnosis NR Disease duration Mean: 9.9 Min: 0 Max: 45 Age at enrollment Mean: 37 Min: 19 Max: 76	Severity NR Location, % Ileal: 44 Ileo-colonic: 36 Colonic: 19 Behavior NR CRP NR	CDAI Mean: 260 Min: 86 Max: 381 HBI Mean: 8.6 Min: 1 Max: 16 Van Hees index Mean: 157 Min: 80 Max: 232	NR	5ASA: 17 Corticosteroids: 20	NR
Singleton, 1995[222]	Placebo, 80 Route: Unknown Dose: NA every 24 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Singleton, 1995[222]	Mesalamine (Pentasa), 75 Route: Oral Dose: 2 g every 24 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Singleton, 1995[222]	Mesalamine (Pentasa), 75 Route: Oral Dose: 4 g every 24 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Singleton, 1995[222]	Mesalamine (Pentasa), 80 Route: Oral Dose: 1 g every 24 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Summers, 1979[56]	Prednisone, 85 Route: Oral Dose: If CDAI<150 then dose of prednisone is 1/4mg/kg, if CDAI = 150-300 then prednisone was dosed at 1/2mg/kg, if CDAI >300 then prednisone is 3/4mg/kg. every 24 hours	Male, %: 52.9 Race, % W: 92.9 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.48 Age at enrollment Mean: 31.8	Severity NR Location, % Ileal: 30.6 Ileo-colonic: 60 Colonic: 9.4 Behavior NR CRP NR	CDAI Mean: 243.4	NR	Corticosteroids: 24.7 Sulfasalazine: 30.6	NR
Summers, 1979[56]	Placebo, 77 Route: Oral Dose: NA	Male, %: 45.5 Race, % W: 93.5 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.97 Age at enrollment Mean: 33.7	Severity NR Location, % Ileal: 32.5 Ileo-colonic: 55.8 Colonic: 11.7 Behavior NR CRP NR	CDAI Mean: 241.9	NR	Corticosteroids: 37.7 sulfasalazine: 35.1	NR

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Sulfasalazine, 74 Route: Oral Dose: 1g/15kg every 24 hours	Male, %: 65.7 Race, % W: 93.2 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.42 Age at enrollment Mean: 29.6	Severity NR Location, % Ileal: 23 Ileo-colonic: 66.2 Colonic: 10.8 Behavior NR CRP NR	CDAI Mean: 256.2	NR	Corticosteroids: 38.4 sulfasalazine: 51.1	NR
Summers, 1979[56]	Azathioprine, 59 Route: Oral Dose: 2.5 mg/kg every 24 hours	Male, %: 52.5 Race, % W: 89.8 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.25 Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 40.7 Ileo-colonic: 44.1 Colonic: 15.3 Behavior NR CRP NR	CDAI Mean: 240.7	NR	Corticosteroids: 37.3 Sulfasalazine: 30.5	NR
Tremaine, 1994[77]	Mesalamine (Asacol), 20 Route: Oral Dose: 800 mg every 6 hours	Male, %: 35 Race, % W: 100 Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 3.5 Min: 0.33 Max: 25 Age at enrollment Median: 31 Min: 20 Max: 62	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 231.7	NR	NR	Corticosteroids: 65 Thiopurines: 0 : 30 : 30 : 0 : 10

Evidence Table 3. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Tremaine, 1994[77]	Placebo, 18 Route: Oral Dose: NA every 6 hours	Male, %: 66.66 Race, % W: 100 Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 5 Min: 0.58 Max: 13 Age at enrollment Median: 38 Min: 22 Max: 65	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 204.8	NR	NR	Corticosteroids: 50 Thiopurines: 0 : 38.9 : 16.7 : 11.1 : 5.6

Abbreviations: 5ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; A = Asian: B = African American; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; DAI = disease activity index; g = grams; H = Hispanic; HBI = Harvey-Bradshaw Index; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; kg = kilogram; Max. = maximum; mg = milligram; Min. = minimum; Mod-sev = moderate to severe; NA = not applicable; NR = not reported; SC = subcutaneous; TNF = tumor necrosis factor; W = White

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2010[45]	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 55 / 169 (32.5%)	Incidence 30 / 170 (17.6%) P: 0.001
Colombel, 2010[45]	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	CDAI (Remission: CDAI < 150) @ 26 wks	NA Yes	Incidence 81 / 169 (47.9%)	Incidence 54 / 170 (31.8%) P: 0.002
Colombel, 2010[45]	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	CDAI (Remission: CDAI < 150) @ 50 wks	NA Yes	Incidence 64 / 169 (38%)	Incidence 41 / 170 (24%) P: 0.006
Colombel, 2010[45]	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	Endoscopic healing (Absence of ulcers) @ 26 wks	NA No	Incidence 28 / 93 (30%)	Incidence 18 / 109 (17%) P: 0.02
Colombel, 2010[45]	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	HR QoL (IBDQ) @ 26 wks	NA Yes	B: Mean, 126.7 (SD, 30) F-B: Mean, 39.9 (SD, 37) G1-G2: -8.5	B: Mean, 122.1 (SD, 30) F-B: Mean, 31.4 (SD, 35) G1-G2: -8.5 P: 0.05
Colombel, 2010[45]	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	HR QoL (IBDQ) @ 26 wks	NA Yes	F-B: Mean, 27.7 (SD, 26) G1-G2: -7.6	F-B: Mean, 20.1 (SD, 24) G1-G2: -7.6 P: 0.007
Colombel, 2010[45]	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	HR QoL (IBDQ) @ 50 wks	NA No	F-B: Mean, 51.6 (SD, 33) G1-G2: -8.6	F-B: Mean, 43 (SD, 33) G1-G2: -8.6
Colombel, 2010[45]	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	Steroid free (steroid-free remission (CDAI < 150)) @ 26 wks	NA Yes	Incidence 75 / 169 (44.4%)	Incidence 51 / 170 (30%) P: 0.006
Colombel, 2010[45]	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	Steroid free (steroid-free remission (CDAI < 150)) @ 50 wks	NA Yes	Incidence 59 / 169 (35%)	Incidence 41 / 170 (24%) P: 0.03

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2010[45]	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	Steroid free (steroid-free remission (CDAI < 150)) @ 6 wks	NA Yes	Incidence 50 / 169 (29.6%)	Incidence 24 / 170 (14.1%)
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 62 / 169 (36.7%)	Incidence 30 / 170 (17.6%) P: <0.001
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	CDAI (Remission: CDAI < 150) @ 26 wks	NA Yes	Incidence 102 / 169 (60.4%)	Incidence 54 / 170 (31.8%) P: <0.001
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	CDAI (Remission: CDAI < 150) @ 50 wks	NA Yes	Incidence 80 / 169 (47%)	Incidence 41 / 170 (24%) P: <0.001
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	Endoscopic healing (Absence of ulcers) @ 26 wks	NA No	Incidence 47 / 107 (44%)	Incidence 18 / 109 (17%)
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	HR QoL (IBDQ) @ 26 wks	NA Yes	F-B: Mean, 31.4 (SD, 30) G1-G2: -11.3	F-B: Mean, 20.1 (SD, 24) G1-G2: -11.3 P: <0.001
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	HR QoL (IBDQ) @ 26 wks	NA Yes	B: Mean, 125.3 (SD, 29) F-B: Mean, 45.2 (SD, 36) G1-G2: -13.8	B: Mean, 122.1 (SD, 30) F-B: Mean, 31.4 (SD, 35) G1-G2: -13.8 P: <0.001
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	HR QoL (IBDQ) @ 50 wks	NA No	F-B: Mean, 56.4 (SD, 33) G1-G2: -13.4	F-B: Mean, 43 (SD, 33) G1-G2: -13.4
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	Steroid free (steroid-free remission (CDAI < 150)) @ 50 wks	NA Yes	Incidence 78 / 168 (46%)	Incidence 41 / 170 (24%) P: <0.001

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	Steroid free (steroid-free remission (CDAI < 150)) @ 6 wks	NA Yes	Incidence 55 / 169 (32.5%)	Incidence 24 / 170 (14.1%) P: <0.001
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Azathioprine + placebo Route: Oral + IV Dose: 2.5 mg/kg daily + NA every 8 wks	Steroid free (steroid-free remission (CDAI < 150)) @ 26 wks	NA Yes	Incidence 96 / 169 (56.8%)	Incidence 51 / 170 (30%) P: <0.001
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 62 / 169 (36.7%)	Incidence 55 / 169 (32.5%) P: 0.38
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	CDAI (Remission: CDAI < 150) @ 26 wks	NA Yes	Incidence 102 / 169 (60.4%)	Incidence 81 / 169 (47.9%) P: 0.02
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	CDAI (Remission: CDAI < 150) @ 50 wks	NA Yes	Incidence 80 / 169 (47%)	Incidence 64 / 169 (38%) P: 0.08
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Endoscopic healing (Absence of ulcers) @ 26 wks	NA No	Incidence 47 / 107 (44%)	Incidence 28 / 93 (30%) P: 0.06
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	HR QoL (IBDQ) @ 26 wks	NA Yes	B: Mean, 125.3 (SD, 29) F-B: Mean, 45.2 (SD, 36) G1-G2: -5.3	B: Mean, 126.7 (SD, 30) F-B: Mean, 39.9 (SD, 37) G1-G2: -5.3 P: 0.13
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	HR QoL (IBDQ) @ 26 wks	NA Yes	F-B: Mean, 31.4 (SD, 30) G1-G2: -3.7	F-B: Mean, 27.7 (SD, 26) G1-G2: -3.7 P: 0.31
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	HR QoL (IBDQ) @ 50 wks	NA No	F-B: Mean, 56.4 (SD, 33) G1-G2: -4.8	F-B: Mean, 51.6 (SD, 33) G1-G2: -4.8

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Steroid free (steroid-free remission (CDAI < 150)) @ 26 wks	NA Yes	Incidence 96 / 169 (56.8%)	Incidence 75 / 169 (44.4%) P: 0.02
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Steroid free (steroid-free remission (CDAI < 150)) @ 50 wks	NA Yes	Incidence 78 / 168 (46%)	Incidence 59 / 169 (35%) P: 0.04
Colombel, 2010[45]	Azathioprine + infliximab Route: Oral + IV Dose: 2.5 mg/kg daily + 5 mg/kg every 8 wks	Infliximab + placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA daily	Steroid free (steroid-free remission (CDAI < 150)) @ 6 wks	NA Yes	Incidence 55 / 169 (32.5%)	Incidence 50 / 169 (29.6%) P: 0.55
Reinisch, 2008[51]	Azathioprine + prednisone Route: Oral + Oral Dose: 2.5 mg/kg daily + 1 mg/kg or ≥ 40 mg daily	Placebo + prednisone Route: Oral + Oral Dose: NA daily + 1mg/kg or ≥ 40mg daily	HR QoL (IBDQ) @ 4 wks	NA No	F-B: Median, 43 G1-G2: -3	F-B: Median, 40 G1-G2: -3
D'Haens, 2008[48]	Budesonide + (6)-methylprednisolone Route: Oral + Oral Dose: 9 mg daily + 32 mg daily	Infliximab + azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	CDAI (Remission: CDAI<150, absence of intestinal resection, absence of corticosteroid therapy) @ 104 wks	NA Yes	Incidence 32 / 64 (50%)	Incidence 36 / 65 (55%) P: 0.431
D'Haens, 2008[48]	Budesonide + (6)-methylprednisolone Route: Oral + Oral Dose: 9 mg daily + 32 mg daily	Infliximab + azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	CDAI (Remission: CDAI<150, absence of intestinal resection, absence of corticosteroid therapy) @ 26 wks	NA Yes	Incidence 23 / 64 (36%)	Incidence 39 / 65 (60%) P: 0.0062
D'Haens, 2008[48]	Budesonide + (6)-methylprednisolone Route: Oral + Oral Dose: 9 mg daily + 32 mg daily	Infliximab + azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	CDAI (Remission: CDAI<150, absence of intestinal resection, absence of corticosteroid therapy) @ 52 wks	NA Yes	Incidence 27 / 64 (42%)	Incidence 40 / 65 (62%) P: 0.0278

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
D'Haens, 2008[48]	Budesonide + (6)-methylprednisolone Route: Oral + Oral Dose: 9 mg daily + 32 mg daily	Infliximab + azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	CDAI (Remission: CDAI<150, absence of intestinal resection, absence of corticosteroid therapy) @ 14 wks	NA Yes	Incidence 20 / 64 (32%)	Incidence 42 / 65 (65%) P: 0.0001
D'Haens, 2008[48]	Budesonide + (6)-methylprednisolone Route: Oral + Oral Dose: 9 mg daily + 32 mg daily	Infliximab + azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Endoscopic healing (Absence of ulcers) @ 104 wks	NA NR	Incidence 7 / 23 (30%)	Incidence 19 / 26 (73%) P: 0.0028
D'Haens, 2008[48]	Budesonide + (6)-methylprednisolone Route: Oral + Oral Dose: 9 mg daily + 32 mg daily	Infliximab + azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Endoscopic healing (SES-CD) @ 104 wks	NA NR	F: Mean, 3.1 (SD, 2.9) P: <0.001	F: Mean, 0.7 (SD, 1.5) P: <0.001
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 16 wks	NA Yes	Incidence 86 / 331 (26%)	Incidence 66 / 328 (20%)
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 43 / 331 (13%)	Incidence 26 / 328 (8%)
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 26 wks	NA Yes	Incidence 95 / 327 (29%)	Incidence 59 / 326 (18%)
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ response (≥16-pt increase)) @ 26 wks	NA Yes	Incidence 140 / 331 (42%)	Incidence 108 / 328 (33%) P: 0.01
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ) @ 26 wks	NA Yes	F-B: Mean, 26.4 (SD, 35) G1-G2: -5.9	F-B: Mean, 20.5 (SD, 33) G1-G2: -5.9 P: 0.03
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Perianal disease (Complete fistula closure) @ 26 wks	NA Yes	Incidence 14 / 46 (30%)	Incidence 19 / 61 (31%)
Targan, 2007[32]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NR every 4 wks	CDAI (Remission: CDAI < 150) @ 12 wks	NA NA	Incidence 97 / 259 (38%)	Incidence 63 / 250 (25%) P: 0.001

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Targan, 2007[32]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NR every 4 wks	CDAI (Remission: CDAI < 150) @ 8 wks	NA NA	Incidence 68 / 259 (26%)	Incidence 40 / 250 (16%) P: 0.002
Targan, 2007[32]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NR every 4 wks	HR QoL (IBDQ) @ 12 wks	NA NA	B: Mean, 123.6 (SD, 31) F-B: Mean, 26.7 (SD, 32) P: <0.001	B: Mean, 122.5 (SD, 28) F-B: Mean, 15.2 (SD, 29) G1-G2: -11.5
Sandborn, 2007[38]	Adalimumab Route: SC	Placebo Route: SC	(Complete fistula closure) @ 4 wks	NA NA	Incidence 1 / 20 (5%)	Incidence 2 / 25 (8%)
Sandborn, 2007[38]	Adalimumab Route: SC	Placebo Route: SC	CDAI (Remission: CDAI < 150) @ 4 wks	NA Yes	Incidence 34 / 159 (21%)	Incidence 12 / 166 (7%)
Sandborn, 2007[38]	Adalimumab Route: SC	Placebo Route: SC	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 10 / 159 (6%)	Incidence 6 / 166 (4%)
Sandborn, 2007[38]	Adalimumab Route: SC	Placebo Route: SC	HR QoL (IBDQ) @ 4 wks	NA NA	F: Mean, 150 P: <0.001	F: Mean, 139 P: <0.001
Sands, 2007[35]	Natalizumab + infliximab Route: IV + IV Dose: 300 mg every 4 wks + 5 mg/kg every 8 wks	Placebo + infliximab Route: IV + IV Dose: NA every 4 wks + 5 mg/kg every 8 wks	CDAI (Remission: CDAI < 150)	NA Yes	Incidence 24 / 52 (46%)	Incidence 11 / 27 (41%)
Sands, 2007[35]	Natalizumab + infliximab Route: IV + IV Dose: 300 mg every 4 wks + 5 mg/kg every 8 wks	Placebo + infliximab Route: IV + IV Dose: NA every 4 wks + 5 mg/kg every 8 wks	HR QoL (IBDQ) @ 6 wks	NA Yes	F-B: 12.3 G1-G2: -3.2	F-B: 9.1 G1-G2: -3.2
Sands, 2007[35]	Natalizumab + infliximab Route: IV + IV Dose: 300 mg every 4 wks + 5 mg/kg every 8 wks	Placebo + infliximab Route: IV + IV Dose: NA every 4 wks + 5 mg/kg every 8 wks	HR QoL (IBDQ) @ 10 wks	NA Yes	F-B: Mean, 18.7 G1-G2: -1.4	F-B: Mean, 17.3 G1-G2: -1.4
Lemann, 2006[46]	Infliximab + azathioprine or 6-MP Route: IV Dose: 5 mg/kg + stable	Placebo + azathioprine or 6-MP Route: IV + Oral Dose: NA + stable	Endoscopic healing (Absence of ulcers) @ 24 wks	NA Yes	Incidence 3 / 11 (27%)	Incidence 3 / 9 (33%) P: 0.77
Lemann, 2006[46]	Infliximab + azathioprine or 6-MP Route: IV Dose: 5 mg/kg + stable	Placebo + azathioprine or 6-MP Route: IV + Oral Dose: NA + stable	Endoscopic healing (CDEIS) @ 24 wks	NA NR	F-B: Median, -6.9 (IQR, -9.5 to -4.1) G1-G2: 5.7	F-B: Median, -1.2 (IQR, -4.4 to 1.5) G1-G2: 5.7 P: 0.05
Lemann, 2006[46]	Infliximab + azathioprine or 6-MP Route: IV Dose: 5 mg/kg + stable	Placebo + azathioprine or 6-MP Route: IV + Oral Dose: NA + stable	Steroid free (steroid-free remission (CDAI < 150)) @ 12 wks	NA Yes	Incidence 41 / 55 (75%) OR: 4.9 (2.2 to 11)	Incidence 21 / 56 (38%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Lemann, 2006[46]	Infliximab + azathioprine or 6-MP Route: IV Dose: 5 mg/kg + stable	Placebo + azathioprine or 6-MP Route: IV + Oral Dose: NA + stable	Steroid free (steroid-free remission (CDAI < 150)) @ 24 wks	NA Yes	Incidence 31 / 54 (57%) OR: 3.3 (1.5 to 7.4) P: 0.003	Incidence 15 / 52 (29%) P: 0.003
Lemann, 2006[46]	Infliximab + azathioprine or 6-MP Route: IV Dose: 5 mg/kg + stable	Placebo + azathioprine or 6-MP Route: IV + Oral Dose: NA + stable	Steroid free (steroid-free remission (CDAI < 150)) @ 52 wks	NA Yes	Incidence 22 / 55 (40%) OR: 2.4 (1 to 5.7) P: 0.04	Incidence 11 / 51 (22%) P: 0.04
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 1 wk	NA Yes	Incidence 12 / 74 (16%)	Incidence 5 / 74 (7%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 4 wks	NA Yes	Incidence 13 / 74 (18%)	Incidence 9 / 74 (12%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (IBDQ) @ 1 wk	NA Yes	B: Mean, 129 F: Mean, 14314	B: Mean, 131 F: Mean, 14110
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (IBDQ) @ 4 wks	NA Yes	B: Mean, 129 F: Mean, 147 P: NS18	B: Mean, 131 F: Mean, 147 P: NS16
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Perianal disease (50% fistula closure) @ 4 wks	NA Yes	Incidence 3 / 4 (75%)	Incidence 2 / 6 (33%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Perianal disease (Complete fistula closure) @ 4 wks	NA Yes	Incidence 3 / 4 (75%)	Incidence 1 / 6 (17%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 1 wk	NA Yes	Incidence 10 / 75 (13%)	Incidence 5 / 74 (7%) P: NS

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 4 wks	NA Yes	Incidence 18 / 75 (24%)	Incidence 9 / 74 (12%) P: NS
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (IBDQ) @ 1 wk	NA Yes	B: Mean, 128 F: Mean, 146 F-B: Mean: 18	B: Mean, 131 F: Mean, 141 F-B: Mean: 10
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (IBDQ) @ 4 wks	NA Yes	B: Mean, 128 F: Mean, 157 P: <0.0529	B: Mean, 131 F: Mean, 147 P: <0.0516
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Perianal disease (50% fistula closure) @ 4 wks	NA Yes	Incidence 2 / 10 (20%)	Incidence 2 / 6 (33%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Perianal disease (Complete fistula closure) @ 4 wks	NA Yes	Incidence 0 / 10 (0%)	Incidence 1 / 6 (17%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 1 wk	NA Yes	Incidence 12 / 76 (16%)	Incidence 5 / 74 (7%) P: NS
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 4 wks	NA Yes	Incidence 27 / 76 (36%)	Incidence 9 / 74 (12%) P: 0.001
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (IBDQ) @ 1 wk	NA Yes	B: Mean, 127 F: Mean, 14619	B: Mean, 131 F: Mean, 14110
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (IBDQ) @ 4 wks	NA Yes	B: Mean, 127 F: Mean, 157 P: <0.0530	B: Mean, 131 F: Mean, 147 P: <0.0516

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Perianal disease (50% fistula closure) @ 4 wks	NA Yes	Incidence 1 / 12 (8%)	Incidence 2 / 6 (33%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Perianal disease (Complete fistula closure) @ 4 wks	NA Yes	Incidence 0 / 12 (0%)	Incidence 1 / 6 (17%)
Schroder, 2006[47]	Methotrexate + infliximab Route: IV + IV Dose: 20 mg weekly + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 7 / 11 (64%)	Incidence 2 / 8 (25%) P: 0.16
Schroder, 2006[47]	Methotrexate + infliximab Route: IV + IV Dose: 20 mg weekly + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 9 / 11 (82%)	Incidence 4 / 8 (50%) P: 0.32
Schroder, 2006[47]	Methotrexate + infliximab Route: IV + IV Dose: 20 mg weekly + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	CDAI (Remission: CDAI < 150) @ 48 wks	NA Yes	Incidence 5 / 11 (45%)	Incidence 2 / 8 (25%) P: 0.63
Schroder, 2006[47]	Methotrexate + infliximab Route: IV + IV Dose: 20 mg weekly + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	HR QoL (IBDQ) @ 2 wks	NA Yes	B: Mean, 113 (SD, 23) F: Mean, 160 F-B: Mean: 47	B: Mean, 106 (SD, 17) F: Mean, 135 F-B: Mean: 29
Schroder, 2006[47]	Methotrexate + infliximab Route: IV + IV Dose: 20 mg weekly + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	HR QoL (IBDQ) @ 12 wks	NA Yes	B: Mean, 113 (SD, 23) F: Mean, 172 F-B: Mean: 59	B: Mean, 106 (SD, 17) F: Mean, 140 F-B: Mean: 34
Schroder, 2006[47]	Methotrexate + infliximab Route: IV + IV Dose: 20 mg weekly + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	HR QoL (IBDQ) @ 48 wks	NA Yes	B: Mean, 113 (SD, 23) F: Mean, 165 F-B: Mean: 52	B: Mean, 106 (SD, 17) F: Mean, 130 F-B: Mean: 24
Schroder, 2006[47]	Methotrexate + infliximab Route: IV + IV Dose: 20 mg weekly + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	Steroid free (Discontinued corticosteroids) @ 48 wks	NA Yes	Incidence 7 / 7 (100%)	Incidence 2 / 6 (33%) P: 0.02
Sandborn, 2005[33]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 101 / 724 (14%)	Incidence 18 / 181 (10%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Sandborn, 2005[33]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 10 wks	NA Yes	Incidence 268 / 724 (37%)	Incidence 54 / 181 (30%) P: 0.12
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 100 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 13 / 74 (18%)	Incidence 6 / 73 (8%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 100 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 20 / 74 (27%)	Incidence 17 / 73 (23.3%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 100 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ) @ 2 wks	NA Yes	B: Mean, 132.2 F-B: Mean, 16.6 G1-G2: -6	B: Mean, 122.9 F-B: Mean, 10.6 G1-G2: -6 P: <0.05
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 100 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ) @ 12 wks	NA Yes	B: Mean, 132.2 F-B: 22 G1-G2: -6	B: Mean, 122.9 F-B: 16 G1-G2: -6 P: NS
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 100 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ > 170) @ 2 wks	NA Yes	Incidence 24 / 73 (32.9%)	Incidence 13 / 73 (17.8%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 100 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ > 170) @ 12 wks	NA Yes	Incidence 28 / 73 (38.4%)	Incidence 17 / 73 (23.3%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 200 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 7 / 72 (10%)	Incidence 6 / 73 (8%) P: NS
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 200 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 14 / 72 (19.4%)	Incidence 17 / 73 (23.3%) P: NS
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 200 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ) @ 2 wks	NA Yes	B: Mean, 122.9 F-B: Mean, 21.8 G1-G2: -11.2	B: Mean, 122.9 F-B: Mean, 10.6 G1-G2: -11.2 P: <0.05
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 200 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ) @ 12 wks	NA Yes	B: Mean, 122.9 F-B: 20 G1-G2: -4	B: Mean, 122.9 F-B: 16 G1-G2: -4 P: NS
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 200 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ > 170) @ 2 wks	NA Yes	Incidence 14 / 72 (19.4%)	Incidence 13 / 73 (17.8%) P: NS
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 200 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ > 170) @ 12 wks	NA Yes	Incidence 17 / 72 (23.6%)	Incidence 17 / 73 (23.3%) P: NS

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 13 / 72 (18%)	Incidence 6 / 73 (8%) P: NS
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 19 / 72 (26.4%)	Incidence 17 / 73 (23.3%) P: NS
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ > 170) @ 2 wks	NA Yes	Incidence 20 / 72 (27.8%)	Incidence 13 / 73 (17.8%) P: NS
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ > 170) @ 12 wks	NA Yes	Incidence 28 / 72 (38.9%)	Incidence 17 / 73 (23.3%) P: <0.05
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ) @ 2 wks	NA NA	B: Mean, 126.5 (SD, 25) F-B: Mean, 22.8 G1-G2: -12.2	B: Mean, 122.9 (SD, 27) F-B: Mean, 10.6 G1-G2: -12.2
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ) @ 12 wks	NA NR	B: Mean, 126.5 (SD, 25) F: Mean, 156.4 (SD, 37) F-B: Mean, 29.9	B: Mean, 122.9 (SD, 27) F: Mean, 140.5 (SD, 36) F-B: Mean, 17.6 G1-G2: -14 P: <0.05
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 9 / 25 (35%)	Incidence 4 / 25 (16%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 8 / 25 (32%)	Incidence 8 / 25 (32%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 8 / 17 (47.1%)	Incidence 4 / 25 (16%) P: 0.041
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 4 / 17 (23.5%)	Incidence 8 / 25 (32%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 5 / 23 (20%)	Incidence 4 / 25 (16%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 3 / 23 (12%)	Incidence 8 / 25 (32%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Ardizzone, 2003[58]	Methotrexate Route: IV for first 3 mos then oral Dose: 25 mg weekly	Azathioprine Route: Oral Dose: 2 mg/kg daily	Steroid free (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 12 / 27 (44%)	Incidence 9 / 27 (33%)
Ardizzone, 2003[58]	Methotrexate Route: IV for first 3 mos then oral Dose: 25 mg weekly	Azathioprine Route: Oral Dose: 2 mg/kg daily	Perianal disease (Complete fistula closure) @ 24 wks	NA NR	Incidence 4 / 6 (67%)	Incidence 1 / 4 (25%)
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA daily	CDAI (Remission: CDAI < 150) @ 2 wks	NA No	Incidence 31 / 78 (40%)	Incidence 5 / 40 (13%)
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA daily	CDAI (Remission: CDAI < 150) @ 8 wks	NA No	Incidence 41 / 78 (53%)	Incidence 13 / 40 (33%) P: >0.05
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA daily	CDAI (Remission: treatment benefit (CDAI <150 or 100 pt drop)) @ 2 wks	NA No	Incidence 45 / 78 (58%)	Incidence 11 / 40 (27%)
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA daily	CDAI (Remission: treatment benefit (CDAI <150 or 100 pt drop)) @ 8 wks	NA No	Incidence 50 / 78 (64%)	Incidence 18 / 40 (44%)
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA daily	HR QoL (IBDQ) @ 8 wks	NA No	F-B: numerical improvements in total score', 34.1 (SD, 35.2)	F-B: numerical improvements in total score', 29.3 (SD, 35.7) G1-G2: -4.8
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 9 mg daily	Placebo Route: Oral Dose: NA daily	CDAI (Remission: CDAI < 150) @ 2 wks	NA No	Incidence 24 / 79 (31%)	Incidence 5 / 40 (13%)
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 9 mg daily	Placebo Route: Oral Dose: NA daily	CDAI (Remission: CDAI < 150) @ 8 wks	NA No	Incidence 37 / 79 (48%)	Incidence 13 / 40 (33%)
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 9 mg daily	Placebo Route: Oral Dose: NA daily	CDAI (Remission: treatment benefit (CDAI <150 or 100 pt drop)) @ 2 wks	NA No	Incidence 38 / 79 (48%)	Incidence 11 / 40 (27%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 9 mg daily	Placebo Route: Oral Dose: NA daily	CDAI (Remission: treatment benefit (CDAI <150 or 100 pt drop)) @ 8 wks	NA No	Incidence 52 / 79 (66%)	Incidence 18 / 40 (44%)
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 9 mg daily	Placebo Route: Oral Dose: NA daily	HR QoL (IBDQ) @ 8 wks	NA No	F-B: numerical improvements in total score', 36.3 (SD, 32.5)	F-B: numerical improvements in total score', 29.3 (SD, 35.7) G1-G2: -7
Gordon, 2001[34]	Natalizumab Route: IV Dose: 3 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 7 / 18 (39%)	Incidence 1 / 12 (8%) P: 0.1
Gordon, 2001[34]	Natalizumab Route: IV Dose: 3 mg/kg	Placebo Route: IV Dose: NA	HR QoL (IBDQ) @ 4 wks	NA NR	F-B: Mean, 19 P: 0.004	
Mate-Jimenez, 2000[52]	Methotrexate Route: Oral Dose: 15 mg weekly	6-MP Route: Oral Dose: 1.5 mg/kg daily	Steroid free (Remission: CDAI < 150 and normal serum orosmucoid concentration) @ 30 wks	NA NR	Incidence 12 / 15 (80%)	Incidence 15 / 16 (93.7%)
Mate-Jimenez, 2000[52]	Methotrexate Route: Oral Dose: 15 mg weekly	6-MP Route: Oral Dose: 1.5 mg/kg daily	Steroid free (Remission: CDAI < 150 and normal serum orosmucoid concentration) @ 106 wks	NA No	Incidence 8 / 15 (53%)	Incidence 8 / 16 (50%)
Mate-Jimenez, 2000[52]	ASA Route: Oral Dose: 3 g daily	6-MP Route: Oral Dose: 1.5 mg/kg daily	Steroid free (Remission: CDAI < 150 and normal serum orosmucoid concentration)@ 30 wks	NA NR	Incidence 1 / 7 (14%)	Incidence 15 / 16 (93.7%)
Mate-Jimenez, 2000[52]	ASA Route: Oral Dose: 3 g daily	6-MP Route: Oral Dose: 1.5 mg/kg daily	Steroid free (Remission: CDAI < 150 and normal serum orosmucoid concentration) @ 106 wks	NA No	Incidence 0 / 7 (0%)	Incidence 8 / 16 (50%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Mate-Jimenez, 2000[52]	ASA Route: Oral Dose: 3 g daily	Methotrexate Route: Oral Dose: 15 mg weekly	Steroid free (Remission: CDAI < 150 and normal serum orosmucoid concentration)@ 30 wks	NA NR	Incidence 1 / 7 (14%)	Incidence 12 / 15 (80%)
Mate-Jimenez, 2000[52]	ASA Route: Oral Dose: 3 g daily	Methotrexate Route: Oral Dose: 15 mg weekly	Steroid free (Remission: CDAI < 150 and normal serum orosmucoid concentration)@ 106 wks	NA No	Incidence 0 / 7 (0%)	Incidence 8 / 15 (53%)
Sandborn, 1999[59]	Azathioprine + azathioprine Route: IV + Oral Dose: 40 mg/kg + 2 mg/kg daily	Placebo + azathioprine Route: IV + Oral Dose: NA + 2 mg/kg daily	CDAI (Remission: CDAI < 150) @ 8 wks	NA Yes	Incidence 13 / 51 (25%)	Incidence 11 / 45 (24%) P: 0.906
Sandborn, 1999[59]	Azathioprine + azathioprine Route: IV + Oral Dose: 40 mg/kg + 2 mg/kg daily	Placebo + azathioprine Route: IV + Oral Dose: NA + 2 mg/kg daily	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 11 / 51 (22%)	Incidence 10 / 45 (22%) P: 0.939
Sandborn, 1999[59]	Azathioprine + azathioprine Route: IV + Oral Dose: 40 mg/kg + 2 mg/kg daily	Placebo + azathioprine Route: IV + Oral Dose: NA + 2 mg/kg daily	CDAI (Remission: CDAI < 150) @ 16 wks	NA Yes	Incidence 16 / 51 (31%)	Incidence 12 / 45 (27%) P: 0.615
Prantera, 1999[71]	(6)-Methylprednisolone Route: Oral Dose: 40 mg	Mesalamine (Asacol) Route: Oral (tablets) Dose: 4 g daily	CDAI (Remission: CDAI < 150) @ 3 wks	NA Yes	Incidence 19 / 31 (61%)	Incidence 16 / 35 (46%)
Prantera, 1999[71]	(6)-Methylprednisolone Route: Oral Dose: 40 mg	Mesalamine (Asacol) Route: Oral (tablets) Dose: 4 g daily	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 19 / 31 (61%)	Incidence 21 / 35 (60%)
Prantera, 1999[71]	(6)-Methylprednisolone Route: Oral Dose: 40 mg	Mesalamine (Asacol) Route: Oral (granules) Dose: 4 g daily	CDAI (Remission: CDAI < 150) @ 3 wks	NA Yes	Incidence 19 / 31 (61%)	Incidence 17 / 28 (61%)
Prantera, 1999[71]	(6)-Methylprednisolone Route: Oral Dose: 40 mg	Mesalamine (Asacol) Route: Oral (granules) Dose: 4 g daily	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 19 / 31 (61%)	Incidence 22 / 28 (79%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Bar-Meir, 1998[67]	Prednisone + placebo Route: Oral + Oral Dose: 40 mg daily + NA every 8 hrs	Budesonide + placebo Route: Oral Dose: 3 mg every 8 hrs + NA daily	HR QoL (SF-36, physical score) @ 8 wks	NA Yes	B: Mean, 40.8 (SD, 16.3) F: Mean, 62.3 (SD, 22) F-B: 21.5 G1-G2: 8	B: Mean, 44.8 (SD, 16.2) F: Mean, 58.3 (SD, 20.9) F-B: 13.5
Bar-Meir, 1998[67]	Prednisone + placebo Route: Oral + Oral Dose: 40 mg daily + NA every 8 hrs	Budesonide + placebo Route: Oral Dose: 3 mg every 8 hrs + NA daily	HR QoL (SF-36, mental score) @ 8 wks	NA Yes	B: Mean, 42.2 (SD, 19.7) F: Mean, 60.9 (SD, 23.1) F-B: 18.7 G1-G2: 8	B: Mean, 46.5 (SD, 18.9) F: Mean, 56.9 (SD, 20.7) F-B: 10.4
Bar-Meir, 1998[67]	Prednisone + placebo Route: Oral + Oral Dose: 40 mg daily + NA every 8 hrs	Budesonide + placebo Route: Oral Dose: 3 mg every 8 hrs + NA daily	HR QoL (IBDQ) @ 8 wks	NA Yes	B: Mean, 130.1 (SD, 32) F: Mean, 164.4 (SD, 36) F-B: Mean, 34.3 G1-G2: 8	B: Mean, 135.9 (SD, 28) F: Mean, 162 (SD, 34) F-B: Mean, 26.1
Thomsen, 1998[70]	Mesalamine (Pentasa) Route: Oral Dose: 2 g every 12 hrs	Budesonide + placebo Route: Oral + Oral Dose: 9 mg daily + NA daily	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 30 / 83 (36%)	Incidence 39 / 89 (44%)
Thomsen, 1998[70]	Mesalamine (Pentasa) Route: Oral Dose: 2 g every 12 hrs	Budesonide + placebo Route: Oral + Oral Dose: 9 mg daily + NA daily	CDAI (Remission: CDAI < 150) @ 16 wks	NA Yes	Incidence 18 / 50 (36%)	Incidence 48 / 77 (62%)
Thomsen, 1998[70]	Mesalamine (Pentasa) Route: Oral Dose: 2 g every 12 hrs	Budesonide + placebo Route: Oral + Oral Dose: 9 mg daily + NA daily	HR QoL (PGWB) @ 2 wks	NA NA	B: 83 F: Mean, 95 P: <0.05	B: 81 F: Mean, 98 P: <0.05
Thomsen, 1998[70]	Mesalamine (Pentasa) Route: Oral Dose: 2 g every 12 hrs	Budesonide + placebo Route: Oral + Oral Dose: 9 mg daily + NA daily	HR QoL (Psychological General Well-Being index) @ 16 wks	NA Yes	B: Mean, 83 F: Mean, 95 P: 0.01 F-B: Mean, 9 (SD, 21) P: 0.0025 G1-G2: 11.4	B: Mean, 81 F: Mean, 101 P: 0.01 F-B: Mean, 20.4 (SD, 24)
Thomsen, 1998[70]	Mesalamine (Pentasa) Route: Oral Dose: 2 g every 12 hrs	Budesonide + placebo Route: Oral + Oral Dose: 9 mg daily + NA daily	HR QoL (physician's global evaluation score) @ 2 wks	NA Yes	B: Mean, 2.2 F: Mean, 1.7 P: <0.01 F-B: Mean, -0.5	B: Mean, 2.2 F: Mean, 1.3 P: <0.01 F-B: Mean, -0.9
Thomsen, 1998[70]	Mesalamine (Pentasa) Route: Oral Dose: 2 g every 12 hrs	Budesonide + placebo Route: Oral + Oral Dose: 9 mg daily + NA daily	HR QoL (physician's global assessment) @ 16 wks	NA Yes	B: Mean, 2.2 F: 1.8 P: <0.001	B: Mean, 2.2 F: 1.2 P: <0.001
Oren, 1997[57]	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HBI (Remission: HBI<3 and not on steroids) @ 4 wks	NA Yes	Incidence 0 / 32 (0%)	Incidence 1 / 26 (5%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Oren, 1997[57]	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HBI (Remission: HBI<3 and not on steroids) @ 16 wks	NA Yes	Incidence 10 / 32 (30%)	Incidence 7 / 26 (28%)
Oren, 1997[57]	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HBI (Remission: HBI < 3 and not on steroids) @ 38 wks	NA Yes	Incidence 13 / 32 (41%)	Incidence 12 / 26 (46%)
Oren, 1997[57]	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HBI (Relapse rate: HBI increased by 3+ points and/or require restarting steroid treatment at >300 mg/mo) @ 38 wks	NA No	Incidence 5 / 13 (38%)	Incidence 4 / 12 (33%)
Oren, 1997[57]	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HR QoL (Treatment Goal Score for Wellbeing) @ 4 wks	NA NR	B: Mean, 0 F: Mean, 0.8 F-B: 0.8	B: Mean, 0 F: Mean, 0.8 F-B: 0.8
Oren, 1997[57]	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HR QoL (Treatment Goal Score for Wellbeing) @ 16 wks	NA NR	B: Mean, 0 F: Mean, 1.2 F-B: 1.2	B: Mean, 0 F: Mean, 1 F-B: 1
Oren, 1997[57]	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HR QoL (Treatment Goal Score for Wellbeing) @ 38 wks	NA NR	B: Mean, 0 F: Mean, 1.3 F-B: 1.3	B: Mean, 0 F: Mean, 1 F-B: 1
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HBI (Remission: HBI<3 and not on steroids) @ 4 wks	NA Yes	Incidence 2 / 26 (8%)	Incidence 1 / 26 (5%)
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HBI (Remission: HBI<3 and not on steroids) @ 16 wks	NA Yes	Incidence 8 / 26 (30%)	Incidence 7 / 26 (28%)
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HBI (Remission: HBI < 3 and not on steroids) @ 38 wks	NA Yes	Incidence 10 / 26 (38%)	Incidence 12 / 26 (46%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HBI (Relapse rate: HBI increased by 3+ points and/or require restarting steroid treatment at >300mg/mo) @ 38 wks	NA No	Incidence 1 / 10 (10%)	Incidence 4 / 12 (33%)
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HR QoL (Treatment Goal Score for Wellbeing) @ 4 wks	NA NR	B: Mean, 0 F: Mean, 1.2 F-B: 1.2	B: Mean, 0 F: Mean, 0.8 F-B: 0.8
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HR QoL (Treatment Goal Score for Wellbeing) @ 16 wks	NA NR	B: Mean, 0 F: Mean, 1.2 F-B: 1.2	B: Mean, 0 F: Mean, 1 F-B: 1
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	Placebo + placebo Route: Oral + Oral Dose: NA every 24 hrs + NA weekly	HR QoL (Treatment Goal Score for Wellbeing) @ 38 wks	NA NR	B: Mean, 0 F: Mean, 2.7 F-B: 2.7	B: Mean, 0 F: Mean, 1 F-B: 1
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	HBI (Remission: HBI<3 and not on steroids) @ 4 wks	NA Yes	Incidence 2 / 26 (8%)	Incidence 0 / 32 (0%)
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	HBI (Remission: HBI<3 and not on steroids) @ 16 wks	NA Yes	Incidence 8 / 26 (30%)	Incidence 10 / 32 (30%)
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	HBI (Remission: HBI < 3 and not on steroids) @ 38 wks	NA Yes	Incidence 10 / 26 (38%)	Incidence 13 / 32 (41%)
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	HBI (Relapse rate: HBI increased by 3+ points and/or require restarting steroid treatment at >300mg/mo) @ 38 wks	NA No	Incidence 1 / 10 (10%)	Incidence 5 / 13 (38%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	HR QoL (Treatment Goal Score for Wellbeing) @ 4 wks	NA NR	B: Mean, 0 F: Mean, 1.2 F-B: Mean, 1.2	B: Mean, 0 F: Mean, 0.8 F-B: Mean, 0.8
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	HR QoL (Treatment Goal Score for Wellbeing) @ 16 wks	NA NR	B: Mean, 0 F: Mean, 1.2 F-B: Mean, 1.2	B: Mean, 0 F: Mean, 1.2 F-B: Mean, 1.2
Oren, 1997[57]	Methotrexate + placebo Route: Oral + Oral Dose: 12.5 mg weekly + NA every 24 hrs	6-MP + placebo Route: Oral + Oral Dose: 50 mg every 24 hrs + NA weekly	HR QoL (Treatment Goal Score for Wellbeing) @ 38 wks	NA NR	B: Mean, 0 F: Mean, 2.7 F-B: Mean, 2.7	B: Mean, 0 F: Mean, 1.3 F-B: Mean, 1.3
Targan, 1997[43]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 2 wks	NA No	Incidence 10 / 26 (37%)	Incidence 1 / 24 (4%)
Targan, 1997[43]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 12 wks	NA No	Incidence 8 / 27 (30%)	Incidence 2 / 25 (8%)
Targan, 1997[43]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	Endoscopic healing (CDEIS) @ 4 wks	NA Yes	B: Mean, 15 (SE, 7) F: Mean, 6 (SE, 5) P: <0.01 F-B: Mean, -8.7	B: Mean, 8 (SE, 6) F: Mean, 7 (SE, 5) P: <0.01 F-B: Mean, -0.9
Targan, 1997[43]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	HR QoL (IBDQ) @ 4 wks	NA No	B: Mean, 122 (SD, 29) F: Mean, 168 (SD, 36) F-B: Mean, 46	B: Mean, 128 (SD, 29) F: Mean, 133 (SD, 28) F-B: Mean, 5 P: <0.001
Targan, 1997[43]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 2 wks	NA No	Incidence 5 / 23 (20%)	Incidence 1 / 24 (4%) P: NS
Targan, 1997[43]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 12 wks	NA No	Incidence 5 / 28 (18%)	Incidence 2 / 25 (8%)
Targan, 1997[43]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	Endoscopic healing (CDEIS) @ 4 wks	NA Yes	B: Mean, 11 (SE, 8) F: Mean, 4 (SE, 5) P: <0.01 F-B: Mean, -6.3	B: Mean, 8 (SE, 6) F: Mean, 7 (SE, 5) P: <0.01 F-B: Mean, -0.9
Targan, 1997[43]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	HR QoL (IBDQ) @ 4 wks	NA No	B: Mean, 116 (SD, 23) F: Mean, 146 (SD, 41) F-B: Mean, 30	B: Mean, 128 (SD, 29) F: Mean, 133 (SD, 28) F-B: Mean, 5 P: 0.02

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Targan, 1997[43]	Infliximab Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 2 wks	NA No	Incidence 6 / 28 (20%)	Incidence 1 / 24 (4%) P: NS
Targan, 1997[43]	Infliximab Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	CDAI (Remission: CDAI < 150) @ 12 wks	NA No	Incidence 7 / 28 (25%)	Incidence 2 / 25 (8%)
Targan, 1997[43]	Infliximab Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	Endoscopic healing (CDEIS) @ 4 wks	NA Yes	B: Mean, 13.3 (SE, 6.9) F: Mean, 5.2 (SE, 2.8) P: <0.01 F-B: Mean, -8.1	B: Mean, 8.4 (SE, 6.3) F: Mean, 7.5 (SE, 5.4) P: <0.01 F-B: Mean, -0.9
Targan, 1997[43]	Infliximab Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	HR QoL (IBDQ) @ 4 wks	NA No	B: Mean, 118 (SD, 28) F: Mean, 149 (SD, 35) F-B: Mean, 31	B: Mean, 128 (SD, 29) F: Mean, 133 (SD, 28) F-B: Mean, 5 P: 0.03
Campieri, 1997[68]	Budesonide + placebo Route: Oral + Oral Dose: 4.5 mg every 12 hrs + NA every 24 hrs	Prednisolone + placebo Route: Oral + Oral Dose: 40 mg daily + NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 2 wks	NA NR	Incidence 16 / 61 (27%)	Incidence 21 / 58 (37%)
Campieri, 1997[68]	Budesonide + placebo Route: Oral + Oral Dose: 4.5 mg every 12 hrs + NA every 24 hrs	Prednisolone + placebo Route: Oral + Oral Dose: 40 mg daily + NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 12 wks	NA NR	Incidence 31 / 61 (51%)	Incidence 31 / 58 (53%)
Campieri, 1997[68]	Budesonide + placebo Route: Oral + Oral Dose: 9 mg daily + NA every 24 hrs	Prednisolone + placebo Route: Oral + Oral Dose: 40 mg daily + NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 2 wks	NA NR	Incidence 28 / 58 (48%)	Incidence 21 / 58 (37%)
Campieri, 1997[68]	Budesonide + placebo Route: Oral + Oral Dose: 9 mg daily + NA every 24 hrs	Prednisolone + placebo Route: Oral + Oral Dose: 40 mg daily + NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 12 wks	NA NR	Incidence 34 / 58 (58%)	Incidence 31 / 58 (53%)
Candy, 1995[53]	Placebo + prednisolone Route: Oral + Oral Dose: NA + 1 mg/kg daily	Azathioprine + prednisolone Route: Oral + Oral Dose: 2.5 mg/kg daily + 1 mg/kg daily	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 19 / 30 (63%)	Incidence 24 / 33 (73%) P: 0.6
Candy, 1995[53]	Placebo + prednisolone Route: Oral + Oral Dose: NA + 1 mg/kg daily	Azathioprine + prednisolone Route: Oral + Oral Dose: 2.5 mg/kg daily + 1 mg/kg daily	CDAI (Remission: CDAI < 150) @ 60 wks	NA NA	Incidence 2 / 30 (7%)	Incidence 14 / 33 (42%) P: 0.001

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Candy, 1995[53]	Placebo + prednisolone Route: Oral + Oral Dose: NA + 1 mg/kg daily	Azathioprine + prednisolone Route: Oral + Oral Dose: 2.5 mg/kg daily + 1 mg/kg daily	CDAI (Remission: CDAI<175) @ 64 wks	NA Yes	Incidence 14 / 33 (42%) RR: 6.36 (1.6 to 25.7)	Incidence 2 / 30 (7%) P: 0.001
Gross, 1995[72]	(6)-Methylprednisolone Route: Oral Dose: 48 mg/d every 24 hrs	ASA (Salofalk) Route: Oral Dose: 1.5 g every 8 hrs	CDAI (Remission: CDAI<150 and 60-pt drop) @ 2 wks	NA Yes	Incidence 1 / 16 (8%)	Incidence 1 / 15 (8%)
Gross, 1995[72]	(6)-Methylprednisolone Route: Oral Dose: 48 mg/d every 24 hrs	ASA (Salofalk) Route: Oral Dose: 1.5 g every 8 hrs	CDAI (Remission: CDAI<150 and 60-pt drop) @ 8 wks	NA Yes	Incidence 9 / 16 (56.3%)	Incidence 6 / 15 (40%) P: 0.5867
Feagan, 1995[63]	Methotrexate + prednisone Route: IM + Oral Dose: 25 mg weekly	Placebo + prednisone Route: IM + Oral Dose: NA weekly + daily	CDAI (Remission: discontinuation of prednisone therapy and CDAI ≤ 150 pts) @ 16 wks	NA Yes	Incidence 37 / 94 (39%) RR: 1.95 (1.09 to 3.48) P: 0.025 vs. main	Incidence 9 / 47 (19%) P: 0.025
Feagan, 1995[63]	Methotrexate + prednisone Route: IM + Oral Dose: 25 mg weekly	Placebo + prednisone Route: IM + Oral Dose: NA weekly + daily	HR QoL (IBDQ) @ 2 wks	NA Yes	B: Mean, 162 F: Mean, 167 F-B: Mean, 5	B: Mean, 159 F: Mean, 161 F-B: Mean, 2
Feagan, 1995[63]	Methotrexate + prednisone Route: IM + Oral Dose: 25 mg weekly	Placebo + prednisone Route: IM + Oral Dose: NA weekly + daily	HR QoL (IBDQ) @ 16 wks	NA Yes	B: Mean, 162 (SE, 17) F: Mean, 169 (SE, 4) P: <.002 F-B: Mean, 7	B: Mean, 159 (SE, 5) F: Mean, 151 (SE, 6) P: <.002 F-B: Mean, -8
Tremaine, 1994[77]	Mesalamine (Asacol) Route: Oral Dose: 800 mg every 6 hrs	Placebo Route: Oral Dose: NA every 6 hrs	CDAI (Remission: CDAI<150 and 70 pt drop) @ 16 wks	NA Yes	Incidence 9 / 20 (45%)	Incidence 4 / 18 (22%)
Rutgeerts, 1994[69]	Prednisolone + placebo Route: Oral + Oral Dose: 40 mg every 24 hrs + NA daily	Budesonide + placebo Route: Oral + Oral Dose: 9 mg every 24 hrs	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 48 / 88 (56%)	Incidence 39 / 88 (45%) P: 0.22
Rutgeerts, 1994[69]	Prednisolone + placebo Route: Oral + Oral Dose: 40 mg every 24 hrs + NA daily	Budesonide + placebo Route: Oral + Oral Dose: 9 mg every 24 hrs	CDAI (Remission: CDAI < 150) @ 10 wks	NA Yes	Incidence 58 / 88 (66%)	Incidence 47 / 88 (53%) P: 0.12
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 7 / 67 (10%)	Incidence 7 / 66 (11%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 8 wks	NA Yes	Incidence 22 / 67 (33%)	Incidence 13 / 66 (20%) P: 0.13
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI >150 and 60-pt increase)	NA NA	Event rate 124 events	Event rate 39 events
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI >150 and 60-pt increase) @ 52 wks	NA NA	Incidence 23 / 33 (70%)	Incidence 24 / 36 (67%)
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 2 wks	NA Yes	B: Mean, 131 F: Mean, 142 F-B: Mean, 11	B: Mean, 130 F: Mean, 141 F-B: Mean, 11
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 8 wks	NA Yes	B: Mean, 131 F: Mean, 140 F-B: Mean, 9	B: Mean, 130 F: Mean, 141 F-B: Mean, 11
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 12 wks	NA NA	B: Mean, 185 (SD, 21) F: Mean, 170 (SD, 39) F-B: Mean, -15	B: Mean, 181 (SD, 19) F: Mean, 154 (SD, 35) F-B: Mean, -27
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 52 wks	NA NA	B: Mean, 185 (SD, 21) F: Mean, 156 (SD, 39) F-B: Mean, -29	B: Mean, 181 (SD, 19) F: Mean, 150 (SD, 38) F-B: Mean, -31
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI >150 and 60-pt increase)	NA NA	Event rate 178 days	Event rate 39 events / ds
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI >150 and 60-pt increase) @ 52 wks	NA NA	Incidence 22 / 36 (61%)	Incidence 24 / 36 (67%)
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 21 / 61 (34%)	Incidence 7 / 66 (11%)
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 8 wks	NA Yes	Incidence 31 / 61 (51%)	Incidence 13 / 66 (20%) P: <0.001
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 2 wks	NA Yes	B: Mean, 125 F: Mean, 157 P: 0.0002 F-B: Mean, 32	B: Mean, 130 F: Mean, 141 P: 0.0002 F-B: Mean, 11

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 8 wks	NA Yes	B: Mean, 125 F: Mean, 166 P: <0.001 F-B: Mean, 41	B: Mean, 130 F: Mean, 141 P: <0.001 F-B: Mean, 11
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 12 wks	NA NA	B: Mean, 184 (SD, 24) F: Mean, 172 (SD, 35) F-B: Mean, -12	B: Mean, 181 (SD, 19) F: Mean, 154 (SD, 35) F-B: Mean, -27
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 52 wks	NA NA	B: Mean, 184 (SD, 24) F: Mean, 161 (SD, 36) F-B: Mean, -23	B: Mean, 181 (SD, 19) F: Mean, 150 (SD, 38) F-B: Mean, -31
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 7.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 17 / 64 (27%)	Incidence 7 / 66 (11%)
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 7.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 8 wks	NA Yes	Incidence 28 / 64 (43%)	Incidence 13 / 66 (20%) P: 0.009
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 7.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 2 wks	NA Yes	B: Mean, 130 F: Mean, 155 P: 0.006 F-B: Mean, 25	B: Mean, 130 F: Mean, 141 P: 0.006 F-B: Mean, 11
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 7.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 8 wks	NA Yes	B: Mean, 130 F: Mean, 154 P: 0.012 F-B: Mean, 24	B: Mean, 130 F: Mean, 141 P: 0.012 F-B: Mean, 11
Ewe, 1993[54]	Azathioprine + prednisolone Dose: 2.5 mg/kg daily + 60 mg daily	Placebo + prednisolone Dose: 60 mg daily	CDAI (Remission: CDAI < 150)	NA NR	Incidence 16 / 21 (76%)	Incidence 8 / 21 (38%) P: 0.061
Malchow, 1984[64]	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: failure to fall to less than 150 points or rise to above 150) @ 104 wks	NA No	Incidence 25 / 42 (60%)	Incidence 32 / 42 (75%) P: ns
Malchow, 1984[64]	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: rise of CDAI to over 150 during the study period) @ 104 wks	NA No	Incidence 45 / 75 (60%)	P: NS

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Malchow, 1984[64]	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI not coming down to less than 150 even after 2 AP treatments) @ 104 wks	NA No	Incidence 56 / 75 (75%)	P: <0.05
Malchow, 1984[64]	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: increase to more than 150 or in patients with active disease at randomization did not fall to less than 150 after 2 AP treatments) @ 104 wks	NA No	Incidence 49 / 75 (65%)	P: <0.05
Malchow, 1984[64]	(6)-Methylprednisolone Route: IV Dose: 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: failure to fall to less than 150 points or rise to above 150) @ 104 wks	NA No	Incidence 25 / 38 (65%)	Incidence 32 / 42 (75%) P: ns
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: increase to more than 150 or in patients with active disease at randomization did not fall to less than 150 after 2 AP treatments) @ 104 wks	NA No	Incidence 40 / 75 (53%)	P: <0.001
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI not coming down to less than 150 even after 2 AP treatments) @ 104 wks	NA No	Incidence 49 / 75 (65%)	P: <0.001

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: rise of CDAI to over 150 during the study period.) @ 104 wks	NA No	Incidence 38 / 75 (50%)	P: NS
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: failure to fall to less than 150 points or rise to above 150) @ 104 wks	NA No	Incidence 23 / 38 (60%)	Incidence 32 / 42 (75%) P: <0.05
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI not coming down to less than 150 even after 2 AP treatments) @ 104 wks	NA No	Incidence 48 / 74 (65%)	P: <0.001
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: rise of CDAI to over 150 during the study period.) @ 104 wks	NA No	Incidence 48 / 74 (65%)	P: NS
Malchow, 1984[64]	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: increase to more than 150 or in patients with active disease at randomization did not fall to less than 150 after 2 AP treatments) @ 104 wks	NA No	Incidence 49 / 75 (65%)	Incidence 51 / 68 (75%)
Malchow, 1984[64]	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI not coming down to less than 150 even after 2 AP treatments) @ 104 wks	NA No	Incidence 56 / 75 (75%)	Incidence 61 / 68 (90%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Malchow, 1984[64]	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: rise of CDAI to over 150 during the study period.) @ 104 wks	NA No	Incidence 45 / 75 (60%)	Incidence 44 / 68 (65%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: increase to more than 150 or in patients with active disease at randomization did not fall to less than 150 after 2 AP treatments) @ 104 wks	NA No	Incidence 40 / 75 (53%)	Incidence 51 / 68 (75%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI not coming down to less than 150 even after 2 AP treatments) @ 104 wks	NA No	Incidence 49 / 75 (65%)	Incidence 61 / 68 (90%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: rise of CDAI to over 150 during the study period.) @ 104 wks	NA No	Incidence 38 / 75 (50%)	Incidence 44 / 68 (65%)
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: increase to more than 150 or in patients with active disease at randomization did not fall to less than 150 after 2 AP treatments) @ 104 wks	NA No	Incidence 23 / 38 (60%)	Incidence 51 / 68 (75%)
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: rise of CDAI to over 150 during the study period) @ 104 wks	NA No	Incidence 48 / 74 (65%)	Incidence 44 / 68 (65%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI not coming down to less than 150 even after 2 AP treatments) @ 104 wks	NA No	Incidence 48 / 74 (65%)	Incidence 61 / 68 (90%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: IV Dose: 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	CDAI (Relapse rate: failure to fall to less than 150 points or rise to above 150) @ 104 wks	NA No	Incidence 25 / 38 (65%)	Incidence 25 / 42 (60%)
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	CDAI (Relapse rate: failure to fall to less than 150 points or rise to above 150) @ 104 wks	NA No	Incidence 23 / 38 (60%)	Incidence 25 / 42 (60%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	CDAI (Relapse rate: increase to more than 150 or in patients with active disease at randomization did not fall to less than 150 after 2 AP treatments) @ 104 wks	NA No	Incidence 40 / 75 (53%)	Incidence 49 / 75 (65%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	CDAI (Relapse rate: CDAI not coming down to less than 150 even after 2 AP treatments) @ 104 wks	NA No	Incidence 49 / 75 (65%)	Incidence 56 / 75 (75%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	CDAI (Relapse rate: rise of CDAI to over 150 during the study period.) @ 104 wks	NA No	Incidence 38 / 75 (50%)	Incidence 45 / 75 (60%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	CDAI (Relapse rate: increase to more than 150 or in patients with active disease at randomization did not fall to less than 150 after 2 AP treatments) @ 104 wks	NA No	Incidence 23 / 38 (60%)	Incidence 49 / 75 (65%)
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	CDAI (Relapse rate: CDAI not coming down to less than 150 even after 2 AP treatments) @ 104 wks	NA No	Incidence 48 / 74 (65%)	Incidence 56 / 75 (75%)
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	CDAI (Relapse rate: rise of CDAI to over 150 during the study period.) @ 104 wks	NA No	Incidence 48 / 74 (65%)	Incidence 45 / 75 (60%)
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	(6)-Methylprednisolone Route: IV Dose: 48 mg every 24 hrs	CDAI (Relapse rate: failure to fall to less than 150 points or rise to above 150) @ 104 wks	NA No	Incidence 23 / 38 (60%)	Incidence 25 / 38 (65%)
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	CDAI (Relapse rate: increase to more than 150 or in patients with active disease at randomization did not fall to less than 150 after 2 AP treatments) @ 104 wks	NA No	Incidence 23 / 38 (60%)	Incidence 40 / 75 (53%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	CDAI (Relapse rate: rise of CDAI to over 150 during the study period.) @ 104 wks	NA No	Incidence 48 / 74 (65%)	Incidence 38 / 75 (50%)
Malchow, 1984[64]	Sulfasalazine + prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	CDAI (Relapse rate: CDAI not coming down to less than 150 even after 2 AP treatments) @ 104 wks	NA No	Incidence 48 / 74 (65%)	Incidence 49 / 75 (65%)
Present, 1980[60]	6-MP Route: Unknown Dose: 1.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Steroid free (stopping steroid use in patients) @ 104 wks	NA No	Incidence 24 / 44 (55%)	Incidence 14 / 39 (36%)
Singleton, 1979[75]	Sulfasalazine + prednisone Route: Oral + Unknown Dose: 1g per 15kg body weight to 5g max daily + daily	Placebo + prednisone Route: Unknown + Oral Dose: NA + daily	CDAI (Remission: CDAI < 150) @ 8 wks	NA NR	Incidence 25 / 43 (57%)	Incidence 35 / 46 (76%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs daily	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 5 / 74 (7%)	Incidence 4 / 77 (5%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs daily	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 11 / 74 (15%)	Incidence 17 / 77 (22%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs daily	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 39 / 74 (53%)	Incidence 38 / 77 (50%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs daily	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 33 / 74 (45%)	Incidence 23 / 77 (30%) P: 0.08
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs daily	Placebo Route: Oral Dose: NA	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 2 / 9 (22%)	Incidence 1 / 9 (11%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then dose of prednisone is 1/4mg/kg, if CDAI = 150-300 then prednisone was dosed at 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 11 / 85 (13%)	Incidence 4 / 77 (5%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 25 / 85 (29%)	Incidence 17 / 77 (22%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 66 / 85 (78%)	Incidence 38 / 77 (50%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 51 / 85 (60%)	Incidence 23 / 77 (30%) P: <0.0001
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then dose of prednisone is 1/4mg/kg, if CDAI = 150-300 then prednisone was dosed at 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 3 / 10 (30%)	Incidence 1 / 9 (11%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 13 / 59 (22%)	Incidence 17 / 77 (22%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 1 / 59 (2%)	Incidence 4 / 77 (5%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 25 / 59 (43%)	Incidence 23 / 77 (30%) P: 0.17
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 32 / 59 (55%)	Incidence 38 / 77 (50%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 1 / 8 (12%)	Incidence 1 / 9 (11%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 25 / 85 (29%)	Incidence 11 / 74 (15%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 11 / 85 (13%)	Incidence 5 / 74 (7%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 66 / 85 (78%)	Incidence 39 / 74 (53%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 51 / 85 (60%)	Incidence 33 / 74 (45%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 3 / 10 (30%)	Incidence 2 / 9 (22%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 1 / 59 (2%)	Incidence 5 / 74 (7%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 13 / 59 (22%)	Incidence 11 / 74 (15%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 25 / 59 (43%)	Incidence 33 / 74 (45%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 32 / 59 (55%)	Incidence 39 / 74 (53%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 1 / 8 (12%)	Incidence 2 / 9 (22%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 13 / 59 (22%)	Incidence 25 / 85 (29%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	CDAI (Remission: CDAI < 150) @1 wk	NA Yes	Incidence 1 / 59 (2%)	Incidence 11 / 85 (13%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 25 / 59 (43%)	Incidence 51 / 85 (60%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	CDAI (Remission: CDAI < 150) @ 17 wks	NA No	Incidence 32 / 59 (55%)	Incidence 66 / 85 (78%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 then 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 1 / 8 (12%)	Incidence 3 / 10 (30%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
O'Donoghue, 1978[100]	Azathioprine Route: Oral Dose: 2 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	(Relapse rate: Cumulative probability of relapse after 6 mos relapse clinically defined) @ 24 wks	NA No	G1-G2: Mean, 0%	G1-G2: Mean, 25% P: <0.01
O'Donoghue, 1978[100]	Azathioprine Route: Oral Dose: 2 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	(Relapse rate: Cumulative probability of relapse after 6 mos relapse clinically defined) @ 52 wks	NA No	G1-G2: Mean, 5%	G1-G2: Mean, 41% P: <0.01
O'Donoghue, 1978[100]	Azathioprine Route: Oral Dose: 2 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Unnamed disease activity score (Score change from baseline) @ 52 wks	NA No	F-B: Mean, 0.63 P: <0.05 G1-G2: 1.8	F-B: Mean, 2.46 G1-G2: 1.8
Klein, 1974[62]	Azathioprine Route: Oral Dose: 3 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Reduction of steroids (reduction in the average dose of prednisone) @ 16 wks	NA No	B: Mean, 13.3 (SD, 3.5) F: Mean, 6.3 (SD, 1.6) F-B: Mean, -7	B: Mean, 19.8 (SD, 5.9) F: Mean, 7.8 (SD, 3) F-B: Mean, -12
Klein, 1974[62]	Azathioprine Route: Oral Dose: 3 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Reduction of steroids (reduction in the dose of prednisone) @ 32 wks	NA No	B: Mean, 4.4 F: Mean, 1.7 F-B: Mean, -2.7	B: Mean, 5.2 F: Mean, 5 F-B: Mean, -0.2
Klein, 1974[62]	Azathioprine Route: Oral Dose: 3 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	HR QoL (subjective feeling of improvement) @ 16 wks	NA No	Incidence 6 / 13 (46%)	Incidence 6 / 13 (46%)
Klein, 1974[62]	Azathioprine Route: Oral Dose: 3 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	HR QoL (subjective feeling of no change) @ 16 wks	NA No	Incidence 5 / 13 (38%)	Incidence 5 / 13 (38%)
Rhodes, 1971[61]	Azathioprine Route: Oral Dose: 4 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	HR QoL (Subjective feeling of being better after treatment) @ 8 wks	NA NR	Incidence 0 / 8 (0%)	Incidence 0 / 7 (0%)

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Rhodes, 1971[61]	Azathioprine Route: Oral Dose: 4 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	HR QoL (subjective feeling of being worse after treatment) @ 8 wks	NA No	Incidence 2 / 8 (25%)	Incidence 1 / 7 (14%)
Rhodes, 1971[61]	Azathioprine Route: Oral Dose: 4 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	HR QoL (Subjective feeling of 'No difference' after treatment) @ 8 wks	NA No	Incidence 6 / 8 (75%)	Incidence 6 / 7 (86%)
Singleton, 1993[79]	Mesalamine (Pentasa) Route: Oral Dose: 1 g daily	Placebo Route: Oral Dose: NA daily	CDAI (Remission: 50-point drop and a final CDAI < 151) @ 16 wks	NA Yes	Incidence 18 / 80 (23%)	Incidence 14 / 80 (18%)
Singleton, 1993[79]	Mesalamine (Pentasa) Route: Oral Dose: 1 g daily	Placebo Route: Oral Dose: NA daily	HBI (Absolute HBI) @ 16 wks	NA Yes	F-B: Mean, -0.4 (SE, 0.5)	F-B: Mean, -0.9 (SE, 0.5) G1-G2: -0.5 P: NS
Singleton, 1993[79]	Mesalamine (Pentasa) Route: Oral Dose: 2 g daily	Placebo Route: Oral Dose: NA daily	CDAI (Remission: 50-point drop and a final CDAI < 151) @ 16 wks	NA Yes	Incidence 18 / 75 (24%)	Incidence 14 / 80 (18%) P: NS
Singleton, 1993[79]	Mesalamine (Pentasa) Route: Oral Dose: 2 g daily	Placebo Route: Oral Dose: NA daily	HBI (Absolute HBI) @ 16 wks	NA Yes	F-B: Mean, -1.2 (SE, 0.5)	F-B: Mean, -0.9 (SE, 0.5) G1-G2: 0.3 P: NS
Singleton, 1993[79]	Mesalamine (Pentasa) Route: Oral Dose: 4 g daily	Placebo Route: Oral Dose: NA daily	CDAI (Remission: 50-point drop and a final CDAI < 151) @ 16 wks	NA Yes	Incidence 32 / 75 (43%)	Incidence 14 / 80 (18%) P: 0.0017
Singleton, 1993[79]	Mesalamine (Pentasa) Route: Oral Dose: 4 g daily	Placebo Route: Oral Dose: NA daily	HBI (Absolute HBI) @ 16 wks	NA Yes	F-B: Mean, -2.8 (SE, 0.5)	F-B: Mean, -0.9 (SE, 0.5) G1-G2: 1.9 P: 0.0054
Present, 1999[44]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV	Perianal disease (Perianal disease activity index) @ 2 wks	NA No	B: Median, 8 (IQR, 7 to 10) F: Median, 6 (IQR, 3 to 7) P: 0.02	B: Median, 9 (IQR, 7 to 10.5) F: Median, 8 (IQR, 6 to 10) P: 0.02
Present, 1999[44]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV	Perianal disease (Perianal Disease Activity Index) @ 18 wks	NA No	B: Median, 8 (IQR, 7 to 10) F: Median, 4 (IQR, 1 to 7) P: 0.05	B: Median, 9 (IQR, 7 to 10.5) F: Median, 7 (IQR, 4 to 9) P: 0.05

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Present, 1999[44]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV	Perianal disease (50% fistula closure) @ 18 wks	NA Yes	Incidence 21 / 31 (68%)	Incidence 8 / 31 (26%) P: 0.002
Present, 1999[44]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV	Perianal disease (Complete fistula closure) @ 18 wks	NA Yes	Incidence 17 / 31 (55%)	Incidence 4 / 31 (13%) P: 0.001
Present, 1999[44]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV	Perianal disease (Perianal disease activity index) @ 2 wks	NA No	B: Median, 10 (IQR, 8 to 12) F: Median, 6 (IQR, 4 to 8) P: 0.04	B: Median, 9 (IQR, 7 to 10.5) F: Median, 8 (IQR, 6 to 10) P: 0.04
Present, 1999[44]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV	Perianal disease (Perianal Disease Activity Index) @ 18 wks	NA No	B: Median, 10 (IQR, 8 to 12) F: Median, 5 (IQR, 3 to 8) P: 0.14	B: Median, 9 (IQR, 7 to 10.5) F: Median, 7 (IQR, 4 to 9) P: 0.14
Present, 1999[44]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV	Perianal disease (50% fistula closure) @ 18 wks	NA Yes	Incidence 18 / 31 (58%)	Incidence 8 / 31 (26%) P: 0.02
Present, 1999[44]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV	Perianal disease (Complete fistula closure) @ 18 wks	NA Yes	Incidence 12 / 32 (38%)	Incidence 4 / 31 (13%) P: 0.04
Martin F, 1990[73]	Prednisone Route: Oral Dose: 40 mg every 24 hrs	ASA (Salofalk) Route: Oral Dose: 250 mg every 8 hrs	CDAI (Remission: CDAI < 150) @ 12 wks	NA No	Incidence 12 / 26 (46%)	Incidence 9 / 19 (47%)
Martin F, 1990[73]	Prednisone Route: Oral Dose: 40 mg every 24 hrs	ASA (Salofalk) Route: Oral Dose: 250 mg every 8 hrs	HR QoL (McMaster University quality of life index) @ 2 wks	NA No	G1-G2: Mean, 24	G1-G2: Mean, 6 P: <0.005
Martin F, 1990[73]	Prednisone Route: Oral Dose: 40 mg every 24 hrs	ASA (Salofalk) Route: Oral Dose: 250 mg every 8 hrs	HR QoL (McMaster University Quality of life index) @ 12 wks	NA NA	G1-G2: Mean, 38	G1-G2: Mean, 36 P: NS
Martin F, 1990[73]	Prednisone Route: Oral Dose: 40 mg every 24 hrs	ASA (Salofalk) Route: Oral Dose: 250 mg every 8 hrs	HR QoL (McMaster University Quality of life - Bowel symptoms) @ 12 wks	NA NA	G1-G2: Mean, 38	G1-G2: Mean, 38 P: NS
Martin F, 1990[73]	Prednisone Route: Oral Dose: 40 mg every 24 hrs	ASA (Salofalk) Route: Oral Dose: 250 mg every 8 hrs	HR QoL (McMaster University Quality of life index - Emotional function) @ 12 wks	NA No	G1-G2: Mean, 26	G1-G2: Mean, 26 P: NS

Evidence Table 4. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Martin F, 1990[73]	Prednisone Route: Oral Dose: 40 mg every 24 hrs	ASA (Salofalk) Route: Oral Dose: 250 mg every 8 hrs	HR QoL (McMaster University Quality of life index - Social Function) @ 12 wks	NA No	G1-G2: Mean, 38	G1-G2: Mean, 44 P: NS
Martin F, 1990[73]	Prednisone Route: Oral Dose: 40 mg every 24 hrs	ASA (Salofalk) Route: Oral Dose: 250 mg every 8 hrs	HR QoL (McMaster University Quality of life index - systemic symptoms) @ 2 wks	NA No	G1-G2: Mean, 42	G1-G2: Mean, 2 P: <0.05
Martin F, 1990[73]	Prednisone Route: Oral Dose: 40 mg every 24 hrs	ASA (Salofalk) Route: Oral Dose: 250 mg every 8 hrs	HR QoL (McMaster University Quality of life index - systemic symptoms) @ 12 wks	NA No	G1-G2: Mean, 50	G1-G2: Mean, 48 P: NS
Schreiber, 2011[42]	Certolizumab pegol Route: SC Dose: 400 mg sc once	Placebo	Remission (CDAI < 150) @ 2 wks	NA Yes	Incidence 50 / 215 (23%)	Incidence 33 / 209 (16%) P = 0.03
Schreiber, 2011[42]	Certolizumab pegol Route: SC Dose: 400 mg sc once	Placebo	HR QoL (IBDQ Remission) @ 2 wsks	NA Yes	55 / 215 (26%)	38 / 209 (18%) P = 0.059

Abbreviations: 95% CI = 95% Confidence Interval; 6-MP = 6-Mercaptopurine; @ = at; AP = Acute Phase; ASA = Aminosalicylates; CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity; g = gram; g/kgs = gram/kilograms; HBI = Harvey-Bradshaw Index; HR QoL= Health-related Quality of Life; hrs = hours; IBDQ = Inflammatory Bowel Disease Questionnaire; IFX= Infliximab; IM = intramuscular; IV= intravenous; IQR= inter-quartile range; kg = kilogram; Max. = maximum; mg = milligram; mg/d = milligram/day; mg/kg = milligram/kilogram; mg/mo = milligram/month; Min. = minimum; Mo/mos= month(s); NA = Not Applicable; NR= Not Reported; NS = not significant; OR: Odds Ratio; PGWB = Psychological General Well-Being; P = p-value; pt = point; SES-CD = Simplified Endoscopic Activity Score for Crohn's Disease; SC = subcutaneous; SD = standard deviation; SE= standard error; Steroid free = steroid-free remission; TNF = tumor necrosis factor; TPMT= thiopurine methyltransferase; UTD = unable to determine; and wks = weeks.

Evidence Table 5. Quality of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Randomized controlled trials evaluating biologics								
Colombel, 2010[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
D'Haens, 2008[48]	Yes	Yes	No	Unclear	No	Yes	No	Poor
Gordon, 2001[34]	Unclear	Yes	Yes	Yes	No	Yes	Yes	Poor
Hanauer, 2006[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Lemann, 2006[46]	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
Present, 1999[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Sandborn, 2005[33]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Fair
Sandborn, 2007[39]	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor
Sandborn, 2007[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Sands, 2007[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Schreiber, 2005[40]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Fair
Schreiber, 2011[42]	Yes	Yes	Yes	Unclear	No	Yes	Yes	Fair
Schroder, 2006[47]	Unclear	Unclear	No	Unclear	No	No	No	Poor
Targan, 1997[43]	Yes	Yes	Yes	Unclear	No	Yes	Yes	Fair
Targan, 2007[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Winter, 2004[41]	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Fair
Randomized controlled trials evaluating thiopurines								
Ardizzone, 2003[58]	Yes	Yes	No	Yes	Yes	UTD	NA	Good
Candy, 1995[53]	Unclear	Yes	Unclear	Unclear	Yes	UTD	NA	Fair
Ewe, 1993[54]	Unclear	Unclear	Unclear	Yes	Yes	Yes	UTD	Poor
Klein, 1974[62]	Unclear	Unclear	Yes	Yes	Unclear	Yes	UTD	Fair

Evidence Table 5. Quality of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Lemann, 2006[46]	Yes	Yes	Yes	Yes	Yes	Yes	UTD	Good
Markowitz, 2000[192]	Yes	Yes	Yes	Yes	Yes	No	NA	Good
Mate-Jimenez, 2000[52]	Unclear	Unclear	Unclear	Yes	Yes	No	NA	Good
O'Donoghue, 1978[100]	Unclear	Unclear	Yes	Yes	Yes	UTD	NA	Good
Oren, 1997[57]	Unclear	Unclear	Yes	Yes	Unclear	No	NA	Fair
Present, 1980[60]	Yes	Unclear	Unclear	No	No	UTD	UTD	Poor
Reinisch, 2008[51]	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Fair
Rhodes, 1971[61]	Unclear	Unclear	Yes	Yes	No	Yes	UTD	Poor
Sandborn, 1999[59]	Yes	Yes	Yes	Unclear	Yes	UTD	NA	Fair
Summers, 1979[56]	Yes	Yes	No	Yes	No	Yes	NA	Fair
Randomized controlled trials evaluating methotrexate								
Feagan, 1995[63]	Unclear	Unclear	Yes	Yes	Unclear	Yes	No	Fair
Mate-Jimenez, 2000[52]	Unclear	Unclear	Unclear	Yes	Yes	No	NA	Good
Oren, 1997[57]	Unclear	Unclear	Yes	Yes	Unclear	No	NA	Fair
Randomized controlled trials evaluating corticosteroids								
Bar-Meir, 1998[67]	Yes	Yes	Yes	Yes	No	UTD	NA	Good
Campieri, 1997[68]	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Fair
Escher, 2004[190]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Greenberg, 1994[66]	Unclear	Unclear	Unclear	Unclear	No	Yes	Yes	Fair
Gross, 1995[72]	Unclear	Yes	Yes	Yes	No	Yes	UTD	Poor
Levine, 2003[191]	Unclear	Unclear	Unclear	Unclear	Unclear	UTD	NA	Poor
Malchow, 1984[64]	Unclear	Yes	Yes	No	No	Yes	UTD	Fair

Evidence Table 5. Quality of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of inducing remission (KQ1)

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Martin F, 1990[73]	Yes	Yes	Yes	Yes	Yes	UTD	NA	Good
Prantera, 1999[71]	Yes	Yes	Yes	Yes	Unclear	No	NA	Fair
Rutgeerts, 1994[69]	Yes	Yes	Yes	Yes	Yes	Yes	UTD	Good
Schoon, 2005[185]	Yes	Yes	No	Yes	No	Yes	Yes	Poor
Singleton, 1979[75]	Unclear	Unclear	Yes	Yes	Yes	No	NA	Good
Summers, 1979[56]	Yes	Yes	No	Yes	No	Yes	NA	Fair
Thomsen, 1998[70]	Yes	Yes	Yes	No	No	Yes	Yes	Poor
Tremaine, 2002[65]	Yes	Yes	Yes	No	No	Yes	Yes	Poor
Randomized controlled trials evaluating 5-aminosalicylate acids								
Griffiths, 1993[221]	Yes	Unclear	Yes	No	Yes	Yes	UTD	Fair
Malchow, 1984[64]	Unclear	Yes	Yes	No	No	Yes	UTD	Fair
Singleton, 1993[79]	Unclear	Unclear	Yes	Yes	Yes	UTD	NA	Good
Singleton, 1995[222]	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Fair
Summers, 1979[56]	Yes	Yes	No	Yes	No	Yes	NA	Fair
Tremaine, 1994[77]	Unclear	Unclear	Yes	Yes	Yes	Yes	UTD	Fair

Abbreviations: NA = not applicable; UTD = unable to determine

*Study Quality Criteria: Criteria for a judgment of "GOOD" (i.e. low risk of bias): These studies have the least bias and results are considered valid- A study that adheres mostly to the commonly held concepts of high quality including the following: a) A formal randomized controlled study; b)Clear description of the population, setting, interventions, and comparison groups; c) Appropriate measurements of outcomes; d) Appropriate statistical and analytic methods and reporting; e) No reporting errors; f) Low dropout rate; and g) Clear reporting of dropouts. Criteria for a judgment of "FAIR": a) These studies are susceptible to some bias, but it is not sufficient to invalidate the results; b) do not meet all the criteria required for a rating of good qualities because they have some deficiencies, but no flaw is likely to cause major bias; and c) The study may be missing information, making it difficult to assess limitations and potential problems. Criteria for a judgment of "POOR" (i.e. high risk of bias): a) These studies have significant flaws that imply biases of various types that may invalidate the results; b) Have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Evidence Table 6. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for maintenance of remission (KQ2)

Comparison	Outcome	Number of trials (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Natalizumab vs. placebo–wk 48	Disease activity measures	1 (339)[33]	Medium	Unknown (single study)	Direct	Precise	Favors natalizumab RD, 33%; placebo rate, 22% SOE: Moderate
Natalizumab vs. placebo–wk 48	Reduction of steroids	1 (143)[33]	Medium	Unknown (single study)	Direct	Precise	Favors natalizumab RD, 27%; placebo rate, 15% SOE: Moderate
Natalizumab vs. placebo–wk 48	Patient-reported outcomes	1 (217)[81]	Medium	Unknown (single study)	Direct	Precise	Favors natalizumab Absolute between-group difference in change in mean IBDQ from randomization to induction trial, 19 pts; placebo change in mean IBDQ, -23 pts SOE: Moderate
Adalimumab vs. placebo–wk 52	Disease activity measures	2 (554)[82 83 95]	High	Consistent	Direct	Precise	Favors adalimumab RD range, 11% to 39%; placebo rate range, 12% to 44% SOE: Low
Adalimumab vs. placebo–wk 52	Hospitalization	1 (778)[90]	Medium	Unknown (single study)	Direct	Precise	Favors adalimumab for all-cause hospitalizations Favors neither for Crohn's disease related hospitalizations RD range, -6% to -13%; placebo rate range, 16% to 25% SOE: Moderate
Adalimumab vs. placebo–wk 52	Surgery	1 (778)[90]	Medium	Unknown (single study)	Direct	Precise	Favors neither RD, -3.4%; placebo rate, 3.8% SOE: Moderate
Adalimumab vs. placebo–wk 52	Reduction of steroids	2 (219)[82 83]	High	Consistent	Direct	Precise	Favors adalimumab RD, 10% to 31%; placebo rate, 6% to 57% SOE: Low

Evidence Table 6. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for maintenance of remission (KQ2)

Comparison	Outcome	Number of trials (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Adalimumab vs. placebo–wk 52	Patient-reported outcomes	2 (554)[95 96]	High	Consistent	Direct	Precise	Favors neither Absolute between-group difference in change in mean IBDQ from randomization, 14 to 22 pts; placebo mean change, -10 to -25 pts SOE: Low
CP vs. placebo–wk 18	Disease activity measures	1 (428)[84]	Medium	Unknown (single study)	Indirect	Precise	Favors CP RD, 19%; placebo rate, 29% SOE: Low
CP vs. placebo–wk 18	Patient-reported outcomes	1 (424)[84]	Medium	Unknown (single study)	Indirect	Precise	Favors neither Difference in final adjusted mean IBDQ, 8 pts; final placebo mean, 163 pts SOE: Low
Infliximab vs. placebo–wk 52	Disease activity measures	1 (573)[86 94]	High	Unknown (single study)	Direct	Imprecise	Favors neither among all randomized Favors infliximab among responders to induction RD range, 6% to 25%; placebo rate, 15% to 35% SOE: Low
Infliximab vs. placebo–wk 52	Mucosal healing	1(58)[91 94]	High	Unknown (single study)	Direct	Precise	Favors infliximab RD, 26% to 43%; placebo rate, 7% to 18% SOE: Low
Infliximab vs. placebo–wk 40, 52	Hospitalization	2 (855)[92 94]	Medium	Consistent	Direct	Precise	Favors infliximab Crohn's disease-related hospitalizations per 100 patients, 9 to 23 in infliximab group, 19 to 38 in placebo group SOE: Moderate

Evidence Table 6. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for maintenance of remission (KQ2)

Comparison	Outcome	Number of trials (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Infliximab vs. placebo–wk 52	Surgery	1 (573)[94]	Medium	Unknown (single study)	Direct	Precise	Favors neither Rate of Crohn's disease-related surgery, 3%; placebo rate, 8% SOE: Moderate
Infliximab vs. placebo (patients with fistulas) –wk 40	Surgery	1 (195)[92]	Medium	Unknown (single study)	Direct	Precise	Favors infliximab Rate of Crohn's disease-related surgery per 100 patients, 65; placebo rate per 100 patients, 126 SOE: Moderate
Infliximab vs. placebo–wk 52	Reduction of steroids	1 (325)[86]	High	Unknown (single study)	Direct	Precise	Favors infliximab RD, 20%; placebo rate, 9% SOE: Low
Infliximab vs. placebo–wk 40	Fistula response	1 (282)[87]	Medium	Unknown (single study)	Indirect	Precise	Favors infliximab RD, 17%; placebo rate, 19% SOE: Low
Infliximab vs. placebo–wks 36-52	Patient-reported outcomes	3 (603)[85 87 93]	High	Inconsistent	Direct	Imprecise	Favors infliximab Absolute between-group difference in change in median IBDQ -5 to 23 pts; placebo mean change, -31 to 9 pts SOE: Low
Infliximab + azathioprine vs. infliximab–wk 104	Disease activity measures	1 (80)[89]	High	Unknown (single study)	Direct	Imprecise	Favors neither Absolute difference [with regard to need for infliximab stoppage or change in dosage interval], 5%; infliximab alone rate, 55% SOE: Low
Infliximab + azathioprine vs. infliximab–wk 104	Mucosal healing	1 (49)[89]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD for absence of ulcers, 3%; infliximab alone rate, 61% SOE: Low

Evidence Table 6. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for maintenance of remission (KQ2)

Comparison	Outcome	Number of trials (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Infliximab + azathioprine vs. infliximab–wk 104	Patient-reported outcomes	1 (80)[89]	High	Unknown (single study)	Direct	Imprecise	Favors neither Difference in overall median IBDQ, -2 pts; infliximab only median, 176 pts SOE: Low
Infliximab + azathioprine vs. infliximab + hydrocortisone IV premedication–wk 52, 104	Disease activity measures	1 (46)[88]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD across time points, -5%; infliximab and hydrocortisone rate range, 77% to 84% SOE: Low
Azathioprine (1 mg/kg/d) vs. placebo - wks 52, 104	Disease activity measures	1 (155)[56]	Medium	Unknown (single study)	Direct	Imprecise	Favors neither RD, -11 to 5%; placebo rate, 40 to 64% SOE: Low
Azathioprine (1.7 to 2.1 mg/kg/d) vs. placebo - wks 52, 78, 104	Disease activity measures	3 (163)[98 100 101]	Medium	Inconsistent	Direct	Imprecise	Favors azathioprine RD, 13 to 39%; placebo rate, 47 to 79% SOE: Low
Azathioprine vs. placebo - wk 26	Reduction of steroids	1 (20)[104]	Medium	Unknown (single study)	Indirect	Precise	Favors azathioprine Absolute reduction in prednisone use from baseline, 9.4 mg; placebo reduction, 6.1 mg SOE: Low
Azathioprine vs. budesonide - wk 52	Disease activity measures	1 (77)[102]	Medium	Unknown (single study)	Direct	Imprecise	Favors azathioprine RD, 15%; budesonide rate, 64% SOE: Low
Azathioprine vs. prednisone - wk 52	Disease activity measures	1 (115)[56]	High	Unknown (single study)	Direct	Imprecise	Favors azathioprine RD, 12%; prednisone rate, 57% SOE: Low

Evidence Table 6. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for maintenance of remission (KQ2)

Comparison	Outcome	Number of trials (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Azathioprine vs. prednisone - wk 104	Disease activity measures	1 (115)[56]	High	Unknown (single study)	Direct	Imprecise	Favors neither Wk 104: RD, -3%; corticosteroid rate, 32% SOE: Low
Azathioprine vs. budesonide - wk 52	Mucosal healing	1 (77)[102]	Medium	Unknown (single study)	Direct	Precise	Favors azathioprine RD for absence of ulcers, 55%; budesonide rate, 5% SOE: Moderate
Azathioprine vs. sulfasalazine - wks 52, 104	Disease activity measures	1 (115)[56]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD range, -2% to 7%; sulfasalazine rate range, 31% to 62% SOE: Low
Methotrexate (intramuscular) vs. placebo – wk 40	Disease activity measures	1 (76)[105]	Medium	Unknown (single study)	Indirect	Precise	Favors methotrexate RD, 26%; placebo rate, 39% SOE: Low
Budesonide vs. placebo--wk 52	Disease activity measures	5 (557)[106 108-111]	Medium	Inconsistent	Direct	Imprecise	Favors neither 3mg pooled RR, 1.0; CI, 0.8 to 1.2; placebo rate, 33% to 40% 6mg pooled RR, 1.2; CI, 0.9 to 1.5; placebo rate, 33% to 42% SOE: Low
Budesonide vs. placebo--wks 13 and 52	Patient-reported outcomes	2 (122)[107 111]	Medium	Consistent	Direct	Imprecise	Favors neither Absolute between-group difference in change in mean IBDQ from baseline, 2 to 11 pts; placebo mean change, -4 to -31 pts SOE: Low

Evidence Table 6. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for maintenance of remission (KQ2)

Comparison	Outcome	Number of trials (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Prednisone vs. placebo--wks 54 and 104	Disease activity measures	1 (162)[56]	High	Unknown (single study)	Direct	Imprecise	Neither favored RD across time points, 0% to 9%; placebo rate, 59% to 72% SOE: Low
6-methylprednisolone vs. placebo--wks 54 and 104	Disease activity measures	1 (118)[64]	High	Unknown (single study)	Direct	Imprecise	Favors 6-methylprednisolone RD across time points, 11% to 12%; placebo rate, 32% to 48% SOE: Low
Budesonide vs. mesalamine--wk 52	Disease activity measures	1 (57)[113]	Medium	Unknown (single study)	Direct	Precise	Favors budesonide RD, 27%; mesalamine rate, 18% SOE: Moderate
Budesonide vs. mesalamine--wk 52	Patient-reported outcomes	1 (57)[113]	Medium	Unknown (single study)	Direct	Precise	Favors budesonide Absolute between-group difference in change in mean IBDQ, 30 to 36 pts; mesalamine mean change, -51 to -76 pts SOE: Moderate
Prednisone or 6-methylprednisolone vs. sulfasalazine --wks 54, 104	Disease activity measures	2 (248)[56 64]	High	Consistent	Direct	Imprecise	Favors neither RD across time points, 5% to 9%; ASA rate, 37% to 67% SOE: Low
6-methylprednisolone + sulfasalazine vs. placebo--wks 54, 104	Disease activity measures	1 (108)[64]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD across time points, 2% to 5%; placebo rate, 32% to 48% SOE: Low
Steroids + sulfasalazine vs. steroids--wks 26-54, 104	Disease activity measures	2 (181)[64 75]	Medium	Inconsistent	Direct	Imprecise	Favors neither RD across time points, -9% to -6%; steroid rate, 22% to 60% SOE: Low

Evidence Table 6. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for maintenance of remission (KQ2)

Comparison	Outcome	Number of trials (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
6-methylprednisolone + sulfasalazine vs. sulfasalazine--wks 54, 104	Disease activity measures	1(119)[64]	High	Unknown (single study)	Direct	Imprecise	Favors neither RD, -3% to -2%; sulfasalazine rate, 37% to 55% SOE: Low
Mesalamine (controlled-release) vs. placebo—wks 48, 52	Disease activity measures	2 (309)[117 119]	High	Consistent	Direct	Imprecise	Favors mesalamine (controlled-release) RD, 7 to 11%; placebo rate, 22 to 58% SOE: Low
Mesalamine (controlled-release) vs. placebo—wk 104	Disease activity measures	1 (161)[122]	Low	Unknown (single study)	Direct	Imprecise	Favors neither RD, 6%; placebo rate, 58% SOE: Moderate
Mesalamine (controlled-release), vs. placebo--wk 48	Patient-reported outcomes	1 (246)[117]	Medium	Unknown (single study)	Direct	Imprecise	Favors neither Absolute between-group difference in change in mean IBDQ, 1 pt; placebo mean change, -14 pts SOE: Low
Mesalamine (pH-release) vs. placebo—wk 52	Disease activity measures	7 (756)[115 118 120 121 123 125 126]	Medium	Inconsistent	Direct	Precise	Favors mesalamine (pH-release) RR, 1.1; 95% CI, 1.0 to 1.3 SOE: Low
Mesalamine (pH-release) vs. placebo—wk 104	Disease activity measures	1 (117)[118]	High	Unknown (single study)	Direct	Imprecise	Favors placebo RD, -17%; placebo rate, 42% SOE: Low
Mesalamine (pH-release) vs. placebo—wk 208	Disease activity measures	1 (59)[121]	Medium	Unknown (single study)	Direct	Imprecise	Favors mesalamine (pH-release) RD, 18%; placebo rate, 29% SOE: Low

Evidence Table 6. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for maintenance of remission (KQ2)

Olsalazine vs. placebo—wk 52	Disease activity measures	1 (328)[116]	Low	Unknown (single study)	Direct	Imprecise	Favors neither RD, 2%; placebo rate, 74% SOE: Moderate
Sulfasalazine vs. placebo—wks 54, 104	Disease activity measures	2 (274)[56 64]	High	Inconsistent	Direct	Imprecise	Favors neither RD, -5 to 7%; placebo rate, 32 to 72% SOE: Low

Abbreviations: ASA = aminosalicylates; CI = 95% confidence interval; CP = certolizumab pegol; HR = hazard ratio; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; mg = milligrams; NA = not applicable; OR = odds ratio; pts = points; RD = risk difference; RR = relative risk; SOE = strength of evidence; Steroids = corticosteroids; vs = versus; wk = weeks

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Evidence Table 7. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Randomized controlled trials evaluating biologics					
Colombel, 2007[82]	RCT, parallel arms with a 4-week run-in period	Start year: 2003 Duration of assigned treatment: 52 weeks	US, North America, Europe, Australia, Africa Multicenter	No	Adults, CD only, CDAI (220-450), no use of adalimumab, moderate-severe disease, not pregnant, not nursing, using adequate contraception, no short bowel syndrome, no ostomy, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, no cancer, other criteria
Feagan, 2007[81]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 48 weeks	US, North America, Europe, Australia, Africa Multicenter	No	Adults, CD only, CDAI (<220), no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, other criteria
Feagan, 2008[90]	RCT, parallel arms with a 4-week run-in period	Start year: 2003 Duration of assigned treatment: 52 weeks	US, North America, Europe Multicenter	No	Adults, CD only, no previous surgery (bowel resection in past 6 months), CDAI (220-450), no use of adalimumab, moderate-severe disease, not pregnant, not nursing, using adequate contraception, no short bowel syndrome, no ostomy, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, no cancer, other criteria
Hanauer, 2002[86]	RCT, parallel arms with a 2-week run-in period	Start year: 1999 Duration of assigned treatment: 52 weeks	US, North America, Europe, Israel Multicenter	No	Adults, CD only, CDAI (220-400), previous use of antibiotics, 5-aminosalicylate acids, corticosteroids, thiopurines, methotrexate, no use of TNF-alpha inhibitors, infliximab, other criteria
Mantzaris, 2009[88]	RCT, parallel arms with a 6-week run-in period	Start year: NR Duration of assigned treatment: 2 years	Europe Number of centers NR	Yes Yes	Adults, CD only, CDAI (>180), active disease, not pregnant, not nursing, no history of TB, other criteria
Rutgeerts, 1999[85]	RCT, parallel arms with a 16-week run-in period	Start year: 1995 Duration of assigned treatment: 36 weeks	US, North America, Europe Multicenter	Yes Yes	Adults, CD only, no previous surgery (proctocolectomy or total colectomy), CDAI (220-400), no ostomy, no obstructive symptoms with strictures, other criteria

Evidence Table 7. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Sandborn, 2007[83]	RCT, parallel arms with a 4-week run-in period	Start year: 2002 Duration of assigned treatment: 52 weeks	US, North America, Europe Multicenter	No	Adults, CD only, CDAI (<150), in remission for >4 weeks, inactive disease, using adequate contraception, other criteria
Sands, 2004[87]	RCT, parallel arms with a 14-week run-in period	Start year: 2000 Duration of assigned treatment: 40 weeks	US, North America, Europe, Israel Multicenter	No	Adults, CD only, no use of infliximab, no abscess, no obstructive symptoms with strictures, other criteria
Schreiber, 2007[84]	RCT, parallel arms with a 6-week run-in period	Start year: 2004 Duration of assigned treatment: 18 weeks	Worldwide Multicenter	No	Adults, CD only, CDAI (220-450), no use of TNF-alpha inhibitors, infliximab, adalimumab, certolizumab pegol, no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, no cancer, other criteria
Van Assche, 2008[89]	RCT, parallel arms	Start year: 2004 Duration of assigned treatment: 2 years	Europe Multicenter	No	Pediatrics, adults, CD only, previous use of methotrexate, infliximab, immunosuppressives (azathioprine/6-MP or methotrexate), perianal fistulizing, not pregnant, not nursing, other criteria
Randomized controlled trials evaluating thiopurines					
Candy, 1995[53]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 weeks	Africa Single center	No	Pediatrics, adults, CD only, no previous surgery (extensive surgery for Crohn's disease), CDAI (>200), not pregnant, not nursing, other criteria
Lemann, 2005[98]	RCT, parallel arms	Start year: 1995 Duration of assigned treatment: 18 months	Europe Multicenter	No	Adults, CD only, no previous surgery (except limited perianal surgery in past 42 months), CDAI (<150), in remission for >42 months, previous use of azathioprine, no use of antibiotics, 5-aminosalicylate acids, corticosteroids, inactive disease, other criteria

Evidence Table 7. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Mantzaris, 2009[102]	RCT, parallel arms	Start year: 1998 Duration of assigned treatment: 1.5 years	Europe Number of centers NR	Yes Yes	Adults, CD only, no previous surgery (intestinal resection), CDAI (<150), previous use of corticosteroids, no use of infliximab, mesalamine-only maintenance therapy, effective prior treatment with azathioprine, perianal fistulizing, not pregnant, not nursing, no history of TB, other criteria
O'Donoghue, 1978[100]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 6 months	Europe Single center	Yes Yes	Adults, CD only, in remission for >6 months, previous use of azathioprine, inactive disease
Rosenberg, 1975[104]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 26 weeks	US Single center	Yes Yes	Adults, CD only, previous use of corticosteroids, not pregnant, not nursing, other criteria
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 24 months	US Multicenter	No	Adults, CD only, CDAI (<150), inactive disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Vilien, 2004[101]	RCT, parallel arms	Start year: 2000 Duration of assigned treatment: 1 year	Location: NR Number of centers NR	No	CD only, no previous surgery (in past 3 months), previous use of thiopurines, azathioprine, no use of corticosteroids, inactive disease, other criteria
Willoughby JM, 1971[99]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 24 weeks	Europe Single center	No	CD only, previous use of corticosteroids, active and inactive disease

Evidence Table 7. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Randomized controlled trials evaluating methotrexate					
Feagan, 2000[105]	RCT, parallel arms	Start year: 1993 Duration of assigned treatment: NR	US, North America Multicenter	Yes Yes	Adults, CD only, previous use of methotrexate, inactive disease, not pregnant, no cancer, other criteria
Randomized controlled trials evaluating corticosteroids					
Bergman, 1976[223]	RCT, parallel arms	Start year: 1969 Duration of assigned treatment: 33 weeks	Europe Multicenter	Yes Yes	Adults, CD only, no use of corticosteroids, salazopyrine, azathioprine, other criteria
Brignola, 1988[112]	RCT, parallel arms with a 4-week run-in period	Start year: 1983 Duration of assigned treatment: 6 months	Europe Multicenter	No	Adults, CD only, CDAI (<150), LI >100, other criteria
Cortot, 2001[107]	RCT, parallel arms	Start year: 1996 Duration of assigned treatment: 22 weeks	Europe, Asia, Africa Multicenter	No	Adults, CD only, no previous surgery (resection of ileum of >100 cm or who require immediate surgery), CDAI (<201), previous use of corticosteroids, inactive disease, not pregnant, not nursing, no ostomy, no abscess, no history of TB, other criteria
de Franchis, 1997[118]	RCT, parallel arms with a 4-8-week run-in period	Start year: 1991 Duration of assigned treatment: 24 months	Europe Multicenter	Yes Yes	Adults, CD only, CDAI (<150), previous use of corticosteroids, no use of immunomodulators in past 3 months, not pregnant, not nursing, no obstructive symptoms with strictures, other criteria
Ferguson, 1998[108]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 months	Europe, Australia Multicenter	Yes Yes	Adults, CD only, no previous surgery (ileostomy or previous small bowel resection of >100 cm), CDAI (<150), inactive disease, not pregnant, not nursing, no ostomy, no abscess, other criteria

Evidence Table 7. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Greenberg, 1994[66]	RCT, parallel arms	Start year: 1991 Duration of assigned treatment: 8 weeks	North America Multicenter	Yes Yes	Adults, CD only, CDAI (>200), not pregnant, not nursing, no cancer, other criteria
Greenberg, 1996[111]	RCT, parallel arms with a 8-week run-in period	Start year: 1992 Duration of assigned treatment: 52 weeks	North America Multicenter	Yes No	Adults, CD only, CDAI (<150), inactive disease, not pregnant, not nursing, no ostomy, no cancer, other criteria
Gross, 1998[109]	RCT, parallel arms	Start year: NR Duration of assigned treatment: NR	Europe Multicenter	Yes Yes	Adults, CD only, CDAI (<150), in remission for >8 weeks, previous use of prednisolone
Hanauer, 2005[106]	RCT, parallel arms	Start year: 1995 Duration of assigned treatment: 52 weeks	US Multicenter	Yes Yes	Adults, CD only, no previous surgery (ileostomy, colostomy, gastric surgery other than for closure of perforation or selective vagotomy or resection of ileum >100cm), CDAI (<150), in remission for >10 weeks, no use of immunomodulators in past 90 days, corticosteroids in past 14 days, mesalamine or NSAIDs for more than 3 consecutive days, inactive disease, not pregnant, not nursing, no history of TB, no cancer, other criteria
Issenman, 1993[196]	Prospective cohort	Start year: NR Mean followup duration: 2 years	North America Single center	NA	Pediatrics, CD only, males, active disease
Lofberg, 1996[110]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 months	Europe Multicenter	Yes Yes	Adults, CD only, no previous surgery (ilestomy or prior small bowel resection >100 cm), CDAI (<150), no short bowel syndrome, no ostomy, other criteria

Evidence Table 7. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Malchow, 1984[64]	RCT, parallel arms	Start year: 1975 Duration of assigned treatment: 6 weeks	Europe Multicenter	Yes Yes	Adults, CD only, not pregnant, no abscess, no obstructive symptoms with strictures, other criteria
Mantzaris, 2003[113]	RCT, parallel arms with a 1-month run-in period	Start year: 1994 Duration of assigned treatment: 1 year	Europe Single center	No	Adults, CD only, no previous surgery (intestinal resection), CDAI (<150), no use of mesalamine maintenance therapy, azathioprine unless withdrawn at least 3 months before start of trial due to side effects, inactive disease, not pregnant, not nursing, other criteria
Singleton, 1979[75]	RCT, parallel arms with a 8-week run-in period	Start year: NR Duration of assigned treatment: 6 months	US Multicenter	Yes Yes	Adults, CD only, CDAI (<150), previous use of prednisone, sulfasalazine and prednisone, inactive disease, other criteria
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 24 months	US Multicenter	No	Adults, CD only, CDAI (<150), inactive disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Randomized controlled trials evaluating aminosalicylates					
Arber, 1995[121]	RCT, parallel arms	Start year: 1991 Duration of assigned treatment: 12 months	Israel Multicenter	Yes Yes	CD only, HBI (<4), in remission for >6 months, other criteria
Bresci G, 1995[125]	RCT, parallel arms with a 6-week run-in period	Start year: 1988 Duration of assigned treatment: 4 years	Europe Single center	Yes Yes	Adults, CD only, no previous surgery , CDAI (<150), Laboratory Index (LI) <100, inactive disease, not pregnant, other criteria

Evidence Table 7. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Brignola, 1992[124]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 4 months	Location: NR Single center	Yes Yes	CD only, CDAI (<150), Laboratory activity (LA) >100, in remission for >4 weeks, no use of corticosteroids, corticosteroids in past 4 weeks, inactive disease
Cezard, 2009[194]	RCT, parallel arms	Start year: 1991 Duration of assigned treatment: 1 year	Europe Multicenter	No	Pediatrics, CD only, HBI (>5), no use of 5-aminosalicylate acids, thiopurines, methotrexate, active disease, other criteria
Gendre, 1993[122]	RCT, parallel arms	Start year: 1985 Duration of assigned treatment: 2 years	Europe Multicenter	Yes Yes	CD only, CDAI (<150), in remission for >24 months, no use of corticosteroids, corticosteroids and immunomodulators in past month, inactive disease, not pregnant, other criteria
Mahmud, 2001[116]	RCT, parallel arms	Start year: 1992 Duration of assigned treatment: 52 weeks	Europe Multicenter	No	Adults, CD only, CDAI (<150), in remission for >1 months, no use of corticosteroids, thiopurines, immunomodulators (other than ASA) not pregnant, not nursing, no obstructive symptoms with strictures, other criteria
Malchow, 1984[64]	RCT, parallel arms	Start year: 1975 Duration of assigned treatment: 6 weeks	Europe Multicenter	Yes Yes	Adults, CD only, not pregnant, no abscess, no obstructive symptoms with strictures, other criteria
Prantera, 1992[123]	RCT, parallel arms	Start year: 1988 Duration of assigned treatment: 12 months	Europe Multicenter	Yes Yes	Adults, CD only, CDAI (<150), perianal fistulizing, no obstructive symptoms with strictures, other criteria

Evidence Table 7. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Prantera, 2005[115]	RCT, parallel arms with a 8-week run-in period	Start year: 2000 Duration of assigned treatment: 12 months	Europe Multicenter	No	CD only, CDAI (150-400), mild-moderate disease, other criteria
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 24 months	US Multicenter	No	Adults, CD only, CDAI (<150), inactive disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Sutherland, 1997[117]	RCT, parallel arms	Start year: 1990 Duration of assigned treatment: 11 months	North America Multicenter	Yes Yes	Adults, CD only, no previous surgery (proctocolectomy or history of >3 resections in the last 10 years), CDAI (<150), no use of azathioprine, 6-MP or cyclosporine in past 90 days, steroids in past 30 days, mesalamine or metronidazole in past 7 days, perianal fistulizing, no short bowel syndrome, no cancer, other criteria
Thomson, 1990[224]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 months	North America, Europe, Africa Multicenter	Yes Yes	Pediatrics, CD only, CDAI (<150), no use of azathioprine, metronidazole, no ostomy, no obstructive symptoms with strictures, other criteria
Thomson, 1995[120]	RCT, parallel arms	Start year: 1988 Duration of assigned treatment: 12 months	US, North America, Europe, Asia, Africa Multicenter	Yes No	Adults, CD only, no previous surgery (ileostomy, colostomy, or bowel resection with >100 cm of bowel removed; or bowel resection in past 3 months), CDAI (<150), no use of azathioprine, immunomodulators or systemic corticosteroids in past month, not pregnant, not nursing, using adequate contraception, no short bowel syndrome, no obstructive symptoms with strictures, no cancer, other criteria
Wellmann W, 1988[126]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 1 year	Europe Number of centers NR	Yes Yes	CD only, CDAI (<120), in remission for >3 months, no use of corticosteroids, corticosteroids in past 3 months, inactive disease

Abbreviations: 6-MP = 6-mercaptopurine; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; HBI = Harvey-Bradshaw Index; NA = not applicable; NR = not reported; RCT = randomized controlled trial; TAS = Trial of Adjunctive Sulfasalazine in Crohn's disease; TB = tuberculosis; US = United States

Evidence Table 7. Study design characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Randomized controlled trials evaluating biologics								
Colombel, 2007[82]	Adalimumab, 157 Route: SC Dose: 40 mg every 1 week	Male, %: 39 Race NR Smoking, % Current smoker, 32 CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36.9	Severity NR Location, % Ileal: 76 Ileo-colonic: 54 Colonic: 76 Behavior NR CRP NR	CDAI Mean: 160 IBDQ Mean: 165	5ASA: 69 Antibiotics Corticosteroids Methotrexate: 12 Thiopurines: 38 Immunomodulators: 50	TNF-alpha inhibitors: 45	Adalimumab: 100
Colombel, 2007[82]	Adalimumab, 172 Route: SC Dose: 40 mg every 2 weeks	Male, %: 36 Race NR Smoking, % Current smoker, 34 CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36.4	Severity NR Location, % Ileal: 73 Ileo-colonic: 47 Colonic: 73 Behavior NR CRP NR	CDAI Mean: 155 IBDQ Mean: 175	5ASA: 38 Antibiotics Corticosteroids Methotrexate: 10 Thiopurines: 36 Immunomodulators: 45	TNF-alpha inhibitors: 50	Adalimumab: 100
Colombel, 2007[82]	Placebo, 170 Route: SC Dose: NA every 2 weeks	Male, %: 38 Race NR Smoking, % Current smoker, 37 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36.9	Severity NR Location, % Ileal: 66 Ileo-colonic: 44 Colonic: 76 Behavior NR CRP NR	CDAI Mean: 170 IBDQ Mean: 165	5ASA: 46 Antibiotics Corticosteroids Methotrexate: 8 Thiopurines: 42 Immunomodulators: 49	TNF-alpha inhibitors: 48	Adalimumab: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Feagan, 2007[81]	Placebo, 33 Route: IV Dose: NA every 4 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Feagan, 2007[81]	Placebo, 171 Route: IV Dose: NA every 4 weeks	Male, %: 34.5 Race NR Smoking, % >10 cigarettes/day, 26.3 CD NR	Age at diagnosis NR Disease duration Mean: 9.7 Age at enrollment Mean: 37	Severity NR Location, % Ileal: 23.4 Ileo-colonic: 49.7 Colonic: 26.9 Behavior NR CRP Mean: 9.4 Median: 3.9 Min: 0 Max: 120	CDAI Mean: 118 IBDQ Mean: 121	5ASA: 54.4 Antibiotics: 5.8 Corticosteroids: 44.4 Methotrexate: 4.7 Thiopurines: 30.4 Prednisone: 31.6 Budesonide: 14 >/= 1 corticosteroid or immunomodulators: 60.2 Corticosteroids and immunosuppressants: 19.3	TNF-alpha inhibitors: 39.8	Natalizumab: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Feagan, 2007[81]	Natalizumab, 168 Route: IV Dose: 300 mg every 4 weeks	Male, %: 45.8 Race NR Smoking, % >10 cigarettes/day, 16.1 CD NR	Age at diagnosis NR Disease duration Mean: 9.9 Age at enrollment Mean: 37	Severity NR Location, % Ileal: 24.4 Ileo-colonic: 50.6 Colonic: 25 Behavior NR CRP Mean: 8.9 Median: 4.3 Min: 0 Max: 97	CDAI Mean: 105 IBDQ Mean: 125	5ASA: 45.2 Antibiotics: 8.9 Corticosteroids: 39.9 Methotrexate: 4.8 Thiopurines: 32.1 Prednisone: 26.2 Budesonide: 12.5 >/= 1 corticosteroid or immunomodulators: 57.1 Corticosteroids and immunosuppressants: 17.9	TNF-alpha inhibitors: 32.7	Natalizumab: 100
Feagan, 2007[81]	Natalizumab, 35 Route: IV Dose: 300 mg every 4 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Feagan, 2008[90]	Placebo, 261 Route: SC Dose: NA every 2 weeks	Male, %: 37.9 Race, % W: 94.3 B: 3.1 A: 1.1 Other: 1.5 Smoking, % Smoker, 36.8 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36.9	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 209	Corticosteroids: 41	NR	Adalimumab: 100
Feagan, 2008[90]	Adalimumab, 257 Route: SC Dose: 40 mg every 1 week	Male, %: 38.9 Race, % W: 89.9 B: 4.7 A: 2.7 Other: 2.7 Smoking, % Smoker, 34.6 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 37.8	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 209	Corticosteroids: 41.6	NR	Adalimumab: 100
Feagan, 2008[90]	Adalimumab, 260 Route: SC Dose: 40 mg every 2 weeks	Male, %: 37.3 Race, % W: 94.2 B: 2.7 A: 1.5 Other: 1.5 Smoking, % Smoker, 35.4 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36.8	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 195	Corticosteroids: 38.1	NR	Adalimumab: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hanauer, 2002[86]	Placebo, 110 Route: IV Dose: NA every 8 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 155 Median: 160 IBDQ Mean: 170 Median: 173	5ASA Corticosteroids Immunomodulators	5ASA Antibiotics Corticosteroids Methotrexate Thiopurines	Infliximab: 100
Hanauer, 2002[86]	Infliximab, 113 Route: IV Dose: 5 mg/kg every 8 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 154 Median: 156 IBDQ Mean: 170 Median: 169	5ASA Corticosteroids Immunomodulators	5ASA Antibiotics Corticosteroids Methotrexate Thiopurines	Infliximab: 100
Hanauer, 2002[86]	Infliximab, 112 Route: IV Dose: 10 mg/kg every 8 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 152 Median: 151 IBDQ Mean: 168 Median: 173	5ASA Corticosteroids Immunomodulators	5ASA Antibiotics Corticosteroids Methotrexate Thiopurines	Infliximab: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Mantzaris, 2009[88]	Hydrocortisone + Infliximab, 23 Route: IV Dose: 250 mg every 8 weeks + 5 mg/kg every 8 weeks	Male, %: 52.2 Race NR Smoking, % Smoker, 47.8 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 35 Min: 20 Max: 57	Severity NR Location, % Ileal: 30.4 Ileo-colonic: 47.8 Colonic: 21.7 Behavior, % Inflammatory: 100 CRP NR	CDAI Mean: 298	NR	5ASA: 91.3 Corticosteroids: 69.6 budesonide: 34.8 NO azathioprine: 26.1 topical ASA: 17.4 : 26.1	Infliximab: 100
Mantzaris, 2009[88]	Azathioprine + Infliximab, 23 Route: Oral + IV Dose: 2.0-2.5 mg/kg every day + 5 mg/kg every 8 weeks	Male, %: 47.8 Race NR Smoking, % Smoker, 43.5 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 37 Min: 21 Max: 62	Severity NR Location, % Ileal: 26.1 Ileo-colonic: 56.5 Colonic: 17.4 Behavior, % Inflammatory: 100 CRP NR	CDAI Mean: 287	NR	5ASA: 87 Corticosteroids: 69.6 budesonide: 34.8 NO azathioprine: 100 topical ASA: 13 : 100	Infliximab: 100
Rutgeerts, 1999[85]	Infliximab, 37 Route: IV Dose: 10 mg/kg every 8 weeks	Male, %: 40.5 Race, % W: 100 Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 9.4 Min: 1.1 Max: 30.8 Age at enrollment Median: 34 Min: 20 Max: 64	Severity NR Location, % Ileal: 13.5 Ileo-colonic: 62.2 Colonic: 24.3 Behavior NR CRP Median: 0.5	CDAI Median: 175 IBDQ Median: 165	NR	NR	TNF-alpha inhibitors: 91.9

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Rutgeerts, 1999[85]	Placebo, 36 Route: Unknown Dose: NA every 8 weeks	Male, %: 63.9 Race, % W: 100 Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 12.1 Min: 0.3 Max: 32.8 Age at enrollment Median: 39 Min: 20 Max: 65	Severity NR Location, % Ileal: 13.9 Ileo-colonic: 47.2 Colonic: 38.9 Behavior NR CRP Median: 0.4	CDAI Median: 170 IBDQ Median: 170	NR	NR	TNF-alpha inhibitors: 97.2
Sandborn, 2007[83]	Placebo, 18 Route: SC Dose: NA every 1 week	Male, %: 33 Race NR Smoking, % Patients who smoked, 67 CD, %: 100	Age at diagnosis NR Disease duration Mean: 8.24 Age at enrollment Mean: 36	Severity NR Location NR Behavior NR CRP NR	IBDQ Mean: 188	5ASA: 44 Antibiotics: 6 Corticosteroids: 56 Methotrexate: 6 Thiopurines: 11.1 Immunomodulators: 17	NR	TNF-alpha inhibitors: 100
Sandborn, 2007[83]	Adalimumab, 18 Route: SC Dose: 40 mg every 1 week	Male, %: 50 Race NR Smoking, % Patients who smoked, 56 CD, %: 100	Age at diagnosis NR Disease duration Mean: 9.13 Age at enrollment Mean: 38	Severity NR Location NR Behavior NR CRP NR	IBDQ Mean: 191	5ASA: 67 Antibiotics: 0 Corticosteroids: 50 Methotrexate: 0 Thiopurines: 28 Immunomodulators: 28	NR	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 2007[83]	Adalimumab, 19 Route: SC Dose: 40 mg every 2 weeks	Male, %: 37 Race NR Smoking, % Patients who smoked, 68 CD NR	Age at diagnosis NR Disease duration Mean: 7.73 Age at enrollment Mean: 34	Severity NR Location NR Behavior NR CRP NR	IBDQ Mean: 187	5ASA: 74 Antibiotics: 0 Corticosteroids: 47 Methotrexate: 0 Thiopurines: 21 Immunomodulators: 21	NR	NR
Sands, 2004[87]	Infliximab, 96 Route: IV Dose: 5 mg/kg every 8 weeks	Male, %: 55 Race NR Smoking, % Current smoker, 45 CD, %: 100	Age at diagnosis NR Disease duration Median: 10.5 Min: 0.2 Max: 32.2 Age at enrollment Median: 37	Severity NR Location, % Ileal: 19 Ileo-colonic: 46 Colonic: 35 Behavior NR CRP Median: 0.6	IBDQ Median: 155	5ASA: 43 Antibiotics: 29 Corticosteroids: 26 Methotrexate: 1 Thiopurines: 30	Antibiotics: 96 Methotrexate: 5 Thiopurines: 72 cyclosporine or tacrolimus: 3	Infliximab: 100
Sands, 2004[87]	Placebo, 99 Route: IV Dose: NA every 8 weeks	Male, %: 48 Race NR Smoking, % Current smoker, 38 CD, %: 100	Age at diagnosis NR Disease duration Median: 12.3 Min: 0.5 Max: 31.6 Age at enrollment Median: 36	Severity NR Location, % Ileal: 16 Ileo-colonic: 54 Colonic: 30 Behavior NR CRP Median: 0.7	IBDQ Median: 168	5ASA: 49 Antibiotics: 26 Corticosteroids: 30 Methotrexate: 2 Thiopurines: 35	Antibiotics: 93 Methotrexate: 8 Thiopurines: 64 cyclosporine or tacrolimus: 7	Infliximab: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schreiber, 2007[84]	Certolizumab pegol, 216 Route: SC Dose: 400 mg every 4 weeks	Male, %: 43 Race NR Smoking, % Current smoker, 30 CD NR	Age at diagnosis NR Disease duration Mean: 9 Median: 7 Min: 1 Max: 33 Age at enrollment Mean: 38 Min: 18 Max: 67	Severity NR Location, % Ileal: 22 Ileo-colonic: 51 Colonic: 27 Behavior, % Inflammatory: 67.4 Stricturing: 11.6 Penetrating: 20.9 CRP Mean: 10 Min: 2 Max: 183	CDAI Mean: 306 Min: 179 Max: 504	Corticosteroids: 22 Immunomodulators: 27 Glucocorticoids + immunomodulators: 13 Neither glucocoricoids nor immunosuppresives: 38	5ASA: 34.4 Corticosteroids: 49.3 Immunomodulators: 21.4 infliximab: 24	Certolizumab pegol: 100
Schreiber, 2007[84]	Placebo, 212 Route: SC Dose: NA every 4 weeks	Male, %: 52 Race NR Smoking, % Current smoker, 36 CD NR	Age at diagnosis NR Disease duration Mean: 7 Median: 5 Min: 1 Max: 43 Age at enrollment Mean: 38 Min: 18 Max: 69	Severity NR Location, % Ileal: 25 Ileo-colonic: 46 Colonic: 29 Behavior, % Inflammatory: 67.1 Stricturing: 9.5 Penetrating: 23.3 CRP Mean: 10 Min: 2 Max: 244	CDAI Mean: 301 Min: 183 Max: 583	Corticosteroids: 21 Immunomodulators: 25 Glucocorticoids + immunomodulators: 16 Neither glucocorticoids nor immunomodulators: 38	5ASA: 34.3 Corticosteroids: 46.7 Immunomodulators: 20.5 infliximab: 24	Certolizumab pegol: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Van Assche, 2008[89]	Infliximab + Immunomodulator, 40 Route: IV + Oral Dose: 5 mg/kg every 8 weeks + see below	Male, %: 42.5 Race NR Smoking, % Smoker, 45 CD NR	Age at diagnosis NR Disease duration Median: 9 Min: 1 Max: 36 Age at enrollment Mean: 35.6	Severity NR Location, % Colonic: 32.5 Behavior NR CRP Median: 3.4	CDAI Mean: 137.6	TNF-alpha inhibitors: 100 Methotrexate Thiopurines	TNF-alpha inhibitors: 100 Methotrexate Thiopurines	NR
Van Assche, 2008[89]	Infliximab, 40 Route: IV Dose: 5 mg/kg every 8 weeks	Male, %: 47.5 Race NR Smoking, % Smoker, 47.5 CD NR	Age at diagnosis NR Disease duration Median: 9 Min: 2 Max: 25 Age at enrollment Mean: 35.4	Severity NR Location, % Colonic: 12.5 Behavior NR CRP Median: 3.2	CDAI Mean: 138.1	TNF-alpha inhibitors: 100	TNF-alpha inhibitors: 100 Methotrexate Thiopurines	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Randomized controlled trials evaluating thiopurines								
Candy, 1995[53]	Placebo + Prednisolone, 30 Route: Oral + Oral Dose: NA + 1 mg/kg every day	Male, %: 37 Race NR Smoking, % Smoker, 67 CD NR	Age at diagnosis NR Disease duration Median: 3.7 Min: 0.1 Max: 18.7 Age at enrollment Median: 31.8 Min: 21 Max: 62	Severity, % Severe disease: 43 Location, % Ileal: 20 Ileo-colonic: 63.3 Colonic: 16.7 Behavior NR CRP Median: 3.9 Min: 2.8 Max: 5.3	CDAI Median: 282 Min: 240 Max: 356	Corticosteroids: 100	Corticosteroids corticosteroids in the last 6 months: 63 no previous corticosteroids: 7 : 7	NR
Candy, 1995[53]	Azathioprine + Prednisolone, 33 Route: Oral + Oral Dose: 2.5 mg/kg every day + 1 mg/kg every day	Male, %: 21 Race NR Smoking, % Smoker, 67 CD NR	Age at diagnosis NR Disease duration Median: 2.6 Min: 0.1 Max: 19.3 Age at enrollment Median: 33.9 Min: 15 Max: 60	Severity, % Severe disease: 52 Location, % Ileal: 24.2 Ileo-colonic: 60.6 Colonic: 15.2 Behavior NR CRP Median: 5.4 Min: 2.9 Max: 7.3	CDAI Median: 301 Min: 264 Max: 358	Corticosteroids: 100 Thiopurines: 100	corticosteroids in previous 6-12 mo: 67 no previous corticosteroids: 15 : 15	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lemann, 2005[98]	Azathioprine, 40 Route: Oral Dose: as taken before enrollment every day	Male, %: 47 Race NR Smoking, % Smoker, 42 CD NR	Age at diagnosis NR Disease duration Mean: 11 Age at enrollment Mean: 40	Severity NR Location, % Ileal: 13 Ileo-colonic: 40 Colonic: 48 Perianal: 43 Behavior NR CRP Mean: 5.3	CDAI Mean: 41 CDEIS Mean: 2.5	Corticosteroids <10mg/day: 8	azathioprine: 100	NR
Lemann, 2005[98]	Placebo, 43 Route: Oral Dose: NA every day	Male, %: 42 Race NR Smoking, % Smoker, 42 CD NR	Age at diagnosis NR Disease duration Mean: 11 Age at enrollment Mean: 36	Severity NR Location, % Ileal: 9 Ileo-colonic: 51 Colonic: 40 Perianal: 44 Behavior NR CRP Mean: 6.9	CDAI Mean: 39 CDEIS Mean: 2.4	Corticosteroids <10mg/day: 5	azathioprine: 100	NR
Mantzaris, 2009[102]	Budesonide, 39 Route: Oral Dose: 09-Jun mg every day	Male, %: 43.6 Race NR Smoking, % Smoker, 92.3 CD NR	Age at diagnosis NR Disease duration Mean: 1.9 Age at enrollment Median: 34.5 Min: 19 Max: 62	Severity, % Remission: 100 Location, % Ileo-colonic: 66.7 Colonic: 33.3 Behavior, % Inflammatory: 100 CRP NR	CDAI Mean: 129 CDEIS Mean: 7.1	NR	Corticosteroids: 100	Corticosteroids: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Mantzaris, 2009[102]	Azathioprine, 38 Route: Oral Dose: 2.0-2.5 mg/kg every day	Male, %: 44.7 Race NR Smoking, % Smoker, 92.1 CD NR	Age at diagnosis NR Disease duration Mean: 1.8 Age at enrollment Median: 34.3 Min: 19 Max: 59	Severity, % Remission: 100 Location, % Ileo-colonic: 63.2 Colonic: 36.8 Behavior, % Inflammatory: 100 CRP NR	CDAI Mean: 132 CDEIS Mean: 7.2	NR	Corticosteroids: 100	Corticosteroids: 100
O'Donoghue, 1978[100]	Azathioprine, 24 Route: Oral Dose: 2 mg/kg every 24 hours	Male, %: 45.8 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.25 Min: 1.5 Max: 20 Age at enrollment Mean: 40 Min: 21 Max: 78	Severity, % Remission: 100 Location, % Ileal: 12.5 Ileo-colonic: 41.7 Colonic: 45.8 Behavior NR CRP NR	Unnamed clinical scoring system Mean: 2.33 Min: 0 Max: 9	Corticosteroids and/or sulfasalazine: 33.3	NR	Thiopurines: 100
O'Donoghue, 1978[100]	Placebo, 27 Route: Oral Dose: NA	Male, %: 40.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.05 Min: 1.5 Max: 15 Age at enrollment Mean: 40.5 Min: 22 Max: 65	Severity, % Remission: 100 Location, % Ileal: 25.9 Ileo-colonic: 11.1 Colonic: 63 Behavior NR CRP NR	Unnamed clinical scoring system Mean: 2 Min: 0 Max: 7	Prednisolone and sulfasalazine collectively: 25.9	NR	Thiopurines: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Rosenberg, 1975[104]	Azathioprine, 10 Route: Oral Dose: 2 mg/kg every 24 hours	Male, %: 60 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 32.6	Severity NR Location, % Ileal: 30 Ileo-colonic: 70 Behavior NR CRP NR	Disease activity index NR	Antibiotics: 20 Corticosteroids: 100 Sulfasalazine: 40	Corticosteroids: 100	NR
Rosenberg, 1975[104]	Placebo, 10 Route: Oral Dose: NA	Male, %: 40 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 26.3	Severity NR Location, % Ileal: 10 Ileo-colonic: 90 Behavior NR CRP NR	Disease activity index NR	Antibiotics: 40 Corticosteroids: 100 Sulfasalazine: 30	Corticosteroids: 100	NR
Summers, 1979[56]	Azathioprine, 54 Route: Oral Dose: 1 mg/kg every 24 hours	Male, %: 57.4 Race, % W: 94.4 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.99 Age at enrollment Mean: 31	Severity, % Remission: 100 Location, % Ileal: 37 Ileo-colonic: 56 Colonic: 7 Behavior NR CRP NR	CDAI Mean: 85.9	NR	NR	Corticosteroids: 31.5

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Placebo, 101 Route: Oral Dose: NA	Male, %: 53.5 Race, % W: 94.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.84 Age at enrollment Mean: 31.6	Severity, % Remission: 100 Location, % Ileal: 43 Ileo-colonic: 48 Colonic: 9 Behavior NR CRP NR	CDAI Mean: 83.5	NR	NR	Corticosteroids: 31.7
Summers, 1979[56]	Sulfasalazine, 58 Route: Oral Dose: 1/2 g/ 15 kg every 24 hours	Male, %: 53.4 Race, % W: 98.3 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.11 Age at enrollment Mean: 32.2	Severity, % Remission: 100 Location, % Ileal: 50 Ileo-colonic: 40 Colonic: 10 Behavior NR CRP NR	CDAI Mean: 89.4	NR	NR	Corticosteroids: 32.8
Summers, 1979[56]	Prednisone, 61 Route: Oral Dose: 04-Jan mg/kg every 24 hours	Male, %: 50.8 Race, % W: 95.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 4.37 Age at enrollment Mean: 32.6	Severity, % Remission: 100 Location, % Ileal: 46 Ileo-colonic: 43 Colonic: 11 Behavior NR CRP NR	CDAI Mean: 94.8	NR	NR	Corticosteroids: 34.4

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Vilien, 2004[101]	Discontinued azathioprine, 15	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 5.9 Min: 0 Max: 36 Age at enrollment Median: 47 Min: 23 Max: 73	Severity NR Location, % Colonic: 20 Behavior NR CRP Median: 25 Min: 20 Max: 174	CDAI Median: 61 Min: 15 Max: 166	NR	NR	NR
Vilien, 2004[101]	Azathioprine, 14 Route: Unknown Dose: NR every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 4.9 Min: 0.1 Max: 19.4 Age at enrollment Median: 33 Min: 22 Max: 63	Severity NR Location, % Colonic: 28.6 Behavior NR CRP Median: 54 Min: 25 Max: 395	CDAI Median: 81 Min: 1 Max: 176	NR	NR	NR
Willoughby JM, 1971[99]	Prednisolone + Azathioprine, 5 Route: Oral + Oral Dose: Patient continued on the current steroid dose required to maintain remission every 24 hours + 2 mg/kg every 24 weeks	Male, %: 20 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10.4 Age at enrollment Mean: 32.8	Severity, % Remission: 100 Location, % Ileal: 60 Ileo-colonic: 40 Colonic: 0 Behavior NR CRP NR	Not named Mean: 3.2	NR	Corticosteroids: 100	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Willoughby JM, 1971[99]	Prednisolone + Placebo, 6 Route: Oral + Oral Dose: 60 mg every day + NA every 24 hours	Male, %: 33.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 6.8 Age at enrollment Mean: 29.6	Severity NR Location, % Ileal: 50 Ileo-colonic: 33.3 Colonic: 16.7 Behavior NR CRP NR	Not named Mean: 7.8	NR	NR	NR
Willoughby JM, 1971[99]	Prednisolone + Azathioprine, 6 Route: Oral + Oral Dose: 60 mg every 24 hours + 4 mg/kg every 24 hours	Male, %: 16.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.8 Age at enrollment Mean: 29.2	Severity NR Location, % Ileal: 33.3 Ileo-colonic: 66.7 Colonic: 0 Behavior NR CRP NR	Not named Mean: 10.7	NR	NR	NR
Willoughby JM, 1971[99]	Prednisolone + Placebo, 5 Route: Oral + Oral Dose: current dose the patient is taking to keep him free of relapse every 24 hours + NA every 24 hours	Male, %: 60 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 9.6 Age at enrollment Mean: 33.2	Severity, % Remission: 100 Location, % Ileal: 40 Ileo-colonic: 60 Colonic: 0 Behavior NR CRP NR	Not named Mean: 1.8	NR	Corticosteroids: 100	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Randomized controlled trials evaluating methotrexate								
Feagan, 2000[105]	Methotrexate, 40 Route: IM Dose: 15 mg every 1 week	Male, %: 40 Race NR Smoking, % Cigarette smoker, 50 CD NR	Age at diagnosis NR Disease duration Mean: 7.33 Age at enrollment Mean: 32	Severity, % Remission: 100 Location, % Ileal: 45 Ileo-colonic: 28 Colonic: 28 Behavior NR CRP NR	CDAI Mean: 94	NR	NR	Methotrexate: 100
Feagan, 2000[105]	Placebo, 36 Route: IM Dose: NA every 1 week	Male, %: 61 Race NR Smoking, % Cigarette smoker, 42 CD NR	Age at diagnosis NR Disease duration Mean: 84 Age at enrollment Mean: 34	Severity, % Remission: 100 Location, % Ileal: 31 Ileo-colonic: 44 Colonic: 25 Behavior NR CRP NR	CDAI Mean: 84	NR	Methotrexate: 100 Thiopurines: 3	Methotrexate: 100
Randomized controlled trials evaluating corticosteroids								
Bergman, 1976[223]	Sulfasalazine + Prednisone, 49 Route: Oral + Oral Dose: 3 g every 24 hours + 15 mg every 24 hours	Male, %: 40.8 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.9 Age at enrollment NR	Severity, % Remission: 100 Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Bergman, 1976[223]	No treatment, 35	Male, %: 51.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.5 Age at enrollment NR	Severity, % Remission: 100 Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Brignola, 1988[112]	Placebo, 9 Route: Unknown Dose: NA	Male, %: 22.2 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 33	Severity NR Location, % Ileal: 33.3 Ileo-colonic: 44.4 Colonic: 22.2 Behavior NR CRP Mean: 2.3	Disease activity index NR	Folic acid Iron Calcium	NR	Corticosteroids: 44.4
Brignola, 1988[112]	(6)-Methylprednisolone, 9 Route: Unknown Dose: 0.25 mg/kg every 24 hours	Male, %: 66.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 28	Severity NR Location, % Ileal: 33.3 Ileo-colonic: 33.3 Colonic: 33.3 Behavior NR CRP Mean: 2.5	Disease activity index NR	Folic acid Iron Calcium	NR	Corticosteroids: 44.4

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Cortot, 2001[107]	Placebo, 58 Route: Unknown Dose: NA every day	Male, %: 34.5 Race, % W: 91.4 Mixed: 8.6 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.1 Min: 1 Max: 26 Age at enrollment Mean: 32 Min: 18 Max: 66	Severity NR Location, % Ileal: 51.7 Ileo-colonic: 48.3 Colonic: 0 Behavior NR CRP NR	CDAI Mean: 109 Min: -50 Max: 192	5ASA: 48.3 Corticosteroids: 100 Thiopurines: 8.6	NR	NR
Cortot, 2001[107]	Budesonide, 59 Route: Oral Dose: 6 mg every day	Male, %: 47.5 Race, % W: 91.5 Mixed: 8.5 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.9 Min: 1 Max: 25 Age at enrollment Mean: 35 Min: 19 Max: 71	Severity NR Location, % Ileal: 47.5 Ileo-colonic: 49.2 Colonic: 3.4 Behavior NR CRP NR	CDAI Mean: 103 Min: -14 Max: 208	5ASA: 49.2 Corticosteroids: 100 Thiopurines: 15.3	NR	NR
de Franchis, 1997[118]	Placebo + (6)-Methylprednisolone, 59 Route: Oral + Oral Dose: NA every 8 hours + every 24 hours	Male, %: 59.3 Race NR Smoking, % Present smoker, 34 CD NR	Age at diagnosis NR Disease duration Mean: 4 Min: 0.0027 Max: 17.9 Age at enrollment Mean: 35.8 Min: 18 Max: 66	Severity NR Location, % Ileal: 28.8 Ileo-colonic: 39 Colonic: 32.2 Behavior NR CRP NR	CDAI Mean: 70.5	Corticosteroids: 100	NR	Corticosteroids: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
de Franchis, 1997[118]	ASA + (6)-Methylprednisolone, 58 Route: Oral + Oral Dose: 1000 mg every 8 hours + every 24 hours	Male, %: 46.6 Race NR Smoking, % Present smoker, 38 CD NR	Age at diagnosis NR Disease duration Mean: 3.5 Min: 0.0027 Max: 14.9 Age at enrollment Mean: 39.6 Min: 18 Max: 69	Severity NR Location, % Ileal: 27.6 Ileo-colonic: 43.1 Colonic: 29.3 Behavior NR CRP NR	CDAI Mean: 71.2	5ASA: 100 Corticosteroids: 100	NR	Corticosteroids: 100
Ferguson, 1998[108]	Placebo, 27 Route: Oral Dose: NA every day	Male, %: 40.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.8 Min: 0 Max: 27 Age at enrollment Mean: 34 Min: 19 Max: 61	Severity, % Remission: 100 Location NR Behavior NR CRP NR	CDAI Mean: 90 Min: 0 Max: 155	NR	NR	Budesonide: 59.3 Prednisolone: 40.7
Ferguson, 1998[108]	Budesonide + Placebo, 26 Route: Oral + Oral Dose: 3 mg every day + NA every day	Male, %: 53.8 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 6.7 Min: 0 Max: 27 Age at enrollment Mean: 37 Min: 20 Max: 71	Severity, % Remission: 100 Location NR Behavior NR CRP NR	CDAI Mean: 75 Min: 0 Max: 138	NR	NR	Budesonide: 80.8 Prednisolone: 19.2

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Ferguson, 1998[108]	Budesonide, 22 Route: Oral Dose: 6 mg every day	Male, %: 40.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 6.3 Min: 0 Max: 30 Age at enrollment Mean: 37 Min: 20 Max: 63	Severity, % Remission: 100 Location NR Behavior NR CRP NR	CDAI Mean: 102 Min: 15 Max: 210	NR	NR	Budesonide: 63.6 Prednisolone: 36.4
Greenberg, 1994[66]	Budesonide, 64 Route: Oral Dose: 7.5 mg every 12 hours	Male, %: 45.3 Race NR Smoking, % Smoker, 47 CD NR	Age at diagnosis NR Disease duration Median: 6.1 Age at enrollment Median: 31	Severity NR Location, % Ileal: 88 Ileo-colonic: 12 Behavior NR CRP Median: 4	CDAI Median: 285 IBDQ Median: 130	Loperamide	Corticosteroids: 47	NR
Greenberg, 1994[66]	Placebo, 66 Route: Oral Dose: NA every 12 hours	Male, %: 37.9 Race NR Smoking, % Smoker, 57.6 CD NR	Age at diagnosis NR Disease duration Median: 6.3 Age at enrollment Median: 32 Min: 19 Max: 62	Severity NR Location, % Ileal: 84.8 Ileo-colonic: 15.2 Colonic: 0 Behavior NR CRP Median: 4	CDAI Median: 287 IBDQ Median: 130	Loperamide	Corticosteroids: 38	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Greenberg, 1994[66]	Budesonide, 67 Route: Oral Dose: 1.5 mg every 12 hours	Male, %: 29.9 Race NR Smoking, % Smoker, 49 CD NR	Age at diagnosis NR Disease duration Median: 5.3 Age at enrollment Median: 30	Severity NR Location, % Ileal: 81 Ileo-colonic: 19 Colonic: 0 Behavior NR CRP Median: 10	CDAI Median: 293 IBDQ Median: 131	Loperamide	Corticosteroids: 45	NR
Greenberg, 1994[66]	Budesonide, 61 Route: Oral Dose: 4.5 mg every 12 hours	Male, %: 38 Race NR Smoking, % Smoker, 46 CD NR	Age at diagnosis NR Disease duration Median: 5.9 Age at enrollment Median: 37	Severity NR Location, % Ileal: 84 Ileo-colonic: 16 Colonic: 0 Behavior NR CRP Median: 4	CDAI Median: 296 IBDQ Median: 125	Loperamide	Corticosteroids: 43	NR
Greenberg, 1996[111]	Placebo, 36 Route: Oral Dose: NA every day	Male, %: 38.9 Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration Mean: 6.7 Min: 0.2 Max: 29 Age at enrollment Mean: 34 Min: 19 Max: 60	Severity, % Remission: 91.7 Location, % Ileal: 89 Ileo-colonic: 11 Colonic: 0 Behavior NR CRP NR	CDAI Mean: 115 Min: 28 Max: 246 IBDQ Mean: 181 Min: 69 Max: 198	Loperamide	NR	Placebo: 8.3 Budesonide 3mg: 11.1 Budesonide 9mg: 61.1 Budesonide 15mg: 19.4

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Greenberg, 1996[111]	Budesonide, 33 Route: Oral Dose: 3 mg every day	Male, %: 30.3 Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration Mean: 8 Min: 0.2 Max: 23 Age at enrollment Mean: 37 Min: 22 Max: 62	Severity, % Remission: 90.9 Location, % Ileal: 88 Ileo-colonic: 12 Colonic: 0 Behavior NR CRP NR	CDAI Mean: 96 Min: 20 Max: 160 IBDQ Mean: 185 Min: 76 Max: 179	Loperamide	NR	Placebo: 9.1 Budesonide 3mg: 21.2 Budesonide 9mg: 48.5 Budesonide 15mg: 21.2
Greenberg, 1996[111]	Budesonide, 36 Route: Oral Dose: 6 mg every day	Male, %: 50 Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration Mean: 8.7 Min: 0.2 Max: 26 Age at enrollment Mean: 36 Min: 19 Max: 63	Severity, % Remission: 97.2 Location, % Ileal: 81 Ileo-colonic: 19 Colonic: 0 Behavior NR CRP NR	CDAI Mean: 102 Min: 15 Max: 154 IBDQ Mean: 184 Min: 68 Max: 197	Loperamide	NR	Placebo: 13.9 Budesonide 3mg: 19.4 Budesonide 9mg: 41.7 Budesonide 15mg: 25
Gross, 1998[109]	Placebo, 95 Route: Oral Dose: NA every 24 hours	Male, %: 38.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 5 Age at enrollment Mean: 32	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 66	NR	NR	Corticosteroids: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Gross, 1998[109]	Budesonide, 84 Route: Oral Dose: 3 mg every 24 hours	Male, %: 42.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 5.5 Age at enrollment Mean: 32	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 65	NR	NR	Corticosteroids: 100
Hanauer, 2005[106]	Budesonide, 54 Route: Oral Dose: 6 mg every day	Male, %: 31.5 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 40.5 Min: 18	Severity, % Remission: 100 Location, % Ileal: 68.5 Ileo-colonic: 31.5 Colonic: 1.9 Behavior NR CRP NR	CDAI Mean: 97.4 Max: 150	NR	NR	Budesonide: 79.6 Placebo: 20.4
Hanauer, 2005[106]	Placebo, 54 Route: Oral Dose: NA every day	Male, %: 44.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 40.3 Min: 18	Severity, % Remission: 100 Location, % Ileal: 72.2 Ileo-colonic: 29.6 Colonic: 0 Behavior NR CRP NR	CDAI Mean: 87.4 Max: 150	NR	NR	Budesonide: 87 Placebo: 13

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Issenman, 1993[196]	Discontinued corticosteroids, 8	Male, %: 100 Race NR Smoking NR CD, %: 212.5	Age at diagnosis Mean: 13.2 Disease duration NR Age at enrollment Mean: 13.2	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Issenman, 1993[196]	Prednisone, 9 Route: Oral Dose: 2 mg/kg every day	Male, %: 100 Race NR Smoking NR CD NR	Age at diagnosis Mean: 14.5 Disease duration NR Age at enrollment Mean: 14.5	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 64.1	Corticosteroids: 100	5ASA	NR
Lofberg, 1996[110]	Budesonide, 32 Route: Oral Dose: 6 mg every 24 hours	Male, %: 46.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 6.7 Age at enrollment Mean: 37 Min: 21 Max: 71	Severity, % Remission: 100 Location, % Ileal: 72 Ileo-colonic: 28 Colonic: 0 Behavior NR CRP NR	CDAI Mean: 88	NR	NR	Budesonide: 28 Prednisolone: 72

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lofberg, 1996[110]	Budesonide, 31 Route: Oral Dose: 3 mg every 24 hours	Male, %: 32.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.4 Age at enrollment Mean: 33 Min: 18 Max: 69	Severity, % Remission: 100 Location, % Ileal: 71 Ileo-colonic: 29 Colonic: 0 Behavior NR CRP NR	CDAI Mean: 104	NR	NR	Budesonide: 65 Prednisolone: 35
Lofberg, 1996[110]	Placebo, 27 Route: Oral Dose: NA every 24 hours	Male, %: 40.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.7 Age at enrollment Mean: 35 Min: 22 Max: 52	Severity, % Remission: 100 Location, % Ileal: 78 Ileo-colonic: 19 Colonic: 4 Behavior NR CRP NR	CDAI Mean: 107	NR	NR	Prednisolone: 52 Budesonide: 48
Malchow, 1984[64]	Sulfasalazine, 75 Route: Oral Dose: 3 g every 24 hours	Male, %: 48 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 31.2	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 165.2	NR	sulfasalazine: 88 Prednisolone: 54.7 Azathioprine: 5.3 : 54.7	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 74 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 41.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 32.4 Ileo-colonic: 46 Colonic: 21.6 Behavior NR CRP NR	CDAI Mean: 148.2	NR	Sulfasalazine: 83.8 Prednisolone: 59.5 Azathioprine: 6.8 : 59.5	NR
Malchow, 1984[64]	(6)-Methylprednisolone, 38 Route: IV Dose: 48 mg every 24 hours	Male, %: 47.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 26.1	Severity NR Location, % Ileal: 31.6 Ileo-colonic: 57.9 Colonic: 10.5 Behavior NR CRP NR	CDAI Mean: 147.4	NR	NR	NR
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 38 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 42.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.2	Severity NR Location, % Ileal: 23.7 Ileo-colonic: 52.6 Colonic: 23.7 Behavior NR CRP NR	CDAI Mean: 185.3	NR	NR	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Sulfasalazine, 42 Route: Oral Dose: 3 g every 24 hours	Male, %: 50 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 33.1	Severity NR Location, % Ileal: 62.4 Ileo-colonic: 113.3 Colonic: 62.4 Behavior NR CRP NR	CDAI Mean: 181.9	NR	NR	NR
Malchow, 1984[64]	(6)-Methylprednisolone, 75 Route: Unknown Dose: 48 mg every 24 hours	Male, %: 50.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 32.5	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 159.9	NR	Sulfasalazine: 81.3 Prednisolone: 55.4 Azathioprine: 4 : 55.4	NR
Malchow, 1984[64]	Placebo, 68 Route: Oral Dose: NA	Male, %: 44.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.1	Severity NR Location, % Ileal: 33.8 Ileo-colonic: 45.6 Colonic: 20.6 Behavior NR CRP NR	CDAI Mean: 161.4	NR	sulfasalazine: 92.6 Prednisolone: 47.8 Azathioprine: 4.4 : 47.8	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Placebo, 42 Route: Oral Dose: NA	Male, %: 35.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.1	Severity NR Location, % Ileal: 23.8 Ileo-colonic: 52.4 Colonic: 23.8 Behavior NR CRP NR	CDAI Mean: 178.2	NR	NR	NR
Mantzaris, 2003[113]	Mesalamine (Salofalk), 28 Route: Unknown Dose: 1 g every 8 hours	Male, %: 42.9 Race NR Smoking, % Smoker, 82 CD NR	Age at diagnosis NR Disease duration Mean: 3.2 Age at enrollment Mean: 31.8 Min: 19 Max: 65	Severity NR Location, % Ileal: 54 Ileo-colonic: 28 Colonic: 18 Behavior NR CRP NR	CDAI Mean: 138 IBDQ Mean: 186	Corticosteroids: 100	Thiopurines: 43	NR
Mantzaris, 2003[113]	Budesonide, 29 Route: Unknown Dose: 6 mg every day	Male, %: 44.8 Race NR Smoking, % Smoker, 86 CD NR	Age at diagnosis NR Disease duration Mean: 3.5 Age at enrollment Mean: 34.1 Min: 20 Max: 62	Severity NR Location, % Ileal: 52 Ileo-colonic: 38 Colonic: 10 Behavior NR CRP NR	CDAI Mean: 139 IBDQ Mean: 188	Corticosteroids: 100	Thiopurines: 41	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Singleton, 1979[75]	Placebo + Prednisone, 18 Route: Oral + Oral Dose: NA + 0.25 mg/kg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity, % Remission: 100 Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	Corticosteroids: 100 Placebo: 100
Singleton, 1979[75]	Sulfasalazine + Prednisone, 16 Route: Oral + Unknown Dose: 1g/15kg to 5g max every day + 0.25 mg/kg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity, % Remission: 100 Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	Corticosteroids: 100 Placebo: 100
Singleton, 1979[75]	Sulfasalazine + Prednisone, 13 Route: Oral + Oral Dose: 1g per 15kg body wt to max of 5g/day every day + 0.25 mg/kg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity, % Remission: 100 Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	5ASA: 100 Corticosteroids: 100
Singleton, 1979[75]	Placebo + Prednisone, 12 Route: Oral + Oral Dose: NA + 0.25 mg/kg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity, % Remission: 100 Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	5ASA: 100 Corticosteroids: 100

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Azathioprine, 54 Route: Oral Dose: 1 mg/kg every 24 hours	Male, %: 57.4 Race, % W: 94.4 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.99 Age at enrollment Mean: 31	Severity, % Remission: 100 Location, % Ileal: 37 Ileo-colonic: 56 Colonic: 7 Behavior NR CRP NR	CDAI Mean: 85.9	NR	NR	Corticosteroids: 31.5
Summers, 1979[56]	Placebo, 101 Route: Oral Dose: NA	Male, %: 53.5 Race, % W: 94.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.84 Age at enrollment Mean: 31.6	Severity, % Remission: 100 Location, % Ileal: 43 Ileo-colonic: 48 Colonic: 9 Behavior NR CRP NR	CDAI Mean: 83.5	NR	NR	Corticosteroids: 31.7
Summers, 1979[56]	Sulfasalazine, 58 Route: Oral Dose: 1/2 g/ 15 kg every 24 hours	Male, %: 53.4 Race, % W: 98.3 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.11 Age at enrollment Mean: 32.2	Severity, % Remission: 100 Location, % Ileal: 50 Ileo-colonic: 40 Colonic: 10 Behavior NR CRP NR	CDAI Mean: 89.4	NR	NR	Corticosteroids: 32.8

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Prednisone, 61 Route: Oral Dose: 04-Jan mg/kg every 24 hours	Male, %: 50.8 Race, % W: 95.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 4.37 Age at enrollment Mean: 32.6	Severity, % Remission: 100 Location, % Ileal: 46 Ileo-colonic: 43 Colonic: 11 Behavior NR CRP NR	CDAI Mean: 94.8	NR	NR	Corticosteroids: 34.4
Randomized controlled trials evaluating aminosalicylates								
Arber, 1995[121]	Placebo, 31 Route: Oral Dose: NA every 24 hours	Male, %: 58 Race NR Smoking, % Present smoker, 19.31 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36	Severity NR Location, % Ileal: 61.2 Ileo-colonic: 33.58 Colonic: 12.9 Behavior NR CRP NR	HBI Mean: 2.3	NR	NR	5ASA: 64.5 Sulfasalazine: 22.58 None: 12.9
Arber, 1995[121]	ASA, 28 Route: Oral Dose: 1 g every day	Male, %: 67.85 Race NR Smoking, % Present smoker, 17.85 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 38	Severity NR Location, % Ileal: 60.71 Ileo-colonic: 17.85 Colonic: 14.28 Behavior NR CRP NR	HBI Mean: 2.2	5ASA: 100	NR	5ASA: 71.42 Sulfasalazine: 10.71 None: 14.3

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Bresci G, 1995[125]	ASA, 33 Route: Unknown Dose: 2.4 g every 24 hours	Male, %: 54.5 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 5.2 Age at enrollment NR	Severity, % Remission: 100 Location, % Ileal: 66.7 Ileo-colonic: 33.3 Behavior NR CRP NR	CDAI Mean: 54 CDEIS Mean: 3	NR	Corticosteroids: 87.9	NR
Bresci G, 1995[125]	Placebo, 33 Route: Unknown Dose: NA	Male, %: 69.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 4.4 Age at enrollment NR	Severity, % Remission: 100 Location, % Ileal: 51.5 Ileo-colonic: 48.5 Behavior NR CRP NR	CDAI Mean: 48 CDEIS Mean: 2.6	NR	Corticosteroids: 93.9	NR
Brignola, 1992[124]	Placebo, 22 Route: Oral Dose: NA every 24 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.5 Age at enrollment NR	Severity, % Remission: 100 Location, % Ileal: 40.9 Ileo-colonic: 59.1 Behavior NR CRP Mean: 2.4	CDAI Mean: 75	NR	Corticosteroids: 45.5	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Brignola, 1992[124]	ASA (Pentasa), 22 Route: Oral Dose: 2 g every 24 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.2 Age at enrollment NR	Severity, % Remission: 100 Location, % Ileal: 45.5 Ileo-colonic: 54.5 Behavior NR CRP Mean: 2.2	CDAI Mean: 82	NR	Corticosteroids: 40.9	NR
Cezard, 2009[194]	Placebo, 62	Male, %: 58 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 0.6 Age at enrollment Mean: 11.6	Severity NR Location, % Ileal: 11 Ileo-colonic: 69 Colonic: 19 Perianal: 31 Behavior NR CRP NR	HBI Mean: 0.9	NR	NR	NR
Cezard, 2009[194]	Mesalamine (Pentasa), 60 Dose: 50 mg/kg every day	Male, %: 62 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 1.1 Age at enrollment Mean: 12	Severity NR Location, % Ileal: 13 Ileo-colonic: 68 Colonic: 18 Perianal: 33 Behavior NR CRP NR	HBI Mean: 0.7	NR	NR	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Gendre, 1993[122]	Mesalamine (Pentasa), 80 Route: Oral Dose: 500 mg every 6 hours	Male, %: 41 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location, % Ileal: 11 Ileo-colonic: 60 Colonic: 29 Perianal: 11 Behavior NR CRP NR	Disease activity index NR	NR	unspecified medication use in the last 1 month prior to the study: 25	NR
Gendre, 1993[122]	Placebo, 81 Route: Oral Dose: NA every 6 hours	Male, %: 53 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location, % Ileal: 12 Ileo-colonic: 54 Colonic: 33 Perianal: 14 Behavior NR CRP NR	Disease activity index NR	NR	just mentioned as medications in the prior 1 month but not specified: 32	NR
Mahmud, 2001[116]	Olsalazine, 167 Route: Oral Dose: 2 g every day	Male, %: 41.9 Race NR Smoking NR CD NR	Age at diagnosis Mean: 32.9 Disease duration Mean: 7.18 Age at enrollment Mean: 40	Severity NR Location, % Ileo-colonic: 53.3 Colonic: 94 Behavior NR CRP NR	CDAI Mean: 59.8	NR	NR	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Mahmud, 2001[116]	Placebo, 160 Route: Oral Dose: NA every day	Male, %: 50 Race NR Smoking NR CD NR	Age at diagnosis Mean: 31.9 Disease duration Mean: 6.56 Age at enrollment Mean: 38.4	Severity NR Location, % Ileo-colonic: 49.4 Colonic: 96.9 Behavior NR CRP NR	CDAI Mean: 55.8	NR	NR	NR
Malchow, 1984[64]	Placebo, 42 Route: Oral Dose: NA	Male, %: 35.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.1	Severity NR Location, % Ileal: 23.8 Ileo-colonic: 52.4 Colonic: 23.8 Behavior NR CRP NR	CDAI Mean: 178.2	NR	NR	NR
Malchow, 1984[64]	(6)-Methylprednisolone, 38 Route: IV Dose: 48 mg every 24 hours	Male, %: 47.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 26.1	Severity NR Location, % Ileal: 31.6 Ileo-colonic: 57.9 Colonic: 10.5 Behavior NR CRP NR	CDAI Mean: 147.4	NR	NR	NR
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 74 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 41.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 32.4 Ileo-colonic: 46 Colonic: 21.6 Behavior NR CRP NR	CDAI Mean: 148.2	NR	Sulfasalazine: 83.8 Prednisolone: 59.5 Azathioprine: 6.8 : 59.5	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	(6)-Methylprednisolone, 75 Route: Unknown Dose: 48 mg every 24 hours	Male, %: 50.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 32.5	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 159.9	NR	Sulfasalazine: 81.3 Prednisolone: 55.4 Azathioprine: 4 : 55.4	NR
Malchow, 1984[64]	Sulfasalazine, 75 Route: Oral Dose: 3 g every 24 hours	Male, %: 48 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 31.2	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 165.2	NR	sulfasalazine: 88 Prednisolone: 54.7 Azathioprine: 5.3 : 54.7	NR
Malchow, 1984[64]	Placebo, 68 Route: Oral Dose: NA	Male, %: 44.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.1	Severity NR Location, % Ileal: 33.8 Ileo-colonic: 45.6 Colonic: 20.6 Behavior NR CRP NR	CDAI Mean: 161.4	NR	sulfasalazine: 92.6 Prednisolone: 47.8 Azathioprine: 4.4 : 47.8	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 38 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 42.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.2	Severity NR Location, % Ileal: 23.7 Ileo-colonic: 52.6 Colonic: 23.7 Behavior NR CRP NR	CDAI Mean: 185.3	NR	NR	NR
Malchow, 1984[64]	Sulfasalazine, 42 Route: Oral Dose: 3 g every 24 hours	Male, %: 50 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 33.1	Severity NR Location, % Ileal: 62.4 Ileo-colonic: 113.3 Colonic: 62.4 Behavior NR CRP NR	CDAI Mean: 181.9	NR	NR	NR
Prantera, 1992[123]	Placebo, 61 Route: Oral Dose: NA every 8 hours	Male, %: 62 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 6.8 Age at enrollment Mean: 36.6	Severity NR Location, % Ileal: 52 Ileo-colonic: 30 Colonic: 18 Behavior NR CRP NR	CDAI Mean: 49	NR	NR	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Prantera, 1992[123]	ASA (Asacol), 64 Route: Oral Dose: 800 mg every 8 hours	Male, %: 62 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.2 Age at enrollment Mean: 35.2	Severity NR Location, % Ileal: 59 Ileo-colonic: 30 Colonic: 11 Behavior NR CRP NR	CDAI Mean: 55	5ASA: 100	NR	NR
Prantera, 2005[115]	Mesalamine (Asacol), 23 Route: Oral Dose: 4 g	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location, % Ileal: 100 Behavior NR CRP NR	Disease activity index NR	NR	NR	Methylprednisolone: 100
Prantera, 2005[115]	Placebo, 17 Route: Unknown Dose: NA	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location, % Ileal: 100 Behavior NR CRP NR	Disease activity index NR	NR	NR	Methylprednisolone: 100
Summers, 1979[56]	Azathioprine, 54 Route: Oral Dose: 1 mg/kg every 24 hours	Male, %: 57.4 Race, % W: 94.4 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.99 Age at enrollment Mean: 31	Severity, % Remission: 100 Location, % Ileal: 37 Ileo-colonic: 56 Colonic: 7 Behavior NR CRP NR	CDAI Mean: 85.9	NR	NR	Corticosteroids: 31.5

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Prednisone, 61 Route: Oral Dose: 04-Jan mg/kg every 24 hours	Male, %: 50.8 Race, % W: 95.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 4.37 Age at enrollment Mean: 32.6	Severity, % Remission: 100 Location, % Ileal: 46 Ileo-colonic: 43 Colonic: 11 Behavior NR CRP NR	CDAI Mean: 94.8	NR	NR	Corticosteroids: 34.4
Summers, 1979[56]	Sulfasalazine, 58 Route: Oral Dose: 1/2 g/ 15 kg every 24 hours	Male, %: 53.4 Race, % W: 98.3 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.11 Age at enrollment Mean: 32.2	Severity, % Remission: 100 Location, % Ileal: 50 Ileo-colonic: 40 Colonic: 10 Behavior NR CRP NR	CDAI Mean: 89.4	NR	NR	Corticosteroids: 32.8
Summers, 1979[56]	Placebo, 101 Route: Oral Dose: NA	Male, %: 53.5 Race, % W: 94.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.84 Age at enrollment Mean: 31.6	Severity, % Remission: 100 Location, % Ileal: 43 Ileo-colonic: 48 Colonic: 9 Behavior NR CRP NR	CDAI Mean: 83.5	NR	NR	Corticosteroids: 31.7

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sutherland, 1997[117]	Placebo, 128 Route: Oral Dose: NA every 6 hours	Male, %: 45 Race NR Smoking, % Smoker, 35 CD NR	Age at diagnosis Mean: 29 Disease duration NR Age at enrollment NR	Severity NR Location, % Ileal: 49.2 Ileo-colonic: 50 Behavior NR CRP NR	CDAI Mean: 75.2 IBDQ Mean: 193	NR	NR	NR
Sutherland, 1997[117]	Mesalamine (Pentasa), 118 Route: Oral Dose: 750 mg every 6 hours	Male, %: 40 Race NR Smoking NR CD NR	Age at diagnosis Mean: 29.7 Disease duration NR Age at enrollment NR	Severity NR Location, % Ileal: 50 Ileo-colonic: 49.2 Behavior NR CRP NR	CDAI Mean: 74.5 IBDQ Mean: 193.4	NR	NR	NR
Thomson, 1995[120]	Placebo, 43 Route: Oral Dose: NA every 12 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 70	NR	NR	NR
Thomson, 1995[120]	Placebo, 105 Route: Oral Dose: NA every 12 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 56.9	NR	NR	NR

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Thomson, 1995[120]	Mesalamine, 36 Route: Oral Dose: 1.5 g every 12 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 74.7	NR	NR	NR
Thomson, 1995[120]	Mesalamine, 102 Route: Oral Dose: 1.5 g every 12 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 61.7	NR	NR	NR
Thomson, 1990[224]	5-ASA, 101 Dose: 500 mg every 8 hours	Male, %: 42.6 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 6 Age at enrollment Mean: 34.1	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 51.8	NR	sulphasalazine: 15.8	Thomson, 1990[224]
Thomson, 1990[224]	Placebo, 105 Route: Oral Dose: NA every 8 hours	Male, %: 45.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 5.3 Age at enrollment Mean: 37.4	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 60.1	NR	sulphasalazine: 16.2	Thomson, 1990[224]

Evidence Table 8. Population characteristics of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Wellmann W, 1988[126]	mesalamine (NR), 31 Route: Oral Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity, % Remission: 100 Location, % Ileal: 35.5 Ileo-colonic: 29 Colonic: 35.5 Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Wellmann W, 1988[126]	Placebo, 35 Route: Oral Dose: NA	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity, % Remission: 100 Location, % Ileal: 31.4 Ileo-colonic: 28.6 Colonic: 40 Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Abbreviations: ASA = Aminosalicylates; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity; CRP = C-reactive protein; g = gram; HBI = Harvey-Bradshaw Index; IBDQ = Inflammatory Bowel Disease Questionnaire; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; kg = kilogram; Max. = maximum; mg = milligram; Min. = minimum; NA = not applicable; NR = not reported; SC = subcutaneous; TNF = tumor necrosis factor; W = white

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Mantzaris, 2009[88]	Hydrocortisone + infliximab Route: IV Dose: 250 mg every 8 wks + 5 mg/kg every 8 wks	Azathioprine + infliximab Route: Oral + IV Dose: 2.0-2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	CDAI (Remission: CDAI < 150) @ 104 wks	NA Yes	Incidence 18 / 23 (78%)	Incidence 17 / 23 (74%) P: 1
Mantzaris, 2009[102]	Azathioprine Route: Oral Dose: 2.0-2.5 mg/kg every 1 d	Budesonide Route: Oral Dose: 6-9 mg every 1 d	CDAI (Relapse rate definition: CDAI increase >100 and >150 total) @ 52 wks	NA Yes	Incidence 8 / 38 (21%)	Incidence 14 / 39 (36%) P: 0.2
Mantzaris, 2009[102]	Azathioprine Route: Oral Dose: 2.0-2.5 mg/kg every 1 d	Budesonide Route: Oral Dose: 6-9 mg every 1 d	CDAI (Relapse rate definition: CDAI increase >100 and >150 total) @ 78 wks	NA Yes	Incidence 9 / 38 (24%)	Incidence 25 / 39 (64%) P: 0.03
Mantzaris, 2009[102]	Azathioprine Route: Oral Dose: 2.0-2.5 mg/kg every 1 d	Budesonide Route: Oral Dose: 6-9 mg every 1 d	Endoscopic healing (CDEIS) @ 52 wks	NA Yes	B: Mean, 7.2 (SD, 3.1) F: Mean, 1.62 (SD, 2.58) P: <0.0001 F-B: Mean, -5.58 P: <0.001 G1-G2: 5.7	B: Mean, 7.1 (SD, 3.5) F: Mean, 7.2 (SD, 3.2) P: <0.0001 F-B: Mean, 0.1 P: 1
Mantzaris, 2009[102]	Azathioprine Route: Oral Dose: 2.0-2.5 mg/kg every 1 d	Budesonide Route: Oral Dose: 6-9 mg every 1 d	Endoscopic healing (complete or near complete mucosal healing') @ 52 wks	NA Yes	Incidence 32 / 38 (83%)	Incidence 9 / 39 (24%) P: 0.0001
Mantzaris, 2009[102]	Azathioprine Route: Oral Dose: 2.0-2.5 mg/kg every 1 d	Budesonide Route: Oral Dose: 6-9 mg every 1 d	AHS-average histology score @ 52 wks	NA Yes	B: Mean, 5.92 (SD, 1.7) F: Mean, 2.92 (SD, 1.93) P: <0.01 F-B: Mean, -3 (SD, 0.23) P: <0.01 G1-G2: 3.3	B: Mean, 5.72 (SD, 1.63) F: Mean, 6.01 (SD, 1.72) P: <0.01 F-B: Mean, 0.29 (SD, 0.09) P: 0.31
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Need for surgery (CD-related surgeries except for drainage of abscess and placement of a seton - responders) @ 52 wks	NA No	Incidence 1 / 172 (0.6%)	Incidence 7 / 170 (4.1%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (all-cause hospitalizations - responders) @ 52 wks	NA No	Incidence 25 / 172 (14.3%) RH: 0.47 (0.25 to 0.89) vs. main	Incidence 42 / 170 (24.8%)
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (CD-related hospitalizations - responders) @ 52 wks	NA No	Incidence 17 / 172 (9.7%) RH: 0.55 (0.25 to 1.22) vs. main	Incidence 23 / 170 (13.4%) P: 0.12
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Need for surgery (CD-related surgeries except for drainage of abscess and placement of a seton - responders) @ 52 wks	NA No	Incidence 0 / 157 (0%)	Incidence 7 / 170 (4.1%)
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (CD-related hospitalizations - responders) @ 52 wks	NA No	Incidence 4 / 157 (2.8%) RH: 0.15 (0.04 to 0.51) vs. main	Incidence 23 / 170 (13.4%) P: <0.01
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (all-cause hospitalizations - responders) @ 52 wks	NA No	Incidence 9 / 157 (5.6%) RH: 0.16 (0.06 to 0.39) vs. main	Incidence 42 / 170 (24.8%) P: <0.02
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Need for surgery (major CD-related surgeries, excluding drainage of abscess and placement of a seton) @ 52 wks	NA Yes	Incidence 1 / 260 (0.4%)	Incidence 10 / 261 (3.8%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (CD-related hospitalizations) @ 52 wks	NA Yes	Incidence 16 / 260 (6%)	Incidence 26 / 261 (10%)
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (all-cause hospitalizations) @ 8 wks	NA Yes	Incidence 14 / 260 (5.2%)	Incidence 34 / 261 (13.1%)
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (CD-related hospitalizations) @ 8 wks	NA NA	Incidence 7 / 260 (2.8%)	Incidence 23 / 261 (9%)
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (CD-related hospitalizations) @ 52 wks	NA Yes	Incidence 21 / 260 (8%) RH: 0.5 (0.26 to 0.94) P: 0.03 vs. main	Incidence 40 / 261 (15.5%)
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (all-cause hospitalizations) @ 52 wks	NA Yes	Incidence 32 / 260 (12.2%) Hazard ratio: 0.45 (0.27 to 0.75) P: 0.003 vs. main	Incidence 66 / 261 (25.2%)
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Need for surgery (major CD-related surgeries, excluding drainage of abscess and placement of a seton) @ 52 wks	NA Yes	Incidence 2 / 257 (0.8%)	Incidence 10 / 261 (3.8%) P: <0.05
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (all-cause hospitalizations) @ 8 wks	NA Yes	Incidence 13 / 257 (4.9%)	Incidence 34 / 261 (13.1%) P: <0.01

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (CD-related hospitalizations) @ 8 wks	NA NA	Incidence 9 / 257 (3.4%)	Incidence 23 / 261 (9%) P: <0.02
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (CD-related hospitalizations) @ 52 wks	NA Yes	Incidence 14 / 257 (5.6%) RH: 0.34 (0.17 to 0.68) P: 0.002 vs. main	Incidence 40 / 261 (15.5%)
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (all-cause hospitalizations) @ 52 wks	NA Yes	Incidence 26 / 257 (10%) Hazard ratio: 0.36 (0.21 to 0.62) vs. main	Incidence 66 / 261 (25.2%) P: <0.01
Feagan, 2008[90]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Number of hospitalizations (CD-related hospitalizations) @ 52 wks	NA Yes	Incidence 13 / 257 (5%)	Incidence 26 / 261 (10%)
Van Assche, 2008[89]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Infliximab + immunomodulator Route: IV + Oral Dose: 5 mg/kg every 8 wks	CDAI (Absolute CDAI) @ 104 wks	NA Yes	F: Median, 104 (IQR, 55 to 165)	F: Median, 92 (IQR, 34 to 164)
Van Assche, 2008[89]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Infliximab + immunomodulator Route: IV + Oral Dose: 5 mg/kg every 8 wks	Endoscopic healing (SES-CD) @ 104 wks	NA NA	F: Median, 2.5	F: Median, 1
Van Assche, 2008[89]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Infliximab + immunomodulator Route: IV + Oral Dose: 5 mg/kg every 8 wks	Endoscopic healing (Absence of ulcers) @ 104 wks	NA NR	Incidence 14 / 23 (61%)	Incidence 16 / 25 (64%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	CDAI (Remission) @ 4 wks	NA No	Incidence 30 / 130 (23%)	Incidence 35 / 120 (29%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	CDAI (Remission) @ 16 wks	NA No	Incidence 61 / 130 (47%)	Incidence 80 / 120 (67%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	CDAI (Remission: Maintenance of remission) @ 48 wks	NA No	Incidence 79 / 130 (61%)	Incidence 102 / 120 (85%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	HR QoL: Global Assessment) @ 12 wks	NA Yes	F: Mean, 44.2 P: 0.032	F: Mean, 30.3 P: 0.032
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	CDAI (Relapse rate) @ 4 wks	NA Yes	Incidence 20 / 168 (12%)	Incidence 31 / 170 (18%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	CDAI (Relapse rate) @ 16 wks	NA Yes	Incidence 57 / 168 (34%)	Incidence 102 / 170 (60%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	CDAI (Relapse rate) @ 48 wks	NA Yes	Incidence 77 / 168 (46%)	Incidence 136 / 170 (80%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	HR QoL (IBDQ) @ 12 wks	NA Yes	Incidence 123 / 168 (73%) B: 185 F: Mean, 181 P: <0.01 F-B: Mean, 51.6 (SD, 31) G1-G2: -7.8	Incidence 80 / 171 (46.9%) B: 178 F: Mean, 163 P: <0.01 F-B: Mean, 43.8 (SD, 35) G1-G2: -7.8 P: <0.01
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	HR QoL (IBDQ) @ 48 wks	NA Yes	Incidence 120 / 168 (71.3%) B: Mean, 185 F: Mean, 181 P: <0.001 F-B: Mean, 53.9 (SD, 33.6) G1-G2: -18.4	Incidence 68 / 171 (40%) B: Mean, 178 F: Mean, 157 P: <0.001 F-B: Mean, 35.5 (SD, 40.3) G1-G2: -18.4 P: <0.001
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	HR QoL (SF-36, MCS) @ 12 wks	NA Yes	B: Mean, 49.5 F: Mean, 49.5 P: <0.01 F-B: Mean, 8.6 (SD, 10.5) G1-G2: -0.6	B: Mean, 49 F: Mean, 44.5 P: <0.01 F-B: Mean, 8 (SD, 11) G1-G2: -0.6 P: NS
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	HR QoL (SF-36, MCS) @ 48 wks	NA Yes	B: Mean, 49.5 F: Mean, 50 P: <0.001 F-B: Mean, 12.6 (SE, 9.4) G1-G2: -5.8	B: Mean, 49 F: Mean, 44 P: <0.001 F-B: Mean, 6.8 (SE, 9.5) G1-G2: -5.8 P: <0.001

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	HR QoL (SF-36, PCS) @ 12 wks	NA Yes	B: Mean, 46.5 F: Mean, 46 P: 0.011 F-B: Mean, 12.5 (SD, 8.5) G1-G2: -3.7	B: Mean, 45.5 F: Mean, 43 P: 0.011 F-B: Mean, 8.8 (SD, 8.9) G1-G2: -3.7 P: <0.01
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	HR QoL (SF-36, PCS) @ 48 wks	NA Yes	B: Mean, 46.5 F: Mean, 46 P: <0.001 F-B: Mean, 12.6 (SD, 9.4) G1-G2: -5.8	B: Mean, 45.5 F: Mean, 41.5 P: <0.001 F-B: Mean, 6.8 (SD, 9.5) G1-G2: -5.8 P: <0.001
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Median time to loss of remission	NA NR	Event rate 336 days	Event rate 86 days
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	CDAI (Relapse rate) @ 24 wks	NA No	Incidence 16 / 35 (46%)	Incidence 15 / 33 (45%) P: 0.58
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	CDAI (Relapse rate) @ 48 wks	NA No	Incidence 18 / 35 (51%)	Incidence 21 / 33 (64%) P: 0.16
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Response: 100 pt drop) @ 18 wks	NA Yes	Incidence 135 / 216 (63%)	Incidence 76 / 212 (36%)
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	CDAI (Remission: CDAI < 150) @ 18 wks	NA Yes	Incidence 103 / 216 (48%)	Incidence 60 / 212 (29%)
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ) @ 18 wks	NA Yes	F: Mean, 175.7 (SD, 29.24) P: 0.001	F: Mean, 167.9 (SD, 32.19) P: 0.001
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ remission (total score ≥170 pts)) @ 18 wks	NA Yes	Incidence 99 / 213 (46.5%)	Incidence 55 / 210 (26.2%) P: 0.001
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ response (≥ 16 pt increase)) @ 18 wks	NA Yes	Incidence 129 / 213 (61%)	Incidence 90 / 210 (43%)
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (IBDQ response (≥ 16 pt increase)) @ 18 wks	NA Yes	Incidence 129 / 216 (60%)	Incidence 90 / 212 (43%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (SF-36 MCS response (+3.9 pts)) @ 18 wks	NA Yes	Incidence 92 / 208 (44.2%)	Incidence 67 / 207 (32.4%) P: 0.016
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (SF-36 MCS) @ 18 wks	NA Yes	F: Mean, 46.9 (SD, 11.53) P: 0.001	F: Mean, 45.2 (SD, 11.83) P: 0.001
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (SF-36 PCS response (+4.1 pts)) @ 18 wks	NA Yes	Incidence 107 / 209 (51.2%)	Incidence 70 / 207 (33.8%) P: 0.001
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (SF-36 PCS) @ 18 wks	NA Yes	F: Mean, 48.1 (SD, 8.17) P: 0.014	F: Mean, 46.4 (SD, 7.69) P: 0.014
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (WPAI:CD Presenteeism) @ 18 wks	NA Yes	F-B: Mean, 4.3 (SD, 23.6) P: NS	F-B: Mean, 13.7 (SD, 30.5) P: <0.001 G1-G2: Mean, 9.4 (95% CI, 2.1 to 16.8) P: 0.013
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (WPAI:CD Daily activity impairment) @ 18 wks	NA Yes	F-B: Mean, 5.1 (SD, 29.4) P: <0.05G1-G2: Mean,	F-B: Mean, 15.3 (SD, 30) P: <0.001 G1-G2: Mean, 10.2 (95% CI, 4.3 to 16.1)
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (WPAI:CD Absenteeism) @ 18 wks	NA Yes	F-B: Mean, 4 (SD, 25.1) P: NSG1-G2: Mean,	F-B: Mean, 10.3 (SD, 23.8) P: <0.001 G1-G2: Mean, 6.3 (95% CI, -0.5 to 13.2) P: 0.07
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (WPAI:CD Overall work impairment) @ 18 wks	NA Yes	F-B: Mean, 5.1 (SD, 24.4) P: <0.05G1-G2: Mean,	F-B: Mean, 16.1 (SD, 32.2) P: <0.001 G1-G2: Mean, 11 (95% CI, 2.8 to 19.2) P: 0.01
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (EQ-5D VAS response (9.2-pt increase)) @ 18 wks	NA Yes	Incidence 115 / 211 (57.2%)	Incidence 77 / 203 (37.9%)
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (EQ-5D VAS) @ 18 wks	NA Yes	F: Mean, 74.6 (SD, 17.13) P: 0.002	F: Mean, 70.2 (SD, 18.07) P: 0.002

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (Normal life) @ 18 wks	NA Yes	Incidence 46 / 215 (21.4%)	Incidence 27 / 210 (12.9%) P: 0.019
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	HR QoL (QALY) @ 18 wks	NA Yes	F: Mean, 0.25 (SD, 0.1) P: 0.001	F: Mean, 0.21 (SD, 0.11) P: 0.001
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Perianal disease (Complete fistula closure) @ 18 wks	NA Yes	Incidence 15 / 28 (54%)	Incidence 13 / 30 (43%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 100pt drop) @ 4 wks	NA Yes	Incidence 15 / 19 (79%)	Incidence 12 / 18 (67%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 100pt drop) @ 16 wks	NA Yes	Incidence 18 / 19 (94%)	Incidence 11 / 18 (61%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 100pt drop) @ 52 wks	NA Yes	Incidence 15 / 19 (79%)	Incidence 10 / 18 (56%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 70pt drop) @ 4 wks	NA Yes	Incidence 17 / 19 (89%)	Incidence 16 / 18 (89%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 70pt drop) @ 16 wks	NA Yes	Incidence 18 / 19 (95%)	Incidence 15 / 18 (83%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 70pt drop) @ 52 wks	NA Yes	Incidence 15 / 19 (79%)	Incidence 13 / 18 (72%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Absolute CDAI) @ 52 wks	NA Yes	F-B: Mean, -150.8 (95% CI, -202 to -99.8) G1-G2: 31.2	F-B: Mean, -119.6 (95% CI, -174 to -65.1) G1-G2: 31.2 P: <0.05
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Remission: CDAI < 150) @ 4 wks	NA Yes	Incidence 16 / 19 (85%)	Incidence 10 / 18 (55%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Remission: CDAI < 150) @ 16 wks	NA Yes	Incidence 17 / 19 (91%)	Incidence 9 / 18 (51%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Remission: CDAI < 150) @ 52 wks	NA Yes	Incidence 15 / 19 (79%)	Incidence 8 / 18 (44%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	HR QoL (IBDQ) @ 16 wks	NA Yes	B: Mean, 187 F: Mean, 177-10	B: Mean, 188 F: Mean, 171-17
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	HR QoL (IBDQ) @ 52 wks	NA Yes	B: Mean, 187 F: Mean, 178.4-8.6	B: Mean, 188 F: Mean, 162.4-25.6
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	HR QoL (IBDQ) @ 4 wks	NA Yes	B: Mean, 187 F: Mean, 181 P: NS-6	B: Mean, 188 F: Mean, 179 P: NS-9
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	Steroid free (completely discontinued steroids) @ 52 wks	NA Yes	Incidence 4 / 6 (67%)	Incidence 4 / 7 (56%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 100pt drop) @ 4 wks	NA Yes	Incidence 16 / 18 (89%)	Incidence 12 / 18 (67%) P: NS
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 100pt drop) @ 16 wks	NA Yes	Incidence 15 / 18 (84%)	Incidence 11 / 18 (61%) P: NS
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 100pt drop) @ 52 wks	NA Yes	Incidence 16 / 18 (89%)	Incidence 10 / 18 (56%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 70pt drop) @ 4 wks	NA Yes	Incidence 18 / 18 (100%)	Incidence 16 / 18 (89%) P: NS
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 70pt drop) @ 16 wks	NA Yes	Incidence 17 / 18 (95%)	Incidence 15 / 18 (83%) P: NS
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Response: 70pt drop) @ 52 wks	NA Yes	Incidence 16 / 18 (89%)	Incidence 13 / 18 (72%) P: NS
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Remission: CDAI < 150) @ 4 wks	NA Yes	Incidence 16 / 18 (89%)	Incidence 10 / 18 (55%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Remission: CDAI < 150) @ 16 wks	NA Yes	Incidence 15 / 18 (83%)	Incidence 9 / 18 (51%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Remission: CDAI < 150) @ 52 wks	NA Yes	Incidence 15 / 18 (83%)	Incidence 8 / 18 (44%) P: <0.05
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	CDAI (Absolute CDAI) @ 52 wks	NA Yes	F-B: Mean, -197.7 (95% CI, -248 to -147) G1-G2: 78.1	F-B: Mean, -119.6 (95% CI, -174 to -65.1) G1-G2: 78.1 P: <0.05
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	HR QoL (IBDQ) @ 4 wks	NA Yes	B: Mean, 191 F: Mean, 187 P: NS-4	B: Mean, 188 F: Mean, 179 P: NS-9
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	HR QoL (IBDQ) @ 16 wks	NA Yes	B: Mean, 191 F: Mean, 186-5	B: Mean, 188 F: Mean, 171-17
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	HR QoL (IBDQ) @ 52 wks	NA Yes	B: Mean, 191 F: Mean, 185.6-5.4	B: Mean, 188 F: Mean, 162.4-25.6
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	Steroid free (completely discontinued steroids) @ 52 wks	NA Yes	Incidence 7 / 8 (88%)	Incidence 4 / 7 (56%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Response: 70 pt drop) @ 22 wks	NA Yes	Incidence 93 / 172 (54.1%)	Incidence 48 / 170 (28.2%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Response: 70 pt drop) @ 52 wks	NA Yes	Incidence 74 / 172 (43%)	Incidence 30 / 170 (17.6%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Absolute CDAI) @ 2 wks	NA Yes	B: Mean, 155 F: Mean, 150 F-B: -5	B: Mean, 170 F: Mean, 175 F-B: 5
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Absolute CDAI) @ 16 wks	NA Yes	B: Mean, 155 F: Mean, 135 F-B: -20	B: Mean, 170 F: Mean, 165 F-B: -5
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Absolute CDAI) @ 52 wks	NA Yes	B: Mean, 155 F: Mean, 100 F-B: -55	B: Mean, 170 F: Mean, 135 F-B: -35

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Response: 100 pt drop) @ 22 wks	NA Yes	Incidence 89 / 172 (51.7%)	Incidence 45 / 170 (26.5%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Response: 100 pt drop) @ 52 wks	NA Yes	Incidence 71 / 172 (41.3%)	Incidence 28 / 170 (16.5%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 98 / 172 (57%)	Incidence 56 / 170 (33%) P: 0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 16 wks	NA Yes	Incidence 74 / 172 (43%)	Incidence 36 / 170 (21%) P: 0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 52 wks	NA Yes	Incidence 62 / 172 (36%)	Incidence 20 / 170 (12%) P: 0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (Zung Self-Rating Depression Scale) @ 8 wks	NA Yes	B: Mean, 44.9 (SD, 10.7) F: Mean, 43.4 (SD, 11) F-B: -1.5	B: Mean, 46.1 (SD, 11.9) F: Mean, 47.4 (SD, 12.8) F-B: 1.3 P: <0.01
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (Zung Self-Rating Depression Scale) @ 52 wks	NA Yes	B: Mean, 44.9 (SD, 10.7) F: Mean, 43.7 (SD, 11) F-B: -1.2	B: Mean, 46.1 (SD, 11.9) F: Mean, 47.9 (SD, 13.1) F-B: 1.8 P: <0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (FACIT-Fatigue Scale Scores) @ 8 wks	NA Yes	B: Mean, 35.6 (SD, 10.6) F: Mean, 38.2 (SD, 10.5) F-B: 2.6	B: Mean, 34.6 (SD, 11.3) F: Mean, 33.4 (SD, 12.2) F-B: -1.2 P: <0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (FACIT-Fatigue Scale Scores) @ 52 wks	NA Yes	B: Mean, 35.6 (SD, 10.6) F: Mean, 36.8 (SD, 11.2) F-B: 1.2	B: Mean, 34.6 (SD, 11.3) F: Mean, 32.5 (SD, 12.6) F-B: -2.1 P: <0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (IBDQ) @ 8 wks	NA Yes	B: Mean, 171 F: Mean, 175 P: <0.001 F-B: 4	B: Mean, 168 F: Mean, 160 P: <0.001 F-B: -8
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (IBDQ) @ 52 wks	NA Yes	B: Mean, 171 F: Mean, 177 P: <0.0001 F-B: 6	B: Mean, 168 F: Mean, 159 P: <0.0001 F-B: -9
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (SF-36 MCS) @ 8 wks	NA Yes	B: Mean, 46.2 (SD, 10.4) F: Mean, 48.4 (SD, 10.7) F-B: 2.2	B: Mean, 47.4 (SD, 10.4) F: Mean, 46.2 (SD, 11) F-B: -1.2 P: NS

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (SF-36 MCS) @ 52 wks	NA Yes	B: Mean, 46.2 (SD, 10.4) F: Mean, 48.7 (SD, 10.5) F-B: 2.5	B: Mean, 47.4 (SD, 10.4) F: Mean, 45.9 (SD, 11.2) F-B: -1.5 P: <0.05
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (SF-36, MCS - +5 pt increase) @ 52 wks	NA Yes	Incidence 94 / 140 (67%)	Incidence 57 / 106 (54%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (SF-36 PCS) @ 8 wks	NA Yes	B: Mean, 44.5 (SD, 7.8) F: Mean, 46.9 (SD, 8.6) F-B: 2.4	B: Mean, 44.3 (SD, 8.9) F: Mean, 44.5 (SD, 9) F-B: 0.2 P: <0.01
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (SF-36 PCS) @ 52 wks	NA Yes	B: Mean, 44.5 (SD, 7.8) F: Mean, 47.5 (SD, 8.5) F-B: 3	B: Mean, 44.3 (SD, 8.9) F: Mean, 45.3 (SD, 8.6) F-B: 1 P: <0.05
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (SF-36, PCS - +5 pt increase) @ 52 wks	NA Yes	Incidence 108 / 140 (77%)	Incidence 65 / 106 (61%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (Abdominal pain VAS) @ 8 wks	NA Yes	B: Mean, 27.8 (SD, 19.4) F: Mean, 24 (SD, 21.2) F-B: -3.8	B: Mean, 28.3 (SD, 19.5) F: Mean, 32.9 (SD, 24.5) F-B: 4.6 P: <0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (Abdominal pain VAS) @ 52 wks	NA NA	B: Mean, 27.8 (SD, 19.4) F: Mean, 23.9 (SD, 22.4) F-B: -3.9	B: Mean, 28.3 (SD, 19.5) F: Mean, 36 (SD, 26.5) F-B: 7.7 P: <0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Perianal disease (Mean number of draining fistulas/ day) @ 52 wks	NA No	Event rate 0.93 events among 1 d	Event rate 1.15 events among 1 d
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Steroid free (corticosteroid-free remission (CDAI < 150)) @ 22 wks	NA Yes	Incidence 20 / 58 (35%)	Incidence 2 / 66 (3%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Steroid free (corticosteroid-free remission (CDAI < 150)) @ 52 wks	NA Yes	Incidence 17 / 58 (29%)	Incidence 4 / 66 (6%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Response: 70 pt drop) @ 22 wks	NA Yes	Incidence 88 / 157 (56.1%)	Incidence 48 / 170 (28.2%) P: <0.001

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Response: 70 pt drop) @ 52 wks	NA Yes	Incidence 77 / 157 (49%)	Incidence 30 / 170 (17.6%) P: <0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Absolute CDAI) @ 2 wks	NA Yes	B: Mean, 165 F: Mean, 160 F-B: -5	B: Mean, 170 F: Mean, 175 F-B: 5
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Absolute CDAI) @ 16 wks	NA Yes	B: Mean, 165 F: Mean, 120 F-B: -45	B: Mean, 170 F: Mean, 165 F-B: -5
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Absolute CDAI) @ 52 wks	NA Yes	B: Mean, 165 F: Mean, 80 F-B: -85	B: Mean, 170 F: Mean, 135 F-B: -35
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Response: 100 pt drop) @ 22 wks	NA Yes	Incidence 82 / 157 (52.2%)	Incidence 45 / 170 (26.5%) P: <0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Response: 100 pt drop) @ 52 wks	NA Yes	Incidence 75 / 157 (47.8%)	Incidence 28 / 170 (16.5%) P: <0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 66 / 157 (42%)	Incidence 56 / 170 (33%) P: NS
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 16 wks	NA Yes	Incidence 71 / 157 (45%)	Incidence 36 / 170 (21%) P: 0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	CDAI (Remission: CDAI < 150) @ 52 wks	NA Yes	Incidence 65 / 157 (41%)	Incidence 20 / 170 (12%) P: 0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (FACIT-Fatigue Scale Scores) @ 8 wks	NA Yes	B: Mean, 34.2 (SD, 11.2) F: Mean, 34.6 (SD, 11.5) F-B: 0.4	B: Mean, 34.6 (SD, 11.3) F: Mean, 33.4 (SD, 12.2) F-B: -1.2 P: NS
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (FACIT-Fatigue Scale Scores) @ 52 wks	NA Yes	B: Mean, 34.2 (SD, 11.2) F: Mean, 35 (SD, 12.7) F-B: 0.8	B: Mean, 34.6 (SD, 11.3) F: Mean, 32.5 (SD, 12.6) F-B: -2.1 P: <0.05
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (IBDQ) @ 8 wks	NA Yes	B: Mean, 167 F: Mean, 170 P: <0.05 F-B: 3	B: Mean, 168 F: Mean, 160 P: <0.05 F-B: -8

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (IBDQ) @ 52 wks	NA Yes	B: Mean, 167 F: Mean, 171 P: <0.01 F-B: 4	B: Mean, 168 F: Mean, 159 P: <0.01 F-B: -9
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (Zung Self-Rating Depression Scale) @ 8 wks	NA Yes	B: Mean, 47 (SD, 11.2) F: Mean, 46.1 (SD, 11.5) F-B: -0.9	B: Mean, 46.1 (SD, 11.9) F: Mean, 47.4 (SD, 12.8) F-B: 1.3 P: NS
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (Zung Self-Rating Depression Scale) @ 52 wks	NA Yes	B: Mean, 47 (SD, 11.2) F: Mean, 45.9 (SD, 12.3) F-B: -1.1	B: Mean, 46.1 (SD, 11.9) F: Mean, 47.9 (SD, 13.1) F-B: 1.8 P: <0.05
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (SF-36 PCS) @ 8 wks	NA Yes	B: Mean, 43.7 (SD, 8.4) F: Mean, 46 (SD, 8.6) F-B: 2.3	B: Mean, 44.3 (SD, 8.9) F: Mean, 44.5 (SD, 9) F-B: 0.2
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (SF-36 PCS) @ 52 wks	NA Yes	B: Mean, 43.7 (SD, 8.4) F: Mean, 47.1 (SD, 9.4) F-B: 3.4	B: Mean, 44.3 (SD, 8.9) F: Mean, 45.3 (SD, 8.6) F-B: 1 P: NS
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (SF-36 MCS) @ 8 wks	NA Yes	B: Mean, 45.7 (SD, 9.3) F: Mean, 46.1 (SD, 11.9) F-B: 0.4	B: Mean, 47.4 (SD, 10.4) F: Mean, 46.2 (SD, 11) F-B: -1.2 P: NS
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (SF-36 MCS) @ 52 wks	NA Yes	B: Mean, 45.7 (SD, 9.3) F: Mean, 46.5 (SD, 12.4) F-B: 0.8	B: Mean, 47.4 (SD, 10.4) F: Mean, 45.9 (SD, 11.2) F-B: -1.5 P: NS
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (Abdominal pain VAS) @ 8 wks	NA Yes	B: Mean, 31 (SD, 18.7) F: Mean, 27.8 (SD, 23.1) F-B: -3.2	B: Mean, 28.3 (SD, 19.5) F: Mean, 32.9 (SD, 24.5) F-B: 4.6 P: <0.05
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	HR QoL (Abdominal pain VAS) @ 52 wks	NA NA	B: Mean, 31 (SD, 18.7) F: Mean, 26.7 (SD, 24.2) F-B: -4.3	B: Mean, 28.3 (SD, 19.5) F: Mean, 36 (SD, 26.5) F-B: 7.7 P: <0.001
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Perianal disease (Mean number of draining fistulas/day) @ 52 wks	NA No	Event rate 0.65 events among 1 d	Event rate 1.15 events among 1 d
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Steroid free (corticosteroid-free remission (CDAI < 150)) @ 22 wks	NA Yes	Incidence 22 / 74 (30%)	Incidence 2 / 66 (3%) P: <0.001

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Steroid free (corticosteroid-free remission (CDAI < 150)) @ 52 wks	NA Yes	Incidence 17 / 74 (23%)	Incidence 4 / 66 (6%) P: 0.008
Lemann, 2005[98]	Azathioprine Route: Oral Dose: as taken before enrollment every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Relapse rate: CDAI > 250, a CDAI between 150-250 on 3 consecutive wks with an increase ≥75 pts, or the need for surgery (with the exception of limited perianal surgery)) @ 78 wks	NA Yes	Incidence 3 / 40 (7.9%)	Incidence 9 / 43 (21.3%) P: 0.195
Lemann, 2005[98]	Azathioprine Route: Oral Dose: as taken before enrollment every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Remission duration)	NA Yes	Event rate 17.3 months	Event rate 15.9 months
Prantera, 2005[115]	Mesalamine (Asacol) Route: Oral Dose: 4 g	Placebo Route: Unknown Dose: NA	CDAI (Remission: CDAI < 150) @ 52 wks	NA NR	Incidence 3 / 23 (13%)	Incidence 3 / 17 (18%)
Hanauer, 2005[106]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Relapse rate: CDAI≥150 plus increase of ≥60 pts or clinical deterioration) @ 13 wks	NA NA	Incidence 14 / 55 (25%)	Incidence 21 / 55 (38%)
Hanauer, 2005[106]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Relapse rate: CDAI≥150 plus increase of ≥60 pts or clinical deterioration) @ 52 wks	NA Yes	Incidence 26 / 55 (47%)	Incidence 32 / 55 (58%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Vilien, 2004[101]	Discontinued azathioprine	Azathioprine Route: Unknown Dose: NR every 1 d	CDAI (Relapse rate: CDAI ≥ 75 increase and CDAI >150 or any increased disease activity requiring new medical or surgical treatment) @ 52 wks	NA NR	Incidence 8 / 15 (53%)	Incidence 2 / 14 (14%)
Mantzaris, 2003[113]	Mesalamine (Salofalk) Route: Unknown Dose: 1 g every 8 hrs	Budesonide Route: Unknown Dose: 6 mg every 1 d	CDAI (Relapse rate: >150 and >100 from baseline) @ 52 wks	NA NR	Incidence 23 / 28 (82%)	Incidence 16 / 29 (55%) P: 0.045
Mantzaris, 2003[113]	Mesalamine (Salofalk) Route: Unknown Dose: 1 g every 8 hrs	Budesonide Route: Unknown Dose: 6 mg every 1 d	HR QoL (IBDQ) @ 52 wks	NA NR	G1-G2: Mean, 113 (SD, 33)	G1-G2: Mean, 150 (SD, 44; 15.93 to 58.07)
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	CDAI (Absolute CDAI) @ 16 wks	NA Yes	F-B: Median, -42	F-B: Median, -16 G1-G2: 26 P: 0.004
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	CDAI (Absolute CDAI) @ 40 wks	NA Yes	F-B: Median, -40	F-B: Median, -15 G1-G2: 25 P: 0.04
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (IBDQ) @ 16 wks	NA Yes	F-B: Median, 14	F-B: Median, 4 G1-G2: -10 P: 0.002
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (IBDQ) @ 40 wks	NA Yes	F-B: Median, 10	F-B: Median, 5 G1-G2: -5
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Need for surgery (All surgeries) @ 40 wks	NA Yes	Event rate 49 events among 100 persons	Event rate 100 events among 100 persons
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Need for surgery (All patients and surgeries) @ 40 wks	NA Yes	Event rate 65 events among 100 persons	Event rate 126 events among 100 persons
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Need for surgery (Major surgeries) @ 40 wks	NA Yes	Event rate 2 events among 100 persons	Event rate 16 events among 100 persons

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Need for surgery (Major surgeries) @ 40 wks	NA Yes	Event rate 2 events among 100 persons	Event rate 11 events among 100 persons
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Need for surgery (Inpatient surgeries and procedures) @ 40 wks	NA Yes	Event rate 16 events among 100 persons	Event rate 55 events among 100 persons
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Need for surgery (Inpatient surgeries and procedures) @ 40 wks	NA Yes	Event rate 7 events among 100 persons	Event rate 41 events among 100 persons
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Need for surgery (not specified) @ 40 wks	NA Yes	Incidence 1 / 96 (1%)	Incidence 0 / 99 (0%)
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Number of hospitalizations (mean number of hospitalizations per 100 patients) @ 40 wks	NA Yes	Event rate 19 events among 100 persons	Event rate 32 events among 100 persons
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Number of hospitalizations (mean number of hospitalizations per 100 patients) @ 40 wks	NA Yes	Incidence 7 / 96 (7.3%) Event rate 11 events among 100 persons	Incidence 18 / 99 (18.2%) Event rate 31 events among 100 persons
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Number of hospitalizations (mean number of hospitalization days) @ 40 wks	NA Yes	0.5	2.5
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Number of hospitalizations (mean number of hospitalization days) @ 40 wks	NA Yes	1.6	2.3

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Perianal disease (50% fistula closure) @ 40 wks	NA Yes	Incidence 9 / 43 (21%)	Incidence 7 / 44 (16%)
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Perianal disease (50% fistula closure) @ 40 wks	NA Yes	Incidence 46 / 91 (42%)	Incidence 23 / 98 (23%) P: 0.001
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Perianal disease (Complete fistula closure) @ 40 wks	NA Yes	Incidence 33 / 91 (36%)	Incidence 19 / 98 (19%) P: 0.009
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Perianal disease (Loss of response, defined as recrudescence of draining fistulas, the need for a change in medication, or need for additional medication, the need for surgery, or discontinuation of study due to lack of efficacy) @ 40 wks	NA Yes	Incidence 40 / 96 (42%)	Incidence 61 / 99 (62%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	CDAI (Remission: CDAI < 150) @ 30 wks	NA NA	Incidence 44 / 113 (39%)	Incidence 23 / 110 (21%) P: 0.003
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	CDAI (Remission: CDAI < 150) @ 52 wks	NA Yes	Incidence 34 / 113 (30%)	Incidence 16 / 110 (15%) P: 0.007
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	CDAI (Response: 70 pt drop & at least 25% reduction) @ 28 wks	NA Yes	Incidence 62 / 113 (55%)	Incidence 30 / 110 (27%) P: 0.002
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	CDAI (Response: 70 pt drop & at least 25% reduction) @ 52 wks	NA Yes	Incidence 44 / 113 (39%)	Incidence 20 / 110 (18%) P: 0.001

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (SF-36 MCS) @ 30 wks	NA Yes	F-B: Mean, 4.6 G1-G2: -1.7	F-B: Mean, 2.9 G1-G2: -1.7 P: NS
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (SF-36 MCS) @ 52 wks	NA Yes	F-B: Mean, 5.1 G1-G2: -3.1	F-B: Mean, 2 G1-G2: -3.1 P: NS
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (SF-36 PCS) @ 28 wks	NA Yes	F-B: Mean, 7.3 G1-G2: -4.2	F-B: Mean, 3.1 G1-G2: -4.2 P: <0.01
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (SF-36 PCS) @ 52 wks	NA Yes	F-B: Mean, 6.1 G1-G2: -3.6	F-B: Mean, 2.5 G1-G2: -3.6 P: <0.05
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (IBDQ) @ 28 wks	NA Yes	B: Mean, 170 (SD, 26) F-B: Mean, 27.1 G1-G2: -13.1	B: Mean, 170 (SD, 29) F-B: Mean, 14 G1-G2: -13.1 P: <0.05
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (IBDQ) @ 52 wks	NA Yes	B: Mean, 170 (SD, 26) F-B: Mean, 22.1 G1-G2: -13.2	B: Mean, 170 (SD, 29) F-B: Mean, 8.9 G1-G2: -13.2 P: <0.05
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Steroid free (Steroid-free remission) @ 52 wks	NA Yes	OR: 4.2 (1.5 to 11.5) vs. main	
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	CDAI (Response: 70 pt drop in CDAI & at least 25% reduction) @ 28 wks	NA Yes	Incidence 67 / 112 (60%)	Incidence 30 / 110 (27%) P: <0.001
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	CDAI (Response: 70 pt drop & at least 25% reduction) @ 52 wks	NA Yes	Incidence 53 / 112 (47%)	Incidence 20 / 110 (18%) P: <0.001
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	CDAI (Remission: CDAI < 150) @ 30 wks	NA NA	Incidence 50 / 112 (45%)	Incidence 23 / 110 (21%) P: 0.002

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	CDAI (Remission: CDAI < 150) @ 52 wks	NA Yes	Incidence 45 / 112 (40%)	Incidence 16 / 110 (15%) P: <0.001
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (SF-36 MCS) @ 30 wks	NA Yes	F-B: Mean, 4.9 G1-G2: -2	F-B: Mean, 2.9 G1-G2: -2 P: NS
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (SF-36 MCS) @ 52 wks	NA Yes	F-B: Mean, 5.8 G1-G2: -3.8	F-B: Mean, 2 G1-G2: -3.8 P: <0.05
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (SF-36 PCS) @ 28 wks	NA Yes	F-B: Mean, 7.3 G1-G2: -4.2	F-B: Mean, 3.1 G1-G2: -4.2 P: <0.01
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (SF-36 PCS) @ 52 wks	NA Yes	F-B: Mean, 7.2 G1-G2: -4.7	F-B: Mean, 2.5 G1-G2: -4.7 P: <0.01
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (IBDQ) @ 28 wks	NA Yes	B: Mean, 168 (SD, 31) F-B: Mean, 31.7 G1-G2: -17.7	B: Mean, 170 (SD, 29) F-B: Mean, 14 G1-G2: -17.7 P: <0.01
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	HR QoL (IBDQ) @ 52 wks	NA Yes	B: Mean, 168 (SD, 31) F-B: Mean, 30.2 G1-G2: -21.3	B: Mean, 170 (SD, 29) F-B: Mean, 8.9 G1-G2: -21.3 P: <0.001
Mahmud, 2001[116]	Olsalazine Route: Oral Dose: 2 g every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Relapse rate: CDAI >150 or 60-pt increase) @ 52 wks	NA NR	Incidence 40 / 167 (24%)	Incidence 42 / 161 (26.1%)
Mahmud, 2001[116]	Olsalazine Route: Oral Dose: 2 g every 1 d	Placebo Route: Oral Dose: NA every 1 d	Clinical relapse (need for additional therapy or surgery in exceptional situations where CDAI criteria are not fulfilled) @ 52 wks	NA NR	Incidence 15 / 167 (9%)	Incidence 17 / 161 (10.6%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Cortot, 2001[107]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Unknown Dose: NA every 1 d	CDAI (Relapse rate: >200 and 60 pt increase) @ 13 wks	NA NR	Incidence 19 / 59 (32%)	Incidence 38 / 58 (65%)
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	CDAI (Absolute CDAI) @ 4 wks	NA Yes	B: Median, 175 F: Median, 105	B: Median, 170 F: Median, 160
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	CDAI (Absolute CDAI) @ 16 wks	NA Yes	B: Median, 175 F: Median, 102	B: Median, 170 F: Median, 192
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	CDAI (Absolute CDAI) @ 36 wks	NA Yes	B: Median, 175 F: Median, 150	B: Median, 170 F: Median, 200
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	CDAI (Response: 70 pt drop) @ 4 wks	NA Yes	Incidence 30 / 37 (80%)	Incidence 28 / 36 (77%)
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	CDAI (Response: 70 pt drop) @ 16 wks	NA Yes	Incidence 27 / 37 (73%)	Incidence 21 / 36 (58%)
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	CDAI (Response: 70 pt drop) @ 36 wks	NA Yes	Incidence 20 / 37 (53%)	Incidence 11 / 36 (30%)
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	CDAI (Remission: CDAI < 150) @ 4 wks	NA Yes	Incidence 22 / 37 (59%)	Incidence 14 / 36 (40%)
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	CDAI (Remission: CDAI < 150) @ 16 wks	NA Yes	Incidence 22 / 37 (60%)	Incidence 11 / 36 (30%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	CDAI (Remission: CDAI < 150) @ 36 wks	NA Yes	Incidence 14 / 37 (37%)	Incidence 7 / 36 (20%)
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	CDAI (time to loss of response)	NA Yes	48 wks	37 wks P: 0.057
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	HR QoL (IBDQ) @ 4 wks	NA Yes	B: Median, 166 F: Median, 180	B: Median, 168 F: Median, 166
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	HR QoL (IBDQ) @ 16 wks	NA Yes	B: Median, 166 F: Median, 180	B: Median, 168 F: Median, 160
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	HR QoL (IBDQ) @ 36 wks	NA Yes	B: Median, 166 F: Median, 158	B: Median, 168 F: Median, 137
Ferguson, 1998[108]	Budesonide + placebo Route: Oral + Oral Dose: 3 mg every 1 d + NA every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Relapse rate: CDAI > 150 and 60-pt increase, or any deterioration requiring a different medicine or surgery) @ 52 wks	NA Yes	Incidence 12 / 26 (46%)	Incidence 16 / 27 (60%)
Ferguson, 1998[108]	Budesonide + placebo Route: Oral + Oral Dose: 3 mg every 1 d + NA every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Absolute CDAI) @ 52 wks	NA Yes	B: Mean, 75 F-B: Mean, 71 G1-G2: -3	B: Mean, 90 F-B: Mean, 68 G1-G2: -3
Ferguson, 1998[108]	Budesonide + placebo Route: Oral + Oral Dose: 3 mg every 1 d + NA every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Relapse rate: Median time to relapse)	NA Yes	335 days	310 days

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Ferguson, 1998[108]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Relapse rate: CDAI > 150 and 60-pt increase, or any deterioration requiring a different medicine or surgery) @ 52 wks	NA Yes	Incidence 11 / 22 (48%)	Incidence 16 / 27 (60%)
Ferguson, 1998[108]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Absolute CDAI) @ 52 wks	NA Yes	B: Mean, 102 F-B: Mean, 14 G1-G2: 54	B: Mean, 90 F-B: Mean, 68 G1-G2: 54
Ferguson, 1998[108]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Relapse rate definition: Median time to relapse)	NA Yes	275 days	310 days
Gross, 1998[109]	Budesonide Route: Oral Dose: 3 mg every 24 hrs	Placebo Route: Oral Dose: NA every 24 hrs	CDAI (Relapse rate: CDAI<150 on 2 consecutive wks) @ 52 wks	NA Yes	Incidence 56 / 84 (66.7%)	Incidence 62 / 95 (65.3%)
de Franchis, 1997[118]	ASA + (6)-Methylprednisolone Route: Oral + Oral Dose: 1000 mg every 8 hrs + every 24 hrs	Placebo + (6)-Methylprednisolone Route: Oral + Oral Dose: NA every 8 hrs + every 24 hrs	CDAI (Relapse rate: CDAI > 150 and ≥60 pts increase, and increase in at least 2 of 3 acute phase reactants) @ 4 wks	NA NR	Incidence 58 / 59 (98%) B: Mean, 70.5 (SD, 4.5)	Incidence 57 / 58 (98%) B: Mean, 71.2 (SD, 4.9)
de Franchis, 1997[118]	ASA + (6)-Methylprednisolone Route: Oral + Oral Dose: 1000 mg every 8 hrs + every 24 hrs	Placebo + (6)-Methylprednisolone Route: Oral + Oral Dose: NA every 8 hrs + every 24 hrs	CDAI (Relapse rate: CDAI > 150 and ≥60 pts increase, and increase in at least 2 of 3 acute phase reactants) @ 16 wks	NA NR	Incidence 16 / 58 (27%)	Incidence 10 / 59 (17%)
de Franchis, 1997[118]	ASA + (6)-Methylprednisolone Route: Oral + Oral Dose: 1000 mg every 8 hrs + every 24 hrs	Placebo + (6)-Methylprednisolone Route: Oral + Oral Dose: NA every 8 hrs + every 24 hrs	CDAI (Relapse rate: CDAI > 150 and ≥60 pts increase, and increase in at least 2 of 3 acute phase reactants) @ 52 wks	NA NR	Incidence 34 / 58 (58.3%)	Incidence 31 / 59 (52.2%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Sutherland, 1997[117]	Mesalamine (Pentasa) Route: Oral Dose: 750 mg every 6 hrs	Placebo Route: Oral Dose: NA every 6 hrs	CDAI (Relapse rate: CDAI>150 and ≥ 60 pts increase, or diagnosed flare up or need for steroids or hospitalization) @ 12 wks	NA No	Incidence 14 / 118 (12%)	Incidence 28 / 128 (22%)
Sutherland, 1997[117]	Mesalamine (Pentasa) Route: Oral Dose: 750 mg every 6 hrs	Placebo Route: Oral Dose: NA every 6 hrs	CDAI (Relapse rate: CDAI>150 and ≥ 60 pts increase, or diagnosed flare up or need for steroids or hospitalization) @ 48 wks	NA No	Incidence 41 / 118 (35%)	Incidence 55 / 128 (43%)
Sutherland, 1997[117]	Mesalamine (Pentasa) Route: Oral Dose: 750 mg every 6 hrs	Placebo Route: Oral Dose: NA every 6 hrs	CDAI (Absolute CDAI) @ 48 wks	NA No	B: Mean, 74.5 (SE, 3.7) F: Mean, 91.5 F-B: Mean, 17 P: 0.02 G1-G2: 18	B: Mean, 75.2 (SE, 4) F: Mean, 110 F-B: Mean, 35 P: 0.001 G1-G2: 18
Sutherland, 1997[117]	Mesalamine (Pentasa) Route: Oral Dose: 750 mg every 6 hrs	Placebo Route: Oral Dose: NA every 6 hrs	HR QoL (IBDQ) @ 48 wks	NA No	B: Mean, 193.4 (SE, 1.9) F: Mean, 180-13.4	B: Mean, 193 (SE, 1.8) F: Mean, 179-14
Sutherland, 1997[117]	Mesalamine (Pentasa) Route: Oral Dose: 750 mg every 6 hrs	Placebo Route: Oral Dose: NA every 6 hrs	Time to relapse (not specified)	NA No	119 days	109 days
Lofberg, 1996[110]	Budesonide Route: Oral Dose: 3 mg every 24 hrs	Placebo Route: Oral Dose: NA every 24 hrs	CDAI (Relapse rate: CDAI > 150 and ≥ 60 pt increase) @ 12 wks	NA NR	Incidence 14 / 31 (45%)	Incidence 12 / 27 (44%)
Lofberg, 1996[110]	Budesonide Route: Oral Dose: 3 mg every 24 hrs	Placebo Route: Oral Dose: NA every 24 hrs	CDAI (Relapse rate: CDAI > 150 and ≥ 60 pt increase) @ 52 wks	NA NR	Incidence 23 / 31 (74%)	Incidence 17 / 27 (63%)
Lofberg, 1996[110]	Budesonide Route: Oral Dose: 3 mg every 24 hrs	Placebo Route: Oral Dose: NA every 24 hrs	CDAI (Median time to relapse)	NA NR	175 days	146 days

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Lofberg, 1996[110]	Budesonide Route: Oral Dose: 6 mg every 24 hrs	Placebo Route: Oral Dose: NA every 24 hrs	CDAI (Relapse rate: CDAI > 150 and ≥ 60 pt increase) @ 12 wks	NA NR	Incidence 6 / 32 (19%)	Incidence 12 / 27 (44%)
Lofberg, 1996[110]	Budesonide Route: Oral Dose: 6 mg every 24 hrs	Placebo Route: Oral Dose: NA every 24 hrs	CDAI (Relapse rate: CDAI > 150 and ≥ 60 pt increase) @ 52 wks	NA NR	Incidence 19 / 32 (59%)	Incidence 17 / 27 (63%)
Lofberg, 1996[110]	Budesonide Route: Oral Dose: 6 mg every 24 hrs	Placebo Route: Oral Dose: NA every 24 hrs	CDAI (Median time to relapse)	NA NR	271 days	146 days
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 3 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Median time to relapse ([CDAI ≥150 + 60 pt increase] OR withdrawn because of medical or surgical treatment))	NA Yes	124 days	39 days
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 3 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Relapse rate: CDAI ≥150 and ≥ 60-pt increase or medical or surgical intervention) @ 52 wks	NA Yes	Incidence 23 / 33 (70%)	Incidence 24 / 36 (67%)
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 3 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Absolute CDAI) @ 12 wks	NA NA	B: Mean, 96 (SD, 40) F: Mean, 155 (SD, 88) P: NS F-B: 59	B: Mean, 115 (SD, 40) F: Mean, 197 (SD, 99) P: NS F-B: 82
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 3 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Absolute CDAI) @ 52 wks	NA Yes	B: Mean, 96 (SD, 40) F: Mean, 209 (SD, 106) P: NS F-B: 113	B: Mean, 115 (SD, 40) F: Mean, 210 (SD, 119) P: NS F-B: 95
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 3 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	HR QoL (IBDQ) @ 12 wks	NA Yes	B: Mean, 185 (SD, 21) F: Mean, 170 (SD, 39) P: NS-15	B: Mean, 181 (SD, 19) F: Mean, 154 (SD, 35) P: NS F-B: -27

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 3 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	HR QoL (IBDQ) @ 52 wks	NA Yes	B: Mean, 185 (SD, 21) F: Mean, 156 (SD, 39) P: NS F-B: -29	B: Mean, 181 (SD, 19) F: Mean, 150 (SD, 38) P: NS F-B: -31
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Absolute CDAI) @ 12 wks	NA NA	B: Mean, 102 (SD, 36) F: Mean, 141 (SD, 87) P: NS F-B: 39	B: Mean, 115 (SD, 40) F: Mean, 197 (SD, 99) P: NS F-B: 82
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Absolute CDAI) @ 52 wks	NA Yes	B: Mean, 102 (SD, 36) F: Mean, 182 (SD, 128) P: NS F-B: 80	B: Mean, 115 (SD, 40) F: Mean, 210 (SD, 119) P: NS95
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	CDAI (Relapse rate: CDAI ≥150 and ≥ 60-pt increase or medical or surgical intervention) @ 52 wks	NA Yes	Incidence 22 / 36 (61%)	Incidence 24 / 36 (67%)
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	Median time to relapse ([CDAI ≥150 + 60 pt increase] OR withdrawn because of medical or surgical treatment)	NA Yes	178 days	39 days P: 0.024
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	HR QoL (IBDQ) @ 12 wks	NA Yes	B: Mean, 184 (SD, 24) F: Mean, 172 (SD, 35) P: NS F-B: -12	B: Mean, 181 (SD, 19) F: Mean, 154 (SD, 35) P: NS F-B: -27
Greenberg, 1996[111]	Budesonide Route: Oral Dose: 6 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	HR QoL (IBDQ) @ 52 wks	NA Yes	B: Mean, 184 (SD, 24) F: Mean, 161 (SD, 36) P: NS F-B: -23	B: Mean, 181 (SD, 19) F: Mean, 150 (SD, 38) P: NS F-B: -31
Thomson, 1995[120]	Mesalamine Route: Oral Dose: 1.5 g every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI>150 and ≥ 60 pt increase (colitis/ ileocolitis only)) @ 4 wks	NA Yes	Incidence 10 / 102 (10%)	Incidence 15 / 105 (14%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Thomson, 1995[120]	Mesalamine Route: Oral Dose: 1.5 g every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI>150 and ≥ 60 pt increase (colitis/ ileocolitis only)) @ 12 wks	NA Yes	Incidence 13 / 102 (13%)	Incidence 18 / 105 (17%)
Thomson, 1995[120]	Mesalamine Route: Oral Dose: 1.5 g every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI>150 and ≥ 60 pt increase (colitis/ ileocolitis only)) @ 52 wks	Active Yes Yes	Incidence 28 / 102 (27%) HR: 0.694 (0.289 to 1.666) P: 0.4501 vs. main	Incidence 33 / 105 (31%)
Thomson, 1995[120]	Mesalamine Route: Oral Dose: 1.5 g every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI>150 and ≥ 60 pt increase (ileitis only)) @ 4 wks	NA Yes	Incidence 4 / 36 (12%)	Incidence 3 / 43 (8%) P: NS
Thomson, 1995[120]	Mesalamine Route: Oral Dose: 1.5 g every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI Relapse rate: CDAI>150 and ≥ 60 pt increase (ileitis only)) @ 12 wks	NA Yes	Incidence 6 / 36 (18%)	Incidence 8 / 43 (19%) P: NS P: NS
Thomson, 1995[120]	Mesalamine Route: Oral Dose: 1.5 g every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI>150 and ≥ 60 pt increase (ileitis only)) @ 52 wks	NA Yes	Incidence 14 / 36 (40%) HR: 0.433 (0.1 to 1.878) P: 0.2634 vs. main	Incidence 10 / 43 (23%) P: NS
Candy, 1995[53]	Placebo + prednisolone Route: Oral + Oral Dose: NA + 1 mg/kg every 1 d	Azathioprine + prednisolone Route: Oral + Oral Dose: 2.5 mg/kg every 1 d + 1 mg/kg every 1 d	CDAI (Absolute CDAI) @ 64 wks	NA Yes	B: Median, 301 (IQR, 264 to 358) F-B: Median, -191.5 (IQR, 45.5 to 256.5) P: 0.06 G1-G2: 141.5	B: Median, 282 (IQR, 240 to 356) F-B: Median, -50 (IQR, 8 to 222)
Candy, 1995[53]	Placebo + prednisolone Route: Oral + Oral Dose: NA + 1 mg/kg every 1 d	Azathioprine + prednisolone Route: Oral + Oral Dose: 2.5 mg/kg every 1 d + 1 mg/kg every 1 d	CDAI (Remission: CDAI < 150) @ 12 wks	NA Yes	Incidence 19 / 30 (63%)	Incidence 24 / 33 (73%) P: 0.6
Candy, 1995[53]	Placebo + prednisolone Route: Oral + Oral Dose: NA + 1 mg/kg every 1 d	Azathioprine + prednisolone Route: Oral + Oral Dose: 2.5 mg/kg every 1 d + 1 mg/kg every 1 d	CDAI (Remission: CDAI < 150) @ 60 wks	NA NA	Incidence 2 / 30 (7%)	Incidence 14 / 33 (42%) P: 0.001

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Candy, 1995[53]	Placebo + prednisolone Route: Oral + Oral Dose: NA + 1 mg/kg every 1 d	Azathioprine + prednisolone Route: Oral + Oral Dose: 2.5 mg/kg every 1 d + 1 mg/kg every 1 d	CDAI (Remission: CDAI<175) @ 64 wks	NA Yes	Incidence 14 / 33 (42%) RR: 6.36 (1.6 to 25.7) vs. main	Incidence 2 / 30 (7%) P: 0.001
Arber, 1995[121]	ASA Route: Oral Dose: 1 g every 1 d	Placebo Route: Oral Dose: NA every 24 hrs	HBI (Relapse rate: >4 increase) @ 4 wks	NA Yes	Incidence 0 / 28 (0%)	Incidence 4 / 31 (14%)
Arber, 1995[121]	ASA Route: Oral Dose: 1 g every 1 d	Placebo Route: Oral Dose: NA every 24 hrs	HBI (Relapse rate: >4 increase) @ 16 wks	NA Yes	Incidence 1 / 28 (3%)	Incidence 7 / 31 (21%)
Arber, 1995[121]	ASA Route: Oral Dose: 1 g every 1 d	Placebo Route: Oral Dose: NA every 24 hrs	HBI (Relapse rate: >4 increase) @ 52 wks	NA Yes	Incidence 8 / 28 (27%)	Incidence 17 / 31 (55%)
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI<150 and ≥60 pt increase) @ 52 wks	NA NA	Incidence 23 / 33 (70%)	Incidence 24 / 36 (67%)
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Time to relapse)	NA NA	124 days	39 days
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Absolute CDAI) @ 12 wks	NA NA	B: Mean, 96 (SD, 40) F: Mean, 155 (SD, 88) F-B: 59	B: Mean, 115 (SD, 40) F: Mean, 197 (SD, 99) F-B: 82
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Absolute CDAI) @ 52 wks	NA NA	B: Mean, 96 (SD, 40) F: Mean, 209 (SD, 106) F-B: 113	B: Mean, 115 (SD, 40) F: Mean, 210 (SD, 119) F-B: 95
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 7 / 67 (10%)	Incidence 7 / 66 (11%)
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 8 wks	NA Yes	Incidence 22 / 67 (33%)	Incidence 13 / 66 (20%) P: 0.13
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 2 wks	NA Yes	B: Mean, 131 F: Mean, 142 F-B: 11	B: Mean, 130 F: Mean, 141 F-B: 11

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 8 wks	NA Yes	B: Mean, 131 F: Mean, 140 F-B: 9	B: Mean, 130 F: Mean, 141 F-B: 11
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 12 wks	NA NA	B: Mean, 185 (SD, 21) F: Mean, 170 (SD, 39) F-B: -15	B: Mean, 181 (SD, 19) F: Mean, 154 (SD, 35) F-B: -27
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 1.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 52 wks	NA NA	B: Mean, 185 (SD, 21) F: Mean, 156 (SD, 39) F-B: -29	B: Mean, 181 (SD, 19) F: Mean, 150 (SD, 38) F-B: -31
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 21 / 61 (34%)	Incidence 7 / 66 (11%)
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 8 wks	NA Yes	Incidence 31 / 61 (51%)	Incidence 13 / 66 (20%) P: <0.001
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Time to relapse)	NA NA	178 days	39 days
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Relapse rate: CDAI<150 and ≥60 pt increase) @ 52 wks	NA NA	Incidence 22 / 36 (61%)	Incidence 24 / 36 (67%)
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Absolute CDAI) @ 12 wks	NA NA	B: Mean, 102 (SD, 36) F: Mean, 141 (SD, 87) F-B: 39	B: Mean, 115 (SD, 40) F: Mean, 197 (SD, 99) F-B: 82
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Absolute CDAI) @ 52 wks	NA NA	B: Mean, 102 (SD, 36) F: Mean, 182 (SD, 128) F-B: 80	B: Mean, 115 (SD, 40) F: Mean, 210 (SD, 119) F-B: 95
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 2 wks	NA Yes	B: Mean, 125 F: Mean, 157 P: 0.0002 F-B: 32	B: Mean, 130 F: Mean, 141 P: 0.0002 F-B: 11
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 8 wks	NA Yes	B: Mean, 125 F: Mean, 166 P: <0.001 F-B: 41	B: Mean, 130 F: Mean, 141 P: <0.001 F-B: 11
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 12 wks	NA NA	B: Mean, 184 (SD, 24) F: Mean, 172 (SD, 35) F-B: -12	B: Mean, 181 (SD, 19) F: Mean, 154 (SD, 35) F-B: -27

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 52 wks	NA NA	B: Mean, 184 (SD, 24) F: Mean, 161 (SD, 36) F-B: -23	B: Mean, 181 (SD, 19) F: Mean, 150 (SD, 38) F-B: -31
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 7.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 2 wks	NA Yes	Incidence 17 / 64 (27%)	Incidence 7 / 66 (11%)
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 7.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	CDAI (Remission: CDAI < 150) @ 8 wks	NA Yes	Incidence 28 / 64 (43%)	Incidence 13 / 66 (20%) P: 0.009
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 7.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 2 wks	NA Yes	B: Mean, 130 F: Mean, 155 P: 0.006 F-B: 25	B: Mean, 130 F: Mean, 141 P: 0.006 F-B: 11
Greenberg, 1994[66]	Budesonide Route: Oral Dose: 7.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 12 hrs	HR QoL (IBDQ) @ 8 wks	NA Yes	B: Mean, 130 F: Mean, 154 P: 0.012 F-B: 24	B: Mean, 130 F: Mean, 141 P: 0.012 F-B: 11
Gendre, 1993[122]	Mesalamine (Pentasa) Route: Oral Dose: 500 mg every 6 hrs	Placebo Route: Oral Dose: NA every 6 hrs	Clinical relapses and surgical complications (Relapse rate: CDAI >250 or CDAI between 150 - 250 but over the baseline value by >50 pts with confirmation 2 wks later and surgery for acute complications)	NA NR	Incidence 29 / 80 (36%)	Incidence 34 / 81 (42%)
Gendre, 1993[122]	Mesalamine (Pentasa) Route: Oral Dose: 500 mg every 6 hrs	Placebo Route: Oral Dose: NA every 6 hrs	Probability of relapse or acute complication as a function of treatment and stratum (Relapse rate: CDAI > 300 or between 150 - 300 if the increase was 50 within 1 year)	NA NR	Incidence 17 / 31 (55%)	Incidence 23 / 33 (71%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Prantera, 1992[123]	ASA (Asacol) Route: Oral Dose: 800 mg every 8 hrs	Placebo Route: Oral Dose: NA every 8 hrs	CDAI (Relapse rate: CDAI > 150 and 100 pt increase) @ 12 wks	NA Yes	Incidence 8 / 64 (12%)	Incidence 13 / 61 (22%)
Prantera, 1992[123]	ASA (Asacol) Route: Oral Dose: 800 mg every 8 hrs	Placebo Route: Oral Dose: NA every 8 hrs	CDAI (Relapse rate: CDAI > 150 and 100 pt increase) @ 52 wks	NA Yes	Incidence 22 / 64 (34%)	Incidence 34 / 61 (55%) P: 0.02
Brignola, 1992[124]	ASA (Pentasa) Route: Oral Dose: 2 g every 24 hrs	Placebo Route: Oral Dose: NA every 24 hrs	CDAI (Relapse rate: ileocolonic sub-group) @ 16 wks	NA No	Incidence 8 / 11 (73%)	Incidence 7 / 13 (54%)
Brignola, 1992[124]	ASA (Pentasa) Route: Oral Dose: 2 g every 24 hrs	Placebo Route: Oral Dose: NA every 24 hrs	CDAI (Relapse rate: CDAI >100 pt increase or >150 for more than 2 wks) @ 16 wks	NR Yes No	Incidence 11 / 21 (52%)	Incidence 13 / 22 (59%)
Brignola, 1992[124]	ASA (Pentasa) Route: Oral Dose: 2 g every 24 hrs	Placebo Route: Oral Dose: NA every 24 hrs	CDAI (Relapse rate: ileal subgroup) @ 16 wks	NA No	Incidence 3 / 10 (30%)	Incidence 6 / 9 (67%)
Brignola, 1988[112]	(6)-Methylprednisolone Route: Unknown Dose: 0.25 mg/kg every 24 hrs	Placebo Route: Unknown Dose: NA	CDAI (Relapse rate: Relapse after LI normalization to less than 100)	NA NR	Incidence 5 / 7 (71%)	Incidence 2 / 3 (67%)
Brignola, 1988[112]	(6)-Methylprednisolone Route: Unknown Dose: 0.25 mg/kg every 24 hrs	Placebo Route: Unknown Dose: NA	CDAI (Relapse rate: 100 pt increase or CDAI >150 for more than 2 wks) @ 24 wks	NA NR	Incidence 1 / 9 (11%)	Incidence 7 / 9 (78%)
O'Donoghue, 1978[100]	Azathioprine Route: Oral Dose: 2 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	(Relapse rate: cumulative probability of relapse (clinically defined)) @ 24 wks	NA No	G1-G2: Mean, 0%	G1-G2: Mean, 25% P: <0.01
O'Donoghue, 1978[100]	Azathioprine Route: Oral Dose: 2 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	(Relapse rate: cumulative probability of relapse (clinically defined)) @ 52 wks	NA No	G1-G2: Mean, 5%	G1-G2: Mean, 41% P: <0.01

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
O'Donoghue, 1978[100]	Azathioprine Route: Oral Dose: 2 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Unnamed disease activity score (Absolute score) @ 52 wks	NA No	F-B: Mean, 0.63 P: <0.05 G1-G2: 1.8	F-B: Mean, 2.46 G1-G2: 1.8
Bergman, 1976[223]	Sulfasalazine + prednisone Route: Oral + Oral Dose: 3 g every 24 hrs + 15 mg every 24 hrs	No treatment	(Relapse rate: determined by X ray evidence) @ 132 wks	NA No	Incidence 16 / 49 (33%)	Incidence 10 / 35 (29%)
Bergman, 1976[223]	Sulfasalazine + prednisone Route: Oral + Oral Dose: 3 g every 24 hrs + 15 mg every 24 hrs	No treatment	(Relapse rate: determined by X ray evidence) @ 52 wks	NA No	Incidence 7 / 49 (14%)	Incidence 4 / 35 (11%)
Bergman, 1976[223]	Sulfasalazine + prednisone Route: Oral + Oral Dose: 3 g every 24 hrs + 15 mg every 24 hrs	No treatment	(Relapse rate: determined by X ray evidence of recurrence between 1 to 2 years of surgery)	NA No	Incidence 8 / 42 (19%)	Incidence 4 / 31 (13%)
Bergman, 1976[223]	Sulfasalazine + prednisone Route: Oral + Oral Dose: 3 g every 24 hrs + 15 mg every 24 hrs	No treatment	(Relapse rate: X ray evidence of relapse between 2 to 3 years after surgery)	NA No	Incidence 1 / 34 (3%)	Incidence 2 / 27 (7%)
Bergman, 1976[223]	Sulfasalazine + prednisone Route: Oral + Oral Dose: 3 g every 24 hrs + 15 mg every 24 hrs	No treatment	(Relapse rate: Number of recurrences during study period) @ 132 wks	NA No	Incidence 9 / 31 (29%)	Incidence 2 / 13 (15%)
Rosenberg, 1975[104]	Azathioprine Route: Oral Dose: 2 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Reduction of steroids (average reduction of prednisolone between groups) @ 26 wks	NA NA	B: Mean, 19.1 F: Mean, 3.6 P: <0.05 F-B: -15.5	B: Mean, 17.3 F: Mean, 11.2 F-B: -6.1
Rosenberg, 1975[104]	Azathioprine Route: Oral Dose: 2 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Steroid free (Taper and stopping steroids) @ 26 wks	NA NR	Incidence 5 / 10 (50%)	Incidence 3 / 10 (30%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Feagan, 2000[105]	Methotrexate Route: IM Dose: 15 mg every 1 wks	Placebo Route: IM Dose: NA every 1 wks	CDAI (Relapse rate: CDAI increase of 100 OR initiation of prednisone or antimetabolite) @ 4 wks	NA NA	Incidence 4 / 40 (10%)	Incidence 7 / 36 (20%)
Feagan, 2000[105]	Methotrexate Route: IM Dose: 15 mg every 1 wks	Placebo Route: IM Dose: NA every 1 wks	CDAI (Relapse rate: CDAI increase of 100 pts OR initiation of prednisone or antimetabolite) @ 16 wks	NA NA	Incidence 12 / 40 (29%)	Incidence 15 / 36 (42%)
Feagan, 2000[105]	Methotrexate Route: IM Dose: 15 mg every 1 wks	Placebo Route: IM Dose: NA every 1 wks	CDAI (Relapse rate: CDAI increase of 100 pts OR initiation of prednisone or antimetabolite) @ 40 wks	NA No	Incidence 14 / 40 (35%)	Incidence 22 / 36 (61%) P: 0.04
Bresci G, 1995[125]	ASA Route: Unknown Dose: 2.4 g every 24 hrs	Placebo Route: Unknown Dose: NA	CDAI (Relapse rate: CDAI ≥ 150 or 100-pt increase and LI ≥ 100)	NA No	Incidence 17 / 32 (53.1%)	Incidence 22 / 31 (70.9%)
Wellmann W, 1988[126]	mesalamine (NR) Route: Oral Dose: NR	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI ≥150) @ 52 wks	NA No	Incidence 10 / 31 (32%)	Incidence 14 / 35 (40%)
Willoughby JM, 1971[99]	Prednisolone + azathioprine Route: Oral + Oral Dose: 60 mg every 24 hrs + 4 mg/kg every 24 hrs	Prednisolone + placebo Route: Oral + Oral Dose: 60 mg every 1 d + NA every 24 hrs	Other index: (not specified) @ 24 wks	NA No	B: Mean, 10.7 F: Mean, 2.3 F-B: -8.4	B: Mean, 7.8 F: Mean, 8 F-B: 0.2
Willoughby JM, 1971[99]	Prednisolone + azathioprine Route: Oral + Oral Dose: current + 2 mg/kg every 24 wks	Prednisolone + placebo Route: Oral + Oral Dose: 60 mg every 1 d + NA every 24 hrs	Other index: (not specified) @ 24 wks	NA No	B: Mean, 3.2 F: Mean, 4.4 F-B: 1.2	B: Mean, 7.8 F: Mean, 8 F-B: 0.2

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Willoughby JM, 1971[99]	Prednisolone + placebo Route: Oral + Oral Dose: current dose + NA every 24 hrs	Prednisolone + azathioprine Route: Oral + Oral Dose: 60 mg every 24 hrs + 4 mg/kg every 24 hrs	Other index: (not specified) @ 24 wks	NA No	B: Mean, 1.8 F: Mean, 8.6 F-B: 6.8	B: Mean, 10.7 F: Mean, 2.3 F-B: -8.4
Willoughby JM, 1971[99]	Prednisolone + azathioprine Route: Oral + Oral Dose: current dose + 2 mg/kg every 24 wks	Prednisolone + placebo Route: Oral + Oral Dose: current dose the patient is taking to keep him free of relapse every 24 hrs + NA every 24 hrs	Other index: (not specified) @ 24 wks	NA No	B: Mean, 3.2 F: Mean, 4.4 F-B: 1.2	B: Mean, 1.8 F: Mean, 8.6 F-B: 6.8
Singleton, 1979[75]	Sulfasalazine + prednisone Route: Oral + Unknown Dose: 1g/15kg to 5g max every 1 d + 0.25 mg/kg every 1 d	Placebo + prednisone Route: Oral + Oral Dose: NA + 0.25 mg/kg every 1 d	CDAI (Remission: CDAI < 150) @ 24 wks	NA NR	Incidence 3 / 16 (19%)	Incidence 2 / 18 (11%)
Singleton, 1979[75]	Sulfasalazine + prednisone Route: Oral + Oral Dose: 1g/15kg to 5g max every 1 d + 0.25 mg/kg every 1 d	Placebo + prednisone Route: Oral + Oral Dose: NA + 0.25 mg/kg every 1 d	CDAI (Remission: CDAI < 150) @ 24 wks	NA NR	Incidence 3 / 13 (23%)	Incidence 2 / 18 (11%)
Singleton, 1979[75]	Placebo + prednisone Route: Oral + Oral Dose: NA + 0.25 mg/kg every 1 d	Sulfasalazine + prednisone Route: Oral + Unknown Dose: 1g/15kg to 5g max every 1 d + 0.25 mg/kg every 1 d	CDAI (Remission: CDAI < 150) @ 24 wks	NA NR	Incidence 4 / 12 (33%)	Incidence 3 / 16 (19%)
Singleton, 1979[75]	Sulfasalazine + prednisone Route: Oral + Oral Dose: 1g/15kg to 5g max every 1 d + 0.25 mg/kg every 1 d	Placebo + prednisone Route: Oral + Oral Dose: NA + 0.25 mg/kg every 1 d	CDAI (Remission: CDAI < 150) @ 24 wks	NA NR	Incidence 3 / 13 (23%)	Incidence 4 / 12 (33%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1/2 g/ 15 kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 16 wks	NA Yes	Incidence 8 / 58 (13%)	Incidence 11 / 101 (11%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1/2 g/ 15 kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 52 wks	NA Yes	Incidence 19 / 58 (33%)	Incidence 27 / 101 (27%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1/2 g/ 15 kg every 24 hrs	Placebo Route: Oral Dose: NA	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 1 / 6 (17%)	Incidence 2 / 7 (29%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 04-Jan mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 16 wks	NA Yes	Incidence 9 / 61 (15%)	Incidence 11 / 101 (11%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 04-Jan mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 52 wks	NA Yes	Incidence 18 / 61 (29%)	Incidence 27 / 101 (27%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 04-Jan mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 1 / 2 (50%)	Incidence 2 / 7 (29%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 16 wks	NA Yes	Incidence 9 / 54 (16%)	Incidence 11 / 101 (11%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 52 wks	NA Yes	Incidence 16 / 54 (29%)	Incidence 27 / 101 (27%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 0 / 3 (0%)	Incidence 2 / 7 (29%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Prednisone Route: Oral Dose: 04-Jan mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1/2 g/ 15 kg every 24 hrs	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 16 wks	NA Yes	Incidence 9 / 61 (15%)	Incidence 8 / 58 (13%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 04-Jan mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1/2 g/ 15 kg every 24 hrs	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 52 wks	NA Yes	Incidence 18 / 61 (29%)	Incidence 19 / 58 (33%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 04-Jan mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1/2 g/ 15 kg every 24 hrs	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 1 / 2 (50%)	Incidence 1 / 6 (17%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1/2 g/ 15 kg every 24 hrs	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 16 wks	NA Yes	Incidence 9 / 54 (16%)	Incidence 8 / 58 (13%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1/2 g/ 15 kg every 24 hrs	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 52 wks	NA Yes	Incidence 16 / 54 (29%)	Incidence 19 / 58 (33%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1/2 g/ 15 kg every 24 hrs	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 0 / 3 (0%)	Incidence 1 / 6 (17%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Prednisone Route: Oral Dose: 04-Jan mg/kg every 24 hrs	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 16 wks	NA Yes	Incidence 9 / 54 (16%)	Incidence 9 / 61 (15%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Prednisone Route: Oral Dose: 04-Jan mg/kg every 24 hrs	CDAI (Relapse rate: CDAI>150 and ≥100-pt increase, plus other criteria) @ 52 wks	NA Yes	Incidence 16 / 54 (29%)	Incidence 18 / 61 (29%)

Evidence Table 9. Effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Prednisone Route: Oral Dose: 04-Jan mg/kg every 24 hrs	Perianal disease (Complete fistula closure) @ 104 wks	NA No	Incidence 0 / 3 (0%)	Incidence 1 / 2 (50%)

Abbreviations: 95% CI = 95% Confidence Interval; 6-MP = 6-Mercaptopurine; @ = at; AE = adverse events; AP = Acute Phase; ASA = Aminosalicylates; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity; d= day; EQ-5D VAS = EuroQol (EQ-5D), a generic health index comprises a five-part questionnaire and a visual analogue self-rating scale; FACIT = functional assessment of chronic illness therapy; g = gram; g/kgs = gram/kilograms; h = hour; HBI = Harvey-Bradshaw Index; HR QoL= Health-related Quality of Life; hrs = hours; IBDQ = Inflammatory Bowel Disease Questionnaire; IFX= Infliximab; IM = intramuscular; IV= intravenous; IQR= inter-quartile range; ITT = intention to treat; kg = kilogram; Max. = maximum; MCS = Mental Component Score; mg = milligram; mg/d = milligram/day; mg/kg = milligram/kilogram; mg/mo = milligram/month; Min. = minimum; Mo/mos= month(s); NA = Not Applicable; NR= Not Reported; NS = not significant; OR: Odds Ratio; PCS = Physical Component Score; PGWB = Psychological General Well-Being; P = p-value; pt = point; QALY = Quality-Adjusted Life Year; rx = reaction; SC = subcutaneous; SD = standard deviation; SE= standard error; SES-CD = Simplified Endoscopic Activity Score for Crohn's Disease; SF = Short Form; Steroid free = steroid-free remission; TNF = tumor necrosis factor; TPMT= thiopurine methyltransferase; UTD = unable to determine; VAS = visual analog scale; and wks = weeks; WPAI:CD = Work Productivity and Activity Impairment: Crohn's Disease.

.

Evidence Table 10. Study quality of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Randomized controlled trials evaluating biologics								
Colombel, 2007[82]	Yes	Yes	Yes	No	No	Yes	Yes	Poor
Feagan, 2003[93]	Yes	Yes	Yes	No	No	Yes	Yes	Poor
Feagan, 2007[81]	Yes	Yes	Yes	Unclear	No	Yes	Yes	Fair
Feagan, 2008[90]	Yes	Yes	Yes	Yes	No	Yes	Yes	Fair
Hanauer, 2002[86]	Yes	Yes	Yes	No	No	Yes	Yes	Poor
Lichtenstein, 2005[92]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Fair
Mantzaris, 2009[88]	Unclear	No	No	No	Yes	No	No	Poor
Rutgeerts, 1999[85]	Yes	Yes	Yes	No	Yes	Yes	Yes	Fair
Rutgeerts, 2004[94]	Yes	Yes	Yes	No	Yes	Yes	Yes	Poor
Sandborn, 2005[33]	Yes	Yes	Yes	Unclear	No	Yes	Yes	Fair
Sandborn, 2007[83]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Sands, 2004[87]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Schreiber, 2007[84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Van Assche, 2008[89]	Yes	Yes	No	Yes	No	No	No	Poor
Randomized controlled trials evaluating thiopurines								
Candy, 1995[53]	Unclear	Yes	Unclear	Unclear	Yes	UTD	NA	Fair
Lemann, 2005[98]	Yes	Yes	Yes	Yes	Yes	Yes	UTD	Good
Mantzaris, 2009[102]	Yes	Yes	No	No	Yes	UTD	NA	Fair
O'Donoghue, 1978[100]	Unclear	Unclear	Yes	Yes	Yes	UTD	NA	Good

Evidence Table 10. Study quality of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Rosenberg, 1975[104]	Unclear	Yes	Yes	Yes	Yes	Yes	UTD	Good
Summers, 1979[56]	Yes	Yes	Unclear	Yes	Unclear	No	NA	Poor
Vilien, 2004[101]	Yes	Yes	No	Yes	Yes	UTD	NA	Good
Willoughby JM, 1971[99]	Yes	Yes	Yes	Yes	Yes	UTD	NA	Good
Randomized controlled trials evaluating methotrexate								
Feagan, 2000[105]	Yes	Yes	Yes	No	No	Yes	No	Fair
Randomized controlled trials evaluating corticosteroids								
Bergman, 1976[223]	Yes	No	No	Yes	No	Yes	NA	Poor
Brignola, 1988[112]	Unclear	Unclear	Unclear	Yes	No	UTD	NA	Fair
Cortot, 2001[107]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
de Franchis, 1997[118]	Yes	Yes	Yes	No	Yes	Yes	UTD	Poor
Ferguson, 1998[108]	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Greenberg, 1994[66]	Unclear	Unclear	Unclear	Unclear	No	Yes	Yes	Fair
Greenberg, 1996[111]	Yes	Unclear	Unclear	Unclear	No	Yes	Yes	Poor
Gross, 1998[109]	Unclear	Unclear	Yes	Yes	No	Yes	UTD	Fair
Hanauer, 2005[106]	Yes	Unclear	Unclear	Unclear	No	Yes	Yes	Fair
Lofberg, 1996[110]	Yes	Yes	Yes	Yes	Yes	Yes	UTD	Good
Malchow, 1984[64]	Unclear	Yes	Yes	No	No	Yes	UTD	Fair
Mantzaris, 2003[113]	Unclear	Unclear	No	Yes	Yes	UTD	NA	Fair
Singleton, 1979[75]	Unclear	Yes	Yes	Yes	Yes	No	NA	Good

Evidence Table 10. Study quality of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in terms of maintaining remission (KQ2)

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Summers, 1979[56]	Yes	Yes	Unclear	Yes	Unclear	No	NA	Poor
Randomized controlled trials evaluating 5-aminosalicylate acids								
Arber, 1995[121]	Yes	Yes	Yes	Unclear	Yes	UTD	NA	Fair
Bresci G, 1995[125]	No	No	Unclear	Yes	Yes	UTD	NA	Fair
Brignola, 1992[124]	Unclear	Yes	Yes	Yes	Yes	Yes	No	Good
Cezard, 2009[194]	Yes	Yes	Yes	Unclear	Yes	No	NA	Fair
Gendre, 1993[122]	Unclear	Unclear	Yes	Yes	Yes	No	NA	Good
Mahmud, 2001[116]	Yes	Yes	Yes	Yes	Yes	Yes	UTD	Good
Malchow, 1984[64]	Unclear	Yes	Yes	No	No	Yes	UTD	Fair
Prantera, 1992[123]	Unclear	Unclear	Yes	Yes	Yes		NA	Good
Prantera, 2005[115]	Unclear	Unclear	Unclear	No	No	Yes	Yes	Poor
Summers, 1979[56]	Yes	Yes	Unclear	Yes	Unclear	No	NA	Poor
Sutherland, 1997[117]	Yes	Yes	Yes	No	Unclear	UTD	NA	Poor
Thomson, 1995[120]	Yes	Yes	Yes	Unclear	Unclear	Yes	UTD	Poor
Wellmann W, 1988[126]	Unclear	Yes	Yes	Yes	Yes	UTD	NA	Good

Abbreviations: NA = not applicable; UTD = unable to determine

*Study Quality Criteria: Criteria for a judgment of "GOOD" (i.e. low risk of bias): These studies have the least bias and results are considered valid- A study that adheres mostly to the commonly held concepts of high quality including the following: a) A formal randomized controlled study; b)Clear description of the population, setting, interventions, and comparison groups; c) Appropriate measurements of outcomes; d) Appropriate statistical and analytic methods and reporting; e) No reporting errors; f) Low dropout rate; and g) Clear reporting of dropouts. Criteria for a judgment of "FAIR": a) These studies are susceptible to some bias, but it is not sufficient to invalidate the results; b) do not meet all the criteria required for a rating of good qualities because they have some deficiencies, but no flaw is likely to cause major bias; and c) The study may be missing information, making it difficult to assess limitations and potential problems. Criteria for a judgment of "POOR" (i.e. high risk of bias):a) These studies have significant flaws that imply biases of various types that may invalidate the results; b) Have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Evidence Table 11. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for safety (KQ3)

Comparison	Outcome	Number of studies (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
TNF-alpha inhibitor vs no TNF-alpha inhibitor	Mortality	12 RCTs 3,896 CD 1 prospective 2 retrospective 6,464 CD 1,409 IBD	Moderate	Consistent	Direct	Very imprecise	Neither favored Observational RR range 0.8 – 4.3 Low
Infliximab + IMM vs infliximab	Mortality	3 RCTs 535 CD 3 retrospective 1 unclear 690 CD 221 IBD	High	Inconsistent	Direct	Very imprecise	Neither favored Low
Infliximab + IMM vs IMM	Mortality	1 RCT 340 CD	Moderate	NA	Direct	Very imprecise	Neither favored Low
Infliximab + corticosteroids vs infliximab	Mortality	2 retrospective 71 CD 100 IBD	High	NA	Direct	Very imprecise	Neither favored Low
Infliximab vs IMM	Mortality	1 RCT 324 CD	Moderate	NA	Direct	Very imprecise	Neither favored Low
Natalizumab vs placebo	Mortality	3 RCTs 1,414 CD	Moderate	Consistent	Direct	Very imprecise	Neither favored Low
IMM vs no IMM	Mortality	3 RCTs 425 CD 2 prospective 2 retrospective 11,829 CD 19,486 IBD	High	Inconsistent	Direct	Imprecise	Neither favored Observational RR range 0.7 – 1.3 Low
Azathioprine vs corticosteroids	Mortality	2 RCTs 336 CD	Moderate	Consistent	Direct	Very imprecise	Neither favored Low
Azathioprine vs sulfasalazine	Mortality	1 RCT 245 CD	Moderate	NA	Direct	Very imprecise	Neither favored Low
Azathioprine + prednisone vs prednisone	Mortality	1 RCT 81 CD	Moderate	NA	Direct	Very imprecise	Neither favored Low

Evidence Table 11. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for safety (KQ3)

Comparison	Outcome	Number of studies (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Corticosteroids vs no corticosteroids	Mortality	2 RCTs 547 CD 1 prospective 3 retrospective 15,070 CD 554 IBD	High	Inconsistent	Direct	Imprecise	No corticosteroids favored Observational RR range 1.0 – 2.5 Low
Corticosteroids vs ASA	Mortality	2 RCTs 508 CD	Moderate	Consistent	Direct	Very imprecise	Neither favored Low
Corticosteroids + ASA vs placebo, corticosteroids or ASA	Mortality	1 RCT 452 CD	Moderate	NA	Direct	Very imprecise	Neither favored Low
ASA vs no ASA	Mortality	4 RCTs 674 CD 1 retrospective 3,241 CD	Moderate	Inconsistent	Direct	Imprecise	Neither favored Observational RR 0.7 Low
TNF-alpha inhibitor vs no TNF-alpha inhibitor	Lymphoma	8 RCTs 2,704 CD 3 retrospective 9,389 CD 1,409 IBD	Moderate	Inconsistent	Direct	Imprecise	Neither favored Observational RR range 0.6 – 1.7 Low
TNF-alpha inhibitor + IMM + steroids vs no therapy	Lymphoma	1 retrospective NR CD	High	NA	Direct	Very imprecise	Neither favored Low
Infliximab + IMM vs infliximab	Lymphoma	1 retrospective 100 IBD	High	NA	Direct	Very imprecise	Neither favored Low
TNF-alpha inhibitor + IMM vs no therapy	Lymphoma	1 retrospective NR CD	High	NA	Direct	Imprecise	Neither favored Observational RR = 1.5 Low

Evidence Table 11. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for safety (KQ3)

Comparison	Outcome	Number of studies (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Infliximab + corticosteroids vs infliximab	Lymphoma	1 retrospective 100 IBD	High	NA	Direct	Very imprecise	Neither favored Low
TNF-alpha inhibitor + corticosteroids vs no therapy	Lymphoma	1 retrospective NR CD	High	NA	Direct	Very imprecise	Neither favored Low
Natalizumab vs placebo	Lymphoma	3 RCTs 1,414 CD	Moderate	Consistent	Direct	Very imprecise	Neither favored Low
Natalizumab + infliximab vs infliximab	Lymphoma	1 RCT 79 CD	Low	NA	Direct	Very imprecise	Neither favored Low
IMM vs no IMM	Lymphoma	1 prospective 4 retrospective 1 case-control 8,581 CD 54,939 IBD	High	Inconsistent	Direct	Imprecise	Neither favored Observational RR range 0.3 – 5.3 Low
IMM + corticosteroids vs no therapy	Lymphoma	1 retrospective NR CD	High	NA	Direct	Very imprecise	Neither favored Low
Azathioprine + ASA vs azathioprine	Lymphoma	1 retrospective 104 CD	High	NA	Direct	Very imprecise	Neither favored Low
Corticosteroids vs no therapy	Lymphoma	1 retrospective NR CD	High	NA	Direct	Very imprecise	Neither favored Observation HR 1.0 Low
Corticosteroids vs no corticosteroids	Lymphoma	1 retrospective 15,164 IBD	High	NA	Direct	Imprecise	Neither favored Observational OR 1.0 Low
ASA vs no ASA	Lymphoma	1 retrospective 15,164 IBD	High	NA	Direct	Imprecise	Neither favored Observational OR 1.0 Low

Evidence Table 11. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for safety (KQ3)

Comparison	Outcome	Number of studies (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
TNF-alpha inhibitor vs no TNF-alpha inhibitor	Cervical cancer	1 RCT 371 CD women 3 retrospective 1,567 IBD women	High	Inconsistent	Direct	Imprecise	Neither favored; Low
IMM vs no IMM	Cervical cancer	4 retrospective 1,942 IBD women	High	Inconsistent	Direct	Imprecise	Neither favored; Low
Corticosteroids vs no corticosteroids	Cervical cancer	2 retrospective 1,205 IBD women	High	Inconsistent	Direct	Imprecise	Neither favored; Low
ASA vs no ASA	Cervical cancer	1 retrospective 1,165 IBD women	High	NA	Direct	Imprecise	Neither favored; Low
TNF-alpha inhibitor vs no TNF-alpha inhibitor	Cancers	8 RCTs 3,393 CD 3 retrospective 1,966 CD 1,409 IBD 1 case-control 1,935 CD	Moderate	Inconsistent	Direct	Imprecise	Neither favored Observational RR range 0.2 – 3.6 Low
TNF-alpha inhibitor + IMM + steroids vs no therapy	Cancers	1 retrospective 8,581 CD	High	NA	Direct	Imprecise	Neither favored Observational RR 0.7 – 0.9 Low
TNF-alpha inhibitor + IMM versus no TNF-alpha inhibitor + no IMM	Cancers	1 case-control 1,935 CD	High	NA	Direct	Precise	No TNF + No IMM favored Observational RR range 5.9 – 6.8 Low
Infliximab + IMM vs infliximab	Cancers	3 RCTs 441 CD 2 retrospective 573 CD 100 IBD	Moderate	Inconsistent	Direct	Imprecise	Neither favored Observational RR 2.9 Low
Infliximab + IMM vs IMM	Cancers	2 RCTs 435 CD	Moderate	Consistent	Direct	Very imprecise	Neither favored Low

Evidence Table 11. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for safety (KQ3)

Comparison	Outcome	Number of studies (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
TNF-alpha inhibitor + IMM vs no therapy	Cancers	1 retrospective 8,581 CD	High	NA	Direct	Imprecise	Neither favored Observational RR range 0.9 – 1.1 Low
Infliximab + corticosteroids vs infliximab	Cancers	2 retrospective 221 IBD	High	NA	Direct	Very imprecise	Neither favored Low
TNF-alpha inhibitor + corticosteroids vs no therapy	Cancers	1 retrospective 8,581 CD	High	NA	Direct	Imprecise	Neither favored Observational RR range 0.3 – 0.6 Low
Infliximab vs IMM	Cancers	1 RCT 324 CD	Moderate	NA	Direct	Very imprecise	Neither favored Low
Natalizumab vs placebo	Cancers	3 RCTs 1,414 CD	Moderate	Consistent	Direct	Very imprecise	Neither favored Low
Natalizumab + infliximab vs infliximab	Cancers	1 RCT 79 CD	Low	NA	Direct	Very imprecise	Neither favored Low
IMM vs no IMM	Cancers	1 RCT 291 CD 1 prospective 3 retrospective 5 case-control 10,551 CD 39,527 IBD	High	Inconsistent	Direct	Imprecise	Neither favored Observational RR range 0 – 10.8 Low
IMM + corticosteroids vs no therapy	Cancers	1 retrospective 8,581 CD	High	NA	Direct	Very imprecise	Neither favored Low
Azathioprine vs prednisone	Cancers	1 RCT 259 CD	Moderate	NA	Direct	Very imprecise	Neither favored Low
Azathioprine vs sulfasalazine	Cancers	1 RCT 245 CD	Moderate	NA	Direct	Very imprecise	Neither favored Low
Azathioprine + ASA vs azathioprine	Cancers	1 retrospective 104 CD	High	NA	Direct	Very imprecise	Neither favored Low

Evidence Table 11. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for safety (KQ3)

Comparison	Outcome	Number of studies (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Corticosteroids vs no corticosteroids	Cancers	1 RCT 324 CD 1 retrospective 3 case-control 8,616 CD 1,584 IBD	High	Inconsistent	Direct	Imprecise	Neither favored Observation RR range 1.0 – 1.6 Low
Prednisone vs sulfasalazine	Cancers	1 RCT 278 CD	Moderate	NA	Direct	Very imprecise	Neither favored Low
ASA vs no ASA	Cancers	1 RCT 310 CD 1 retrospective 3 case-control 35 CD 10.328 IBD	High	Inconsistent	Direct	Imprecise	Neither favored Observational RR 0.2 – 1.2 Low
TNF-alpha inhibitor versus no TNF-alpha inhibitor	Infections	13 RCTs 4,059 CD 1 prospective 1 retrospective 1 case-control 6,290 CD 1,709 IBD	Moderate	Inconsistent	Direct	Imprecise	Neither favored RCT RR range 0.3 – 5.5 Observational RR range 0.7 – 11.1 Low
Infliximab + IMM vs infliximab	Infections	3 RCTs 607 CD 1 retrospective 1 uclear 57 CD 121 IBD	Moderate	Inconsistent	Direct	Imprecise	Neither favored RR range 0.8 – 3.2 Low
Infliximab + IMM vs IMM	Infections	2 RCTs 340 CD 1 retrospective 10,141 IBD	Moderate	Inconsistent	Direct	Imprecise	Neither favored RR 1.1 Low
Infliximab + IMM vs corticosteroids	Infections	1 RCT 129 CD	Moderate	NA	Direct	Imprecise	Neither favored Low

Evidence Table 11. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for safety (KQ3)

Comparison	Outcome	Number of studies (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Infliximab vs IMM	Infections	1 RCT 324 CD 1 retrospective 3.404 IBD	Moderate	NA	Direct	Imprecise	Neither favored RCT RR range 0.9 – 1.0 Observational RR range 0.7 – 1.1 Low
TNF-alpha inhibitor + IMM vs no therapy	Infections	1 retrospective 1 case-control 8,581 CD 300 IBD	High	NA	Direct	Imprecise	Neither favored RR range 0.7 – 4.8 Low
TNF-alpha inhibitor + IMM + corticosteroids vs no therapy	Infections	1 retrospective 1 case control 8,581 CD 300 IBD	High	NA	Direct	Imprecise	Neither favored RR range 2.4 – 4.1 Low
TNF-alpha inhibitor + corticosteroids vs no therapy	Infections	1 retrospective 8,581 CD	High	NA	Direct	Imprecise	Neither favored RR range 0.7 – 5.6 Low
Natalizumab versus placebo	Infections	3 RCTs 1,414 CD	Moderate	Inconsistent	Direct	Imprecise	Neither favored RR range 0.3 – 1.3 Low
Natalizumab + infliximab vs infliximab	Infections	1 RCT 79 CD	Moderate	NA	Direct	Imprecise	Neither favored RR 0.9 Low
IMM vs no IMM	Infections	3 RCTs 463 CD 1 retrospective, 1 prospective 6253 CD 302 IBD	Moderate	NA	Direct	Imprecise	Neither favored RR range 0.6 – 2.0 Low
IMM vs no therapy	Infections	1 retrospective 2 case-control 10,141 CD 2,538 IBD	High	NA	Direct	Imprecise	Neither favored RR range 0.6 – 4.1 Low

Evidence Table 11. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for safety (KQ3)

Comparison	Outcome	Number of studies (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
IMM vs corticosteroids	Infections	2 RCTs 336 CD 1 retrospective 10,141 IBD	Moderate	Inconsistent	Direct	Imprecise	Neither favored RR range 0.3 – 2.9 Low
Azathioprine vs sulfasalazine	Infections	1 RCT 245 CD	Moderate	NA	Direct	Imprecise	Neither favored RR 0.6 Low
IMM + steroids vs steroids	Infections	3 RCTs 263 CD	Moderate	Inconsistent	Direct	Imprecise	Neither favored RR range 0.9 – 1.3 Low
Azathioprine + ASA vs azathioprine	Infections	1 retrospective 199 IBD	High	NA	Direct	Very imprecise	Neither favored Low
IMM + corticosteroids vs no therapy	Infections	1 retrospective 2 case-control 8,581 CD 2,538 IBD	High	NA	Direct	Imprecise	Neither favored RR range 1.2 – 17.5 Low
Corticosteroids vs no corticosteroids	Infections	2 RCTs 362 CD 1 prospective 1 retrospective 6,253 CD 554 IBD	Moderate	Inconsistent	Direct	Imprecise	Neither favored RR range 0.4 – 2.9 Low
Corticosteroids vs no therapy	Infections	1 retrospecitvie 2 case-control 8,581 CD 2,538 IBD	High	NA	Direct	Imprecise	Neither favored RR range 0.9 – 3.4 Low
Corticosteroids vs ASA	Infections	2 RCTs 216 CD	Moderate	NA	Direct	Imprecise	Neither favored RR range 0.4 – 2.8 Low
Prednisone + sulfasalazine vs prednisone	Infections	1 RCT 89 CD	Moderate	NA	Direct	Precise	PRED + SUL favored RR = 0.3 Moderate
Sulfasalazine vs placebo	Infections	1 RCT 159 CD	Moderate	NA	Direct	Imprecise	Neither favored RR range 1.1 – 1.8 Low

Evidence Table 11. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for safety (KQ3)

Comparison	Outcome	Number of studies (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Mesalamine vs no therapy	Infections	1 case-control 2,238 IBD	High	NA	Direct	Imprecise	Neither favored RR 0.9 Low
TNF-alpha inhibitor vs placebo	Tuberculosis	5 RCTs 2,374 CD	Moderate	Consistent	Direct	Imprecise	4 cases observed in TNF treated, 0 in untreated Low
Infliximab + azathioprine vs infliximab	Tuberculosis	1 RCT 340 CD	Moderate	NA	Direct	Imprecise	1 case in infliximab + azathioprine, 0 in infliximab Low
Infliximab + IMM vs IMM	Tuberculosis	1 RCT 342 CD	Moderate	NA	Direct	Imprecise	1 case in infliximab + azathioprine, 0 in infliximab Low
TNF-alpha inhibitor vs placebo	Infusion and injection-site reactions	13 RCTs 4,389 CD	Moderate	Inconsistent	Direct	Precise	Placebo favored for infliximab and adalimumab RCT RR range 1.1 – 3.2 Low Neither favored for CP RCT RR range 0.2 – 6.4 Low
Infliximab + IMM vs infliximab	Infusion and injection-site reactions	3 RCTs 468 CD 1 prospective 8 retrospective 1,025 CD 1,184 IBD	Moderate	Inconsistent	Direct	Imprecise	Neither favored RCT RR range 0.3 – 1.5 Observational RR range 0.3 – 1.4 Low
Infliximab + IMM vs IMM	Infusion and injection-site reactions	2 RCTs 453 CD	Moderate	Inconsistent	Direct	Imprecise	Neither favored RCT RR 0.9 Low
Infliximab vs azathioprine	Infusion and injection-site reactions	1 RCT 324 CD	Low	NA	Direct	Precise	Azathioprine favored RCT RR 3.0 High

Evidence Table 11. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for safety (KQ3)

Comparison	Outcome	Number of studies (Participants)	Domains pertaining to strength of evidence				Magnitude of effect Strength of evidence
			Risk of bias	Consistency	Directness	Precision	
Infliximab + thiopurines vs infliximab + methotrexate	Infusion and injection-site reactions	1 prospective 2 retrospective 291 CD 144 IBD	High	Inconsistent	Direct	Imprecise	Neither favored Observational RR range 0.8 – 1.4 Low
Infliximab + steroids vs infliximab + no steroids	Infusion and injection-site reactions	3 retrospective 964 IBD	High	Inconsistent	Direct	Imprecise	Neither favored Low
Natalizumab vs placebo	Infusion and injection-site reactions	3 RCTs 1,414 CD	Moderate	Inconsistent	Direct	Imprecise	Neither favored RCT RR range 0.8 – 1.5 Low
Natalizumab + infliximab vs infliximab	Infusion and injection-site reactions	1 RCT 79 CD	High	NA	Direct	Very imprecise	Neither favored Low
Azathioprine vs placebo	Infusion and injection-site reactions	1 RCT 96 CD	Low	NA	Direct	Precise	Placebo favored RCT RR 5.8 High
Budesonide vs. Prednisolone	Fractures	1 RCT 271 CD	Low	NA	Direct	Imprecise	Neither favored Moderate
Corticosteroids vs. no corticosteroids	Fractures	3 207 CD 554 IBD	High	Consistent	Direct	Imprecise	Neither favored Low

ASA = aminosalicylate; CD = Crohn's disease; CP = certolizumab pegol; HR = hazard ratio; IBD = inflammatory bowel disease; IMM = immunomodulator; NA = not applicable because only one study reported; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk, Steroids = corticosteroids; TNF = tumor necrosis factor; vs = versus

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Studies evaluating biologics					
af Bjorkesten, 2011[163]	Retrospective cohort	Start year: 1999 Median followup duration: 11.5 months	Europe Single center	NA	Adults, CD only, previous use of infliximabactive disease, other criteria
Biancone, 2006[149]	Retrospective cohort	Start year: 1999 Median followup duration: 48-60 months	Europe Multicenter	NA	CD only, other criteria
Caspersen, 2008[225]	Retrospective cohort	Start year: 1999 Median followup duration: 29.1 months	Europe Multicenter	NA	NR
Chaparro, 2011[160] ENEIDA	Prospective cohort	Start year: NR Mean followup duration: 11 months Median followup duration: 11 months	Europe Multicenter	NA	CD only, other criteria
Clare, 2009[181]	Prospective cohort	Start year: 2004 Followup duration: NR	Europe Single center	NA	IBD
Colombel, 2004[137]	Retrospective cohort	Start year: 1998 Median followup duration: 17 months	US Multicenter	NA	CD only

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Colombel, 2007[82]	RCT, parallel arms with a 4-week run-in period	Start year: 2003 Duration of assigned treatment: 52 weeks	US, North America, Europe, Australia, Africa Multicenter	No	Adults, CD only, CDAI (220-450), no use of adalimumab, moderate-severe disease, not pregnant, not nursing, using adequate contraception, no short bowel syndrome, no ostomy, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, no cancer, other criteria
Colombel, 2009[95]	RCT, parallel arms with a 4-week run-in period	Start year: 2009 Duration of assigned treatment: 52 weeks	US, North America, Europe Multicenter	No	Adults, CD only, no previous surgery (bowel resection in past 6 months), CDAI (220-450), no use of adalimumabmoderate-severe disease, not pregnant, not nursing, using adequate contraception, no short bowel syndrome, no ostomy, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, no cancer, other criteria
Colombel, 2010[45]	RCT, parallel arms	Start year: 2005 Duration of assigned treatment: 50 weeks	US, North America, Europe, Asia Multicenter	No	Adults, CD only, no previous surgery (abdominal surgery in past 6 months), CDAI (219-451), previous use of corticosteroids, mesalamine or budesonide, no use of TNF-alpha inhibitors, methotrexate, 6-mercaptopurine, azathioprine, moderate-severe disease, no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, no history of TB, no cancer, other criteria
Cottone, 2011[150]	Retrospective cohort	Start year: 2000 Mean followup duration: 26 months	Europe Multicenter	NA	Adults, IBD, previous use of infliximab, other criteria
Crombe, 2011[226] EPIMAD	Retrospective cohort	Start year: 1988 Median followup duration: 32 months	Europe Multicenter	NA	Pediatrics, CD only, previous use of infliximab, other criteria
de Vries, 2008[227]	Other study design	Start year: 1999 Median followup duration: 9 years	Europe Single center	NA	Pediatrics, adults, IBD, no use of infliximab
D'Haens, 2008[48]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 2 years	Europe Multicenter	Yes Yes	Pediatrics, adults, CD only, CDAI (>200), no use of corticosteroids, antimetabolites, biological agents, active disease, not pregnant, no obstructive symptoms with strictures, no history of TB, no cancer, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Domenech, 2010[228]	Prospective cohort	Start year: 1999 Median followup duration: 76-198 months	Europe Single center	NA	IBD, other criteria
Feagan, 2007[81]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 48 weeks	US, North America, Europe, Australia, Africa Multicenter	No	Adults, CD only, CDAI (<220), no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, other criteria
Fidder, 2009[153]	Retrospective cohort	Start year: 1994 Median followup duration: 58-144 months	Europe Single center	NA	IBD
Hamzaoglu, 2010[164]	Retrospective cohort	Start year: 1998 Median followup duration: 14.3 months	US Single center	NA	CD only
Hanauer, 2002[86]	RCT, parallel arms with a 2-week run-in period	Start year: 1999 Duration of assigned treatment: 52 weeks	US, North America, Europe, Israel Multicenter	No	Adults, CD only, CDAI (220-400), previous use of antibiotics, 5-aminosalicylate acids, corticosteroids, thiopurines, methotrexate, no use of TNF-alpha inhibitors, infliximab, other criteria
Hanauer, 2006[37]	RCT, parallel arms	Start year: 2002 Duration of assigned treatment: 4 weeks	US, North America, Europe Multicenter	No	Adults, CD only, no previous surgery (extensive bowel resection (>100 cm)), CDAI (220-450), no use of TNF-alpha inhibitors, moderate-severe disease, not pregnant, not nursing, using adequate contraception, no short bowel syndrome, no ostomy, no obstructive symptoms with strictures, no history of TB, no cancer, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Keshavarzian, 2007[182]	Retrospective cohort	Start year: 2003 Mean followup duration: 2.3 years Median followup duration: 2.3 years	US Multicenter	NA	CD only, other criteria
Kinney, 2003[162]	Retrospective cohort	Start year: 1998 Mean followup duration: 52 weeks	US Single center	NA	CD only, other criteria
Lawrance, 2010[165]	Retrospective cohort	Start year: 1999 Average duration: NR	Australia, New Zealand Multicenter	NA	IBD, previous use of TNF-alpha inhibitors, other criteria
Lee, 2011[184]	Retrospective cohort	Start year: 2009 Average duration: NR	North America Multicenter	NA	IBD, other criteria
Lees, 2009[145]	Retrospective cohort	Start year: 1999 Median followup duration: 2.4 years	Europe Multicenter	NA	Pediatrics, adults, IBD, not pregnant, other criteria
Lemann, 2006[46]	RCT, parallel arms	Start year: 2000 Duration of assigned treatment: 24 weeks	Europe Multicenter	No	Adults, CD only, previous use of corticosteroids, prednisone, no use of 5-aminosalicylate acids, TNF-alpha inhibitors, topical steroids, budesonide, active disease, not pregnant, not nursing, using adequate contraception, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Lichtenstein, 2006[131]	Prospective cohort	Start year: 1999 Mean followup duration: 1.9 years	US, North America Multicenter	NA	Adults, CD only, other criteria
Lichtiger, 2010[161]	Other study design	Start year: 2006 Mean followup duration: 18 weeks	US Multicenter	NA	Adults, CD only, previous use of infliximab, no use of adalimumab, natalizumab, adalimumab, anakinra, moderate-severe disease, not pregnant, not nursing, using adequate contraception, no demyelinating disease, no cancer, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Lofberg, 2011[158] CARE	Prospective cohort	Start year: 2006 Average duration: NR	Europe Multicenter	NA	Adults, CD only, HBI (>7), no use of TNF-alpha inhibitors, adalimumab, natalizumab, not pregnant, not nursing, using adequate contraception, no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, no cancer, other criteria
Malik, 2011[229] Royal Hospital Sick Children	Retrospective cohort	Start year: 2003 Mean followup duration: 12 months	Europe Single center	NA	Pediatrics, CD only, other criteria
Mantzaris, 2009[88]	RCT, parallel arms with a 6-week run-in period	Start year: NR Duration of assigned treatment: 2 years	Europe Number of centers NR	Yes Yes	Adults, CD only, CDAI (>180), active disease, not pregnant, not nursing, no history of TB, other criteria
Marehbian, 2009[168]	Retrospective cohort	Start year: 2002 Average duration: NR	US Single center	NA	CD only, other criteria
Mortimore, 2001[174]	Retrospective cohort	Start year: 1999 Median followup duration:16.4 weeks	Australia Multicenter	NA	CD only, other criteria
Moss, 2008[148]	Retrospective cohort	Start year: 2000 Median followup duration: 35 months	US Single center	NA	CD only, other criteria
Moss, 2010[147]	Retrospective cohort	Start year: 2000 Median followup duration: 34 months	US Single center	NA	CD only, active disease

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Orlando, 2005[128]	Prospective cohort	Start year: 1999 Median followup duration: NR	Europe Multicenter	NA	No abscess, no obstructive symptoms with strictures, no cancer, other criteria
Present, 1999[44]	RCT, parallel arms	Start year: 1996 Duration of assigned treatment: 6 weeks	US, Europe Multicenter	Yes Yes	Adults, CD only, not pregnant, using adequate contraception, no abscess, other criteria
Ricart, 2001[138]	Retrospective cohort	Start year: 1998 Median followup duration: 34 weeks	US Single center	NA	CD only, other criteria
Rudolph, 2008[175]	Retrospective cohort	Start year: NR Average duration: NR	US Single center	NA	CD only, no use of TNF-alpha inhibitors, other criteria
Rutgeerts, 1999[85]	RCT, parallel arms with a 16-week run-in period	Start year: 1995 Duration of assigned treatment: 36 weeks	US, North America, Europe Multicenter	Yes Yes	Adults, CD only, no previous surgery (proctocolectomy or total colectomy), CDAI (220-400), no ostomy, no obstructive symptoms with strictures, other criteria
Sandborn, 2005[33]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 8 weeks	US, North America, Europe, Australia, Africa Multicenter	Yes Yes	Adults, CD only, CDAI (220-450), no use of TNF-alpha inhibitors in past 3 months, no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, other criteria
Sandborn, 2007[39]	RCT, parallel arms	Start year: 2003 Duration of assigned treatment: 26 weeks	Worldwide Multicenter	No	Adults, CD only, CDAI (220-450), active disease, no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, no cancer, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Sandborn, 2007[38]	RCT, parallel arms	Start year: 2004 Duration of assigned treatment: 4 weeks	US, North America, Europe Multicenter	No	Adults, CD only, no previous surgery (bowel resection in past 6 months), CDAI (220-450), no use of adalimumab, active disease, not pregnant, not nursing, no short bowel syndrome, no ostomy, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, other criteria
Sandborn, 2007[83]	RCT, parallel arms with a 4-week run-in period	Start year: 2002 Duration of assigned treatment: 52 weeks	US, North America, Europe Multicenter	No	Adults, CD only, CDAI (<150), in remission for >4 weeks, inactive disease, using adequate contraception, other criteria
Sands, 2004[87]	RCT, parallel arms with a 14-week run-in period	Start year: 2000 Duration of assigned treatment: 40 weeks	US, North America, Europe, Israel Multicenter	No	Adults, CD only, no use of infliximab, no abscess, no obstructive symptoms with strictures, other criteria
Sands, 2007[35]	RCT, parallel arms	Start year: 2002 Duration of assigned treatment: NR	US Multicenter	No	Adults, CD only, previous use of TNF-alpha inhibitors, no abscess, no obstructive symptoms with strictures, other criteria
Schneeweiss, 2009[230]	Retrospective cohort	Start year: 2001 Mean followup duration: 1.3 years	North America Multicenter	NA	IBD, no cancer, other criteria
Schreiber, 2005[40]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 8 weeks	North America, Europe, Africa, Russia Multicenter	No	Adults, CD only, CDAI (220-450), no use of TNF-alpha inhibitors, certolizumab pegol, sodium cromoglycate, mycophenolate, cyclosporin in past 4 weeks, TNF-alpha inhibitor with a biologic agent in past 12 weeks, moderate-severe disease, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Schreiber, 2007[84]	RCT, parallel arms with a 6-week run-in period	Start year: 2004 Duration of assigned treatment: 18 weeks	Worldwide Multicenter	No	Adults, CD only, CDAI (220-450), no use of TNF-alpha inhibitors, infliximab, adalimumab, certolizumab pegol, no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, no history of TB, no demyelinating disease, no cancer, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Schroder, 2006[47]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 48 weeks	Europe Single center	No	Adults, CD only, no use of TNF-alpha inhibitors, infliximab, active disease, other criteria
Seiderer, 2004[173]	Retrospective cohort	Start year: 2000 Median followup duration: 26 months	Europe Single center	NA	Adults, IBD, other criteria
Sokol, 2010[129] MICISTA Registry--part of French group	Other study design	Start year: NR Median followup duration: 30 months	Europe Single center	NA	IBD, other criteria
Sprakes, 2011[159] Leeds	Prospective cohort	Start year: 2007 Median followup duration: 10 months	Europe Single center	NA	CD only, previous use of infliximab, other criteria
Swoger, 2010[140] Mayo clinic	Retrospective cohort	Start year: 2003 Median followup duration: 13.7 months	US Single center	NA	Adults, CD only, previous use of , other criteria
Targan, 2007[32]	RCT, parallel arms with a 2-week run-in period	Start year: 2004 Duration of assigned treatment: 8 weeks	US, North America, Europe, Australia, Africa Multicenter	Yes Yes	Adults, CD only, no previous surgery (total colectomy), CDAI (220-450), no use of TNF-alpha inhibitors, natalizumab, active disease (moderate-severe), no short bowel syndrome, no ostomy, no abscess, no obstructive symptoms with strictures, other criteria
Thayu, 2010[199]	Case-control study	Start year: NR Mean followup duration: 43 months	US Single center	NA	Pediatrics, CD only, no use of any medications affecting growth and development, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Van Assche, 2008[89]	RCT, parallel arms	Start year: 2004 Duration of assigned treatment: 2 years	Europe Multicenter	No	Pediatrics, adults, CD only, previous use of methotrexate, infliximab, immunosuppressives (azathioprine/6-MP or methotrexate), perianal fistulizing, not pregnant, not nursing, other criteria
Vavricka, 2010[132] FACTS II	Other study design	Start year: 2008 Mean followup duration: 26 weeks	Europe Multicenter	NA	CD only, active disease, other criteria
Vermeire, 2007[154]	Prospective cohort	Start year: 2000 Median followup duration: 4 weeks	Europe Multicenter	NA	CD only, other criteria
Winter, 2004[41]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 12 weeks	Europe, Africa, Israel Multicenter	No	Adults, CD only, no previous surgery (extended bowel resection), CDAI (220-450), moderate-severe disease, no ostomy, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Studies evaluating thiopurines					
Beaugerie, 2009[130]	Prospective cohort	Start year: 2004 Median followup duration: 35 months	Europe Multicenter	NA	Pediatrics, adults, IBD, other criteria
Campbell, 2001[146]	Retrospective cohort	Start year: Median followup duration: 4.3 years	Europe Single center	NA	IBD, other criteria
Ewe, 1993[54]	RCT, parallel arms	Start year: 1987 Duration of assigned treatment: 4 months	Europe Single center	No	Adults, CD only, CDAI (>150), no use of thiopurines, perianal fistulizing, not pregnant, no abscess

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Farrell, 2000[231]	Retrospective cohort	Start year: 1990 Median followup duration: 8 years	Europe Single center	NA	Other criteria
Fraser, 2002[232]	Retrospective cohort	Start year: NR Mean followup duration: 13.7 years	Australia Single center	NA	IBD, other criteria
Govani, 2010[157]	Retrospective cohort	Start year: 2000 Median followup duration: 73 weeks	US Multicenter	NA	Adults, IBD, other criteria
Hutfless, 2007[151]	Retrospective cohort	Start year: 1996 Median followup duration: 6.8 years	US Multicenter	NA	CD only, other criteria
Kane, 2008[141]	Retrospective cohort	Start year: 2004 Average duration: NR	US Single center	NA	IBD, females, other criteria
Lees, 2009[144]	Retrospective cohort	Start year: NR Average duration: NR	Europe Single center	NA	IBD, females, other criteria
Lemann, 2005[98]	RCT, parallel arms	Start year: 1995 Duration of assigned treatment: 18 months	Europe Multicenter	No	Adults, CD only, no previous surgery (except limited perianal surgery in past 42 months), CDAI (<150), in remission for >42 months, previous use of azathioprine, no use of antibiotics, 5-aminosalicylate acids, corticosteroids, inactive disease, other criteria
Lemann, 2006[46]	RCT, parallel arms	Start year: 2000 Duration of assigned treatment: 24 weeks	Europe Multicenter	No	Adults, CD only, previous use of corticosteroids, prednisone, no use of 5-aminosalicylate acids, TNF-alpha inhibitors, topical steroids, budesonide, active disease, not pregnant, not nursing, using adequate contraception, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Lewis, 2001[136]	Retrospective cohort	Start year: 1988 Mean followup duration: 3.7 years	Europe Multicenter	NA	IBD, other criteria
Lichtenstein, 2006[131]	Prospective cohort	Start year: 1999 Mean followup duration: 1.9 years	US, North America Multicenter	NA	Adults, CD only, other criteria
Maher, 2009[176]	Retrospective cohort	Start year: 2005	Africa Single center	NA	IBD, other criteria
Mantzaris, 2009[102]	RCT, parallel arms	Start year: 1998 Duration of assigned treatment: 1.5 years	Europe Number of centers NR	Yes Yes	Adults, CD only, no previous surgery (intestinal resection), CDAI (<150), previous use of corticosteroids, no use of infliximab, mesalamine-only maintenance therapy, effective prior treatment with azathioprine, perianal fistulizing, not pregnant, not nursing, no history of TB, other criteria
Marehbian, 2009[168]	Retrospective cohort	Start year: 2002 Average duration: NR	US Single center	NA	CD only, other criteria
Markowitz, 2000[192]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 18 months	US Multicenter	No	Pediatrics, CD only, moderate-severe disease, other criteria
O'Donoghue, 1978[100]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 6 months	Europe Single center	Yes Yes	Adults, CD only, in remission for >6 months, previous use of azathioprine, inactive disease

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Reinisch, 2008[51]	RCT, parallel arms	Start year: 2004 Duration of assigned treatment: 12 months	North America, Europe, Africa, Russia Multicenter	No	Adults, CD only, no previous surgery (resection of >100 cm of small bowel), CDAI (220-450), previous use of corticosteroids, no use of 5-aminosalicylate acids, TNF-alpha inhibitors, corticosteroids, methotrexate, corticosteroids for current flare >21 days prior to randomization, active disease, perianal fistulizing, no obstructive symptoms with strictures, other criteria
Sandborn, 1999[59]	RCT, parallel arms with a 2-week run-in period	Start year: 1996 Duration of assigned treatment: 16 weeks	US, North America Multicenter	Yes Yes	Adults, CD only, no previous surgery (> 100 cm ileum), CDAI (150-450), previous use of corticosteroids, no use of antibiotics, thiopurines, infliximab, adalimumab, certolizumab pegol, active disease (mild-moderate), perianal fistulizing, no abscess, no obstructive symptoms with strictures, no cancer
Schneeweiss, 2009[230]	Retrospective cohort	Start year: 2001 Mean followup duration: 1.3 years	North America Multicenter	NA	IBD, no cancer, other criteria
Seksik, 2009[155]	Prospective cohort	Start year: 2003 Mean followup duration: 0.9 years	Europe Single center	NA	Adults, IBD, other criteria
Shah, 2008[156]	Retrospective cohort	Start year: NR Followup duration: NR	Europe Multicenter	NA	IBD, previous use of 5-aminosalicylate acids, other criteria
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 17 weeks	US Multicenter	No	Adults, CD only, CDAI (>150), active disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 24 months	US Multicenter	No	Adults, CD only, CDAI (<150), inactive disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Tay, 2003[233]	Retrospective cohort	Start year: 1998 Average duration: NR	US Single center	NA	No previous surgery (first resection with anastomosis or strictureplasty), no ostomy
van Schaik, 2011[234] Netherlands claims database	Retrospective cohort	Start year: 2001 Average duration: NR	Europe Multicenter	NA	Adults, IBD, no previous surgery (subtotal or total colectomy), no cancer, other criteria
Studies evaluating methotrexate					
Feagan, 1995[63]	RCT, parallel arms with a 2-week run-in period	Start year: 1992 Duration of assigned treatment: 16 weeks	US, North America Multicenter	No	CD only, previous use of prednisone, no use of prednisone > 10 mg/day, active disease, not pregnant, no cancer, other criteria
Feagan, 2000[105]	RCT, parallel arms	Start year: 1993 Duration of assigned treatment: NR	US, North America Multicenter	Yes Yes	Adults, CD only, previous use of methotrexate, inactive disease, not pregnant, no cancer, other criteria
Thayu, 2010[199]	Case-control study	Start year: NR Mean followup duration: 43 months	US Single center	NA	Pediatrics, CD only, no use of any medications affecting growth and development, other criteria
Studies evaluating corticosteroids					
Alemzadeh, 2002[200]	Retrospective cohort	Start year: NR Followup duration: NR	Europe Single center	NA	Pediatrics, CD only, other criteria
Campieri, 1997[68]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 weeks	Europe, Australia Multicenter	Yes	Adults, CD only, no previous surgery (ileostomy or more extensive resection of the ileum (>100 cm)), CDAI (>200), active disease, no abscess, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Escher, 2004[190]	RCT, parallel arms	Start year: 1998 Duration of assigned treatment: 12 weeks	Europe Multicenter	No	Pediatrics, CD only, CDAI (>200), no use of corticosteroids, thiopurines, active disease, other criteria
Goldstein, 1967[142]	Retrospective cohort	Start year: 1946 Average duration: NR	US Single center	NA	IBD, other criteria
Hutfless, 2007[151]	Retrospective cohort	Start year: 1996 Median followup duration: 6.8 years	US Multicenter	NA	CD only, other criteria
Issenman, 1993[196]	Prospective cohort	Start year: NR Mean followup duration: 2 years	North America Single center	NA	Pediatrics, CD only, males, active disease
Levine, 2002[198]	Case-control study	Start year: NR Followup duration: NR	Israel Multicenter	NA	Pediatrics, CD only, PCDAI (12.5-40), no use of thiopurines, mild-moderate disease, other criteria
Levine, 2003[191]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 weeks	Israel Multicenter	No	Pediatrics, CD only, no previous surgery (in past 6 weeks), PCDAI (12.5-40), no use of corticosteroids, thiopurines, active disease, other criteria
Lewis, 2001[136]	Retrospective cohort	Start year: 1988 Mean followup duration: 3.7 years	Europe Multicenter	NA	IBD, other criteria
Lichtenstein, 2006[131]	Prospective cohort	Start year: 1999 Mean followup duration: 1.9 years	US, North America Multicenter	NA	Adults, CD only, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Malchow, 1984[64]	RCT, parallel arms	Start year: 1975 Duration of assigned treatment: 6 weeks	Europe Multicenter	Yes Yes	Adults, CD only, not pregnant, no abscess, no obstructive symptoms with strictures, other criteria
Mantzaris, 2003[113]	RCT, parallel arms with a 1-month run-in period	Start year: 1994 Duration of assigned treatment: 1 years	Europe Single center	No	Adults, CD only, no previous surgery (intestinal resection), CDAI (<150), no use of mesalamine maintenance therapy, azathioprine unless withdrawn at least 3 months before start of trial due to side effects, inactive disease, not pregnant, not nursing, other criteria
Saha, 1998[197]	Prospective cohort	Start year: 1982 Followup duration: NR	Europe Single center	NA	Pediatrics, IBD
Schoon, 2005[185]	RCT, parallel arms	Start year: 1996 Duration of assigned treatment: 2 years	Europe, Israel Multicenter	 No	Adults, CD only, no previous surgery (gastric surgery or resection of >100 cm of small bowel or of tissues distal to the mid-transverse colon), no use of hormone replacement therapy in past 6 months, bisphosphonates in past 6 months, androgens/anabolic steroids in past 6 months, no abscess, no obstructive symptoms with strictures, other criteria
Siffledeen, 2007[127]	Other study design	Start year: 2000 Average duration: NR	North America Single center	NA	Adults, CD only, no short bowel syndrome, other criteria
Singleton, 1979[75]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 8 weeks	US Multicenter	Yes Yes	CD only, CDAI (>150), active disease
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 17 weeks	US Multicenter	No	Adults, CD only, CDAI (>150), active disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 24 months	US Multicenter	No	Adults, CD only, CDAI (<150), inactive disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Thayu, 2010[199]	Case-control study	Start year: NR Mean followup duration: 43 months	US Single center	NA	Pediatrics, CD only, no use of any medications affecting growth and development, other criteria
Tremaine, 2002[65]	RCT, parallel arms with a 2-week run-in period	Start year: 1995 Duration of assigned treatment: 8 weeks	US Multicenter	Yes Yes	Adults, CD only, CDAI (200-450), mild-moderate disease, not pregnant, not nursing, no ostomy, other criteria
Tromm, 2011[74]	RCT, parallel arms	Start year: 2004 Duration of assigned treatment: 8 weeks	Europe, Israel Multicenter		Adults, CD only, CDAI (200-400), no use of methotrexate, within 3 months, perianal fistulizing, no short bowel syndrome, no ostomy, no obstructive symptoms with strictures, other criteria
Studies evaluating 5-aminosalicylate acids					
Bernstein, 2011[235] University of Manitoba	Retrospective cohort	Start year: 1995 Average duration: NR	North America Multicenter	NA	IBD, other criteria
Hutfless, 2007[151]	Retrospective cohort	Start year: 1996 Median followup duration: 6.8 years	US Multicenter	NA	CD only, other criteria
Lewis, 2001[136]	Retrospective cohort	Start year: 1988 Mean followup duration: 3.7 years	Europe Multicenter	NA	IBD, other criteria

Evidence Table 12. Study design characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Study design	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Malchow, 1984[64]	RCT, parallel arms	Start year: 1975 Duration of assigned treatment: 6 weeks	Europe Multicenter	Yes Yes	Adults, CD only, not pregnant, no abscess, no obstructive symptoms with strictures, other criteria
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 17 weeks	US Multicenter	No	Adults, CD only, CDAI (>150), active disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria
Summers, 1979[56]	RCT, parallel arms	Start year: 1971 Duration of assigned treatment: 24 months	US Multicenter	No	Adults, CD only, CDAI (<150), inactive disease, not pregnant, no abscess, no obstructive symptoms with strictures, no history of TB, other criteria

Abbreviations: 6-MP = 6-mercaptopurine; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; IBD = irritable bowel disease; mg = milligram; NA = not applicable; NR = not reported; RCT = randomized controlled trial; TB = tuberculosis; TNF = tumor necrosis factor; US = United States

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Studies evaluating biologics								
af Bjorkesten, 2011[163]	Infliximab + Never user corticosteroids, 30 Route: Unknown + Unknown Dose: 5 mg/kg + NA	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Immunomodulators	Immunomodulators	NR
af Bjorkesten, 2011[163]	Infliximab + Corticosteroid, 41 Route: Unknown + Unknown Dose: 5 mg/kg + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Immunomodulators	Immunomodulators	NR
af Bjorkesten, 2011[163]	Infliximab + Never user immunomodulator, 8 Route: Unknown + Unknown Dose: 5 mg/kg + NA	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	Corticosteroids	NR
af Bjorkesten, 2011[163]	Infliximab + immumodulator, 63 Route: Unknown + Unknown Dose: 5 mg/kg + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	Corticosteroids	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Biancone, 2006[149]	No infliximab + 6-MP/azathioprine/ methotrexate, 186	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Biancone, 2006[149]	Infliximab + No immunomodulators, 191	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Biancone, 2006[149]	Infliximab, 404 Route: IV	Male, %: 53 Race NR Smoking, % Smoker, 36 CD NR	Age at diagnosis Median: 28 Min: 7 Max: 80 Disease duration Median: 10 Min: 1 Max: 62 Age at enrollment Median: 41 Min: 13 Max: 82	Severity NR Location, % Ileal: 25 Ileo-colonic: 42 Colonic: 31 Behavior, % Inflammatory: 36 Stricturing: 5 Penetrating: 59 CRP NR	Disease activity index NR	Methotrexate: 5 Thiopurines: 95	Methotrexate	NR
Biancone, 2006[149]	Certolizumab pegol + 6-MP/azathioprine/ methotrexate, 213	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Biancone, 2006[149]	Never user infliximab, 404	Male, %: 53 Race NR Smoking, % Smoker, 36 CD NR	Age at diagnosis Median: 29 Min: 9 Max: 81 Disease duration NR Age at enrollment Median: 40 Min: 14 Max: 82	Severity NR Location, % Ileal: 23 Ileo-colonic: 43 Colonic: 33 Behavior, % Inflammatory: 44 Stricturing: 13 Penetrating: 43 CRP NR	Disease activity index NR	Methotrexate: 3 Thiopurines: 97	Methotrexate	NR
Biancone, 2006[149]	No infliximab + 6-MP/azathioprine/ methotrexate, 218	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Caspersen, 2008[225]	Infliximab + Azathioprine Route: IV Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Caspersen, 2008[225]	Infliximab + Corticosteroid	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Caspersen, 2008[225]	Infliximab Route: IV Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Chaparro, 2011[160]	Adalimumab + IMM, 247 Dose: 2+ induction doses with a primary response	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Disease behavior NR CRP NR	Disease activity index NR	Immunomodulators: 100	NR	NR
Chaparro, 2011[160]	Adalimumab + no IMM, 133 Dose: 2+ induction doses with a primary response	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	TNF-alpha inhibitors	NR
Clare, 2009[181]	Infliximab, 37 Route: IV Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
Clare, 2009[181]	Infliximab + Immunomodulator	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Clare, 2009[181]	Infliximab + Azathioprine, 86 Route: IV Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
Clare, 2009[181]	Infliximab + Methotrexate Route: IV Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Colombel, 2004[137]	Infliximab + Never user corticosteroids, azathioprine, 6-MP, methotrexate, 37 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Colombel, 2004[137]	Infliximab + Thiopurine, 374 Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Colombel, 2004[137]	Infliximab + Methotrexate, 53 Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Colombel, 2004[137]	Infliximab + Corticosteroids and either azathioprine, 6-MP, or methotrexate, 111 Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Colombel, 2004[137]	Infliximab + Corticosteroid, 156 Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Colombel, 2004[137]	Infliximab + corticosteroids, 6-MP, azathioprine, or methotrexate, 463	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Colombel, 2004[137]	Infliximab + Corticosteroid, 45	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Colombel, 2004[137]	Infliximab + Thiopurine, 316	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Colombel, 2007[82]	Adalimumab, 172 Route: SC Dose: 40 mg every 2 weeks	Male, %: 36 Race NR Smoking, % Current smoker, 34 CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36.4	Severity NR Location, % Ileal: 73 Ileo-colonic: 47 Colonic: 73 Behavior NR CRP NR	CDAI Mean: 155 IBDQ Mean: 175	5ASA: 38 Antibiotics Corticosteroids Methotrexate: 10 Thiopurines: 36 Immunomodulators: 45	TNF-alpha inhibitors: 50	Adalimumab: 100
Colombel, 2007[82]	Adalimumab, 157 Route: SC Dose: 40 mg every 1 week	Male, %: 39 Race NR Smoking, % Current smoker, 32 CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36.9	Severity NR Location, % Ileal: 76 Ileo-colonic: 54 Colonic: 76 Behavior NR CRP NR	CDAI Mean: 160 IBDQ Mean: 165	5ASA: 69 Antibiotics Corticosteroids Methotrexate: 12 Thiopurines: 38 Immunomodulators: 50	TNF-alpha inhibitors: 45	Adalimumab: 100

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Colombel, 2007[82]	Placebo, 170 Route: SC Dose: NA every 2 weeks	Male, %: 38 Race NR Smoking, % Current smoker, 37 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36.9	Severity NR Location, % Ileal: 66 Ileo-colonic: 44 Colonic: 76 Behavior NR CRP NR	CDAI Mean: 170 IBDQ Mean: 165	5ASA: 46 Antibiotics Corticosteroids Methotrexate: 8 Thiopurines: 42 Immunomodulators: 49	TNF-alpha inhibitors: 48	Adalimumab: 100
Colombel, 2009[95]	Adalimumab, 260 Route: SC Dose: 40 mg every 2 weeks	Male, %: 37.3 Race, % W: 94.2 B: 2.7 A: 1.5 Other: 1.5 Smoking, % Current smoker, 35.4 CD, %: 100	Age at diagnosis NR Disease duration Median: 7.9 Min: 0.3 Max: 44.1 Age at enrollment Mean: 36.8	Severity NR Location, % Ileal: 75.4 Ileo-colonic: 50.4 Colonic: 73.9 Behavior NR CRP Median: 0.9	CDAI Median: 302 IBDQ Median: 124	5ASA: 36.9 Corticosteroids: 41.9 Immonomodulator: 43.1	TNF-alpha inhibitors: 51.2	Adalimumab: 100
Colombel, 2009[95]	Placebo, 261 Route: SC Dose: NA every 2 weeks	Male, %: 37.9 Race, % W: 94.3 B: 3.1 A: 1.2 Other: 1.5 Smoking, % Current smoker, 36.8 CD, %: 100	Age at diagnosis NR Disease duration Median: 8.4 Min: 0.3 Max: 40.3 Age at enrollment Mean: 36.9	Severity NR Location, % Ileal: 69 Ileo-colonic: 47.9 Colonic: 76.6 Behavior NR CRP Median: 1	CDAI Median: 306 IBDQ Median: 125	5ASA: 44.4 Corticosteroids: 43.7 Immonomodulator: 51	TNF-alpha inhibitors: 49.8	Adalimumab: 100

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Colombel, 2009[95]	Adalimumab, 257 Route: SC Dose: 40 mg every 1 week	Male, %: 38.9 Race, % W: 89.9 B: 4.7 A: 2.7 Other: 2.7 Smoking, % Current smoker, 34.6 CD NR	Age at diagnosis NR Disease duration Median: 7.9 Min: 0.3 Max: 38.8 Age at enrollment Mean: 37.8	Severity NR Location, % Ileal: 75.9 Ileo-colonic: 51.4 Colonic: 73.5 Behavior NR CRP Median: 0.9	CDAI Median: 299 IBDQ Median: 122	5ASA: 36.6 Corticosteroids: 45.1 Immonomodulator: 47.1	TNF-alpha inhibitors: 49.4	Adalimumab: 100
Colombel, 2010[45]	Infliximab + Placebo, 169 Route: IV + Oral Dose: 5 mg/kg every 8 weeks + NA every day	Male, %: 49.7 Race, % W: 86.4 Smoking, % Smoker, 42 CD NR	Age at diagnosis NR Disease duration Median: 2.2 Age at enrollment Median: 35	Severity NR Location, % Ileal: 32 Ileo-colonic: 37.9 Colonic: 26.6 Behavior NR CRP Median: 1.1	CDAI Mean: 284.8	5ASA: 51.5 Corticosteroids: 30.8 Budesonide: 16.6	NR	NR
Colombel, 2010[45]	Azathioprine + Infliximab, 169 Route: Oral + IV Dose: 2.5 mg/kg every day + 5 mg/kg every 8 weeks	Male, %: 52.1 Race, % W: 84 Smoking, % Smoker, 38.5 CD NR	Age at diagnosis NR Disease duration Median: 2.2 Age at enrollment Median: 34	Severity NR Location, % Ileal: 32 Ileo-colonic: 43.2 Colonic: 23.7 Behavior NR CRP Median: 1	CDAI Mean: 289.9	5ASA: 50.3 Corticosteroids: 27.8 Budesonide: 11.2	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Colombel, 2010[45]	Azathioprine + Placebo, 170 Route: Oral + IV Dose: 2.5 mg/kg every day + NA every 8 weeks	Male, %: 52.9 Race, % W: 86.5 Smoking, % Smoker, 35.3 CD NR	Age at diagnosis NR Disease duration Median: 2.4 Age at enrollment Median: 35	Severity NR Location, % Ileal: 40 Ileo-colonic: 40.6 Colonic: 19.4 Behavior NR CRP Median: 1	CDAI Mean: 287.2	5ASA: 61.2 Corticosteroids: 23.5 Budesonide: 14.7	NR	NR
Cottone, 2011[150]	Never user Biologics, 116 Route: Unknown Dose: NR	Male, %: 60.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 70 Min: 65 Max: 80	Severity NR Location, % Ileal: 34.5 Ileo-colonic: 37.9 Colonic: 3.4 Behavior NR CRP NR	Disease activity index NR	Corticosteroids: 89.7	NR	NR
Cottone, 2011[150]	TNF-alpha, 58 Route: Unknown Dose: NR	Male, %: 60.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 71 Min: 65 Max: 84	Severity NR Location, % Ileal: 34.5 Ileo-colonic: 37.9 Colonic: 3.4 Behavior NR CRP NR	CDAI Median: 211 Min: 149 Max: 439	Corticosteroids: 93.1 Immunomodulators: 25.9	NR	NR
Crombe, 2011[226]	Infliximab + immunomodulator, 103 Route: Unknown + Unknown Dose: 5 mg/kg every 8 weeks + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Crombe, 2011[226]	Infliximab + no IMM, 17 Route: Unknown Dose: NA	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids	NR	NR
de Vries, 2008[227]	Infliximab + No corticosteroids, 45	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Immunomodulators	NR	NR
de Vries, 2008[227]	Infliximab + Corticosteroid, 102	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Immunomodulators	NR	NR
de Vries, 2008[227]	Infliximab + No immunomodulator, 54	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
de Vries, 2008[227]	Infliximab + Immunomodulator, 93	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
D'Haens, 2008[48]	Infliximab + Azathioprine, 65 Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Male, %: 33.8 Race, % W: 98.5 Smoking, % Current smoker, 43.1 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30	Severity NR Location, % Ileo-colonic: 47.7 Colonic: 30.8 Behavior NR CRP Median: 19	CDAI Mean: 330 IBDQ Mean: 122	TNF-alpha inhibitors: 100 Methotrexate Azathioprine: 100 Methylprednisolone	5ASA: 4.6	NR
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone, 64 Route: Oral + Oral Dose: 9 mg every day + 32 mg every day	Male, %: 42.2 Race, % W: 95.3 Smoking, % Current smoker, 35.9 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 28.7	Severity NR Location, % Ileo-colonic: 43.8 Colonic: 32.8 Behavior NR CRP Median: 25	CDAI Mean: 306 IBDQ Mean: 136	TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines Budesonide	5ASA: 3.1	NR
Domenech, 2010[228]	Infliximab + No concomitant immunomodulator, 15	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Domenech, 2010[228]	Infliximab + Thiopurines or methotrexate, 61	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	Corticosteroids	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Feagan, 2007[81]	Natalizumab, 168 Route: IV Dose: 300 mg every 4 weeks	Male, %: 45.8 Race NR Smoking, % >10 cigarettes/day, 16.1 CD NR	Age at diagnosis NR Disease duration Mean: 9.9 Age at enrollment Mean: 37	Severity NR Location, % Ileal: 24.4 Ileo-colonic: 50.6 Colonic: 25 Behavior NR CRP Mean: 8.9 Median: 4.3 Min: 0 Max: 97	CDAI Mean: 105 IBDQ Mean: 125	5ASA: 45.2 Antibiotics: 8.9 Corticosteroids: 39.9 Methotrexate: 4.8 Thiopurines: 32.1 Prednisone: 26.2 Budesonide: 12.5 >/= 1 corticosteroid or immunomodulators: 57.1 Corticosteroids and immunomodulators: 17.9	TNF-alpha inhibitors: 32.7	Natalizumab: 100
Feagan, 2007[81]	Natalizumab, 35 Route: IV Dose: 300 mg every 4 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Feagan, 2007[81]	Placebo, 171 Route: IV Dose: NA every 4 weeks	Male, %: 34.5 Race NR Smoking, % >10 cigarettes/day, 26.3 CD NR	Age at diagnosis NR Disease duration Mean: 9.7 Age at enrollment Mean: 37	Severity NR Location, % Ileal: 23.4 Ileo-colonic: 49.7 Colonic: 26.9 Behavior NR CRP Mean: 9.4 Median: 3.9 Min: 0 Max: 120	CDAI Mean: 118 IBDQ Mean: 121	5ASA: 54.4 Antibiotics: 5.8 Corticosteroids: 44.4 Methotrexate: 4.7 Thiopurines: 30.4 Prednisone: 31.6 Budesonide: 14 >/= 1 corticosteroid or immunomodulators: 60.2 Corticosteroids and immunosuppressants: 19.3	TNF-alpha inhibitors: 39.8	Natalizumab: 100
Feagan, 2007[81]	Placebo, 33 Route: IV Dose: NA every 4 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Fidder, 2009[153]	Infliximab, 743 Route: IV Dose: NR	Male, %: 43 Race NR Smoking NR CD, %: 80.3	Age at diagnosis Median: 24 Disease duration Median: 7 Age at enrollment Median: 35	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids: 27 Methotrexate: 23 Thiopurines: 67 No thiopurines, methotrexate, cyclosporin: 18 Cyclosporin: 0	NR	NR
Fidder, 2009[153]	Never user infliximab, 666	Male, %: 50 Race NR Smoking NR CD, %: 79.4	Age at diagnosis Median: 26 Disease duration Median: 8 Age at enrollment Median: 34	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids: 66 Methotrexate: 6 Thiopurines: 58 No thiopurines, methotrexate, cyclosporin: 42 Cyclosporin: 6	NR	NR
Hamzaoglu, 2010[164]	Infliximab + Corticosteroid, 50 Route: IV + Unknown	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hamzaoglu, 2010[164]	Infliximab + aza, 6mo or mtx, 62 Route: IV + Unknown Dose: NR	Male, %: 44 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 14.2 Min: 1 Max: 39 Age at enrollment Mean: 43.6 Min: 19 Max: 81	Severity NR Location, % Ileal: 17.7 Ileo-colonic: 116.1 Colonic: 79 Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hamzaoglu, 2010[164]	Infliximab + no steroid, 6mp, aza, mtx, 160 Route: IV	Male, %: 40 Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration Median: 13.8 Age at enrollment Mean: 41.1	Severity NR Location, % Ileal: 10 Ileo-colonic: 47.5 Colonic: 38.1 Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hamzaoglu, 2010[164]	Infliximab + steroid + 6mp/aza/mtx, 25 Route: IV + Unknown	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hanauer, 2002[86]	Placebo, 110 Route: IV Dose: NA every 8 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 155 Median: 160 IBDQ Mean: 170 Median: 173	5ASA Corticosteroids Immunomodulators	5ASA Antibiotics Corticosteroids Methotrexate Thiopurines	Infliximab: 100

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hanauer, 2002[86]	Infliximab, 113 Route: IV Dose: 5 mg/kg every 8 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 154 Median: 156 IBDQ Mean: 170 Median: 169	5ASA Corticosteroids Immunomodulators	5ASA Antibiotics Corticosteroids Methotrexate Thiopurines	Infliximab: 100
Hanauer, 2002[86]	Infliximab, 112 Route: IV Dose: 10 mg/kg every 8 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 152 Median: 151 IBDQ Mean: 168 Median: 173	5ASA Corticosteroids Immunomodulators	5ASA Antibiotics Corticosteroids Methotrexate Thiopurines	Infliximab: 100
Hanauer, 2006[37]	Adalimumab, 75 Route: SC Dose: 80 mg then 40 mg every 2 weeks	Male, %: 33 Race NR Smoking, % Current smoker, 43 CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 38	Severity NR Location, % Ileal: 63 Ileo-colonic: 9 Colonic: 23 Perianal: 1 Behavior NR CRP Mean: 2 Median: 0.9 Min: 0 Max: 14.9	CDAI Mean: 301 IBDQ Median: 128 Min: 63 Max: 200	5ASA: 53 Antibiotics: 9 Corticosteroids: 43 Methotrexate: 4 Thiopurines: 25.3 Immunomodulators: 28	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hanauer, 2006[37]	Placebo, 74 Route: SC Dose: NA every 2 weeks	Male, %: 50 Race NR Smoking, % Current smoker, 38 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 37	Severity NR Location, % Ileal: 68 Ileo-colonic: 9 Colonic: 19 Perianal: 0 Behavior NR CRP Mean: 1.8 Median: 0.9 Min: 0 Max: 17.3	CDAI Mean: 296 IBDQ Median: 131 Min: 52 Max: 200	5ASA: 50 Antibiotics: 7 Corticosteroids: 34 Methotrexate: 1 Thiopurines: 28.4 Immunomodulators: 30	NR	NR
Hanauer, 2006[37]	Adalimumab, 76 Route: SC Dose: 160 mg then 80 mg every 2 weeks	Male, %: 47 Race NR Smoking, % Current smoker, 42 CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 39	Severity NR Location, % Ileal: 53 Ileo-colonic: 11 Colonic: 29 Perianal: 1 Behavior NR CRP Mean: 1.4 Median: 0.7 Min: 0 Max: 9.3	CDAI Mean: 295 IBDQ Median: 127 Min: 37 Max: 192	5ASA: 51 Antibiotics: 5 Corticosteroids: 32 Methotrexate: 1 Thiopurines: 27.6 Immunomodulators: 29	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hanauer, 2006[37]	Adalimumab, 74 Route: SC Dose: 40 mg then 20 mg every 2 weeks	Male, %: 53 Race NR Smoking, % Current smoker, 34 CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 39	Severity NR Location, % Ileal: 61 Ileo-colonic: 5 Colonic: 31 Perianal: 0 Behavior NR CRP Mean: 1.6 Median: 0.9 Min: 0 Max: 11.3	CDAI Mean: 299 IBDQ Median: 129 Min: 81 Max: 218	5ASA: 50 Antibiotics: 14 Corticosteroids: 23 Methotrexate: 5 Thiopurines: 25.7 Immunomodulators: 31	NR	NR
Keshavarzian, 2007[182]	Immunomodulators + Infliximab, 322	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Keshavarzian, 2007[182]	Never user immunomodulators + Infliximab, 125 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Kinney, 2003[162]	Infliximab + Methotrexate, 23 Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 13 Age at enrollment Mean: 43	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Corticosteroids	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Kinney, 2003[162]	Infliximab + Thiopurine, 58 Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 12 Age at enrollment Mean: 40	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Corticosteroids	NR	NR
Kinney, 2003[162]	Infliximab, 36 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 15 Age at enrollment Mean: 46	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Corticosteroids	NR	NR
Lawrance, 2010[165]	TNF-alpha + Never user corticosteroids OR thio/mtx, 44 Route: IV or SC Dose: 5 mg/kg for infliximab 160/80 mg for adalimumab + NA	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lawrance, 2010[165]	TNF-alpha + Corticosteroid, 36 Route: IV or SC + Unknown Dose: 5 mg/kg for infliximab 160/80 mg for adalimumab + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lawrance, 2010[165]	TNF-alpha + steroid + aza/6mp/mtx, 232 Route: IV or SC + Unknown Dose: 5 mg/kg for infliximab 160/80 mg for adalimumab + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lawrance, 2010[165]	TNF-alpha + aza/6mp/mtx, 177 Route: IV or SC Dose: 5 mg/kg for infliximab 160/80 mg for adalimumab + NA	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lee, 2011[184]	Infliximab + Immunosuppressants, 116 Route: IV Dose: 5 mg/kg	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lee, 2011[184]	Infliximab + No IMM (AZA,6mp/MTX), 97 Route: IV Dose: 5 mg/kg	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lee, 2011[184]	Infliximab + No premed with steroids or, 47 Route: IV Dose: 5 mg/kg	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lee, 2011[184]	Infliximab + steroid premed, 171 Dose: 5 mg/kg	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lees, 2009[145]	Infliximab + Corticosteroid, 32 Route: IV + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lees, 2009[145]	Infliximab + Azathioprine, 51 Route: IV Dose: NR + NR	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lees, 2009[145]	Adalimumab, 30	Male, %: 36.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Median: 32.3	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lees, 2009[145]	Infliximab + Never user concomitant azathioprine/6-MP/methotrexate /corticosteroids, 19 Route: IV Dose: NR	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lees, 2009[145]	Infliximab + Azathioprine/6-MP/methotrexate + corticosteroids, 55 Route: IV + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lemann, 2006[46]	Infliximab + Azathioprine or 6-MP, 57 Route: IV Dose: 5 mg/kg + stable	Male, %: 47.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Min: 1 Max: 10 Age at enrollment Min: 22 Max: 38	Severity NR Location, % Ileal: 28.1 Ileo-colonic: 50.9 Colonic: 21.1 Perianal: 33.3 Behavior NR CRP Min: 4 Max: 47	CDAI Min: 90 Max: 281	NR	Thiopurines: 100	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lemann, 2006[46]	Placebo + Azathioprine or 6-MP, 56 Route: IV + Oral Dose: NA + stable mg/kg every day	Male, %: 42.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Min: 1 Max: 11 Age at enrollment Min: 22 Max: 36	Severity NR Location, % Ileal: 12.5 Ileo-colonic: 48.2 Colonic: 39.3 Perianal: 10.7 Behavior NR CRP Min: 4 Max: 35	CDAI Min: 42 Max: 262	NR	Thiopurines: 100	NR
Lichtenstein, 2006[131]	Immunomodulator, 3764 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lichtenstein, 2006[131]	No reported prednisone usage, 2396 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lichtenstein, 2006[131]	Prednisone, 3894 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lichtenstein, 2006[131]	No immunomodulators, 2526 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lichtenstein, 2006[131]	Never user infliximab, 3111 Route: IV	Male, %: 40.8 Race, % W: 89.3 H: 1.4 B: 6.2 A: 0.3 Other: 0.6 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10.9 Age at enrollment NR	Severity, % Mild-mod disease: 47.9 Mod-sev disease: 10.3 Severe disease: 0.6 Location, % Ileal: 32.4 Ileo-colonic: 35.4 Colonic: 28 Behavior NR CRP NR	Disease activity index NR	Immunomodulators: 32.2 Prednisone: 16.1 Narcotic analgesics: 5.4	NR	NR
Lichtenstein, 2006[131]	Infliximab, 3179 Route: IV	Male, %: 40.5 Race, % W: 88.8 H: 1.2 B: 7.2 A: 0.5 Other: 0.7 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10.7 Age at enrollment NR	Severity, % Mild-mod disease: 50.1 Mod-sev disease: 30.8 Severe disease: 2.5 Location, % Ileal: 25.1 Ileo-colonic: 43.2 Colonic: 28.2 Behavior NR CRP NR	Disease activity index NR	Prednisone: 27.4 Immunomodulator: 49.4 narcotic analgesic: 9.8	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lichtiger, 2010[161]	Adalimumab + Never user ASA, 434 Route: SC + Unknown Dose: 40 mg every 2 weeks + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Antibiotics Corticosteroids Methotrexate Thiopurines	5ASA Antibiotics TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines Immunomodulators	NR
Lichtiger, 2010[161]	Adalimumab + immunomodulator, 277 Route: SC + Unknown Dose: 40 mg every 2 weeks + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Corticosteroids	NR	NR
Lichtiger, 2010[161]	Adalimumab + 5-ASA, 239 Route: SC + Unknown Dose: 40 mg every 2 weeks + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Antibiotics Corticosteroids Methotrexate Thiopurines	5ASA Antibiotics TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines Immunomodulators	NR
Lichtiger, 2010[161]	Adalimumab + Never user immunomodulator, 396 Route: SC + Unknown Dose: 40 mg every 2 weeks + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Corticosteroids	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lichtiger, 2010[161]	Adalimumab + Corticosteroid, 285 Route: SC + Unknown Dose: 40 mg every 2 weeks + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Methotrexate Thiopurines	NR	NR
Lichtiger, 2010[161]	Adalimumab + Never user corticosteroids, 388 Route: SC + Unknown Dose: 40 mg every 2 weeks + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Antibiotics Methotrexate Thiopurines	NR	NR
Lofberg, 2011[158] CARE	Adalimumab + steroid +/- IMM, 706	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP Median: 1.1	HBI Median: 10	Corticosteroids	NR	NR
Lofberg, 2011[158] CARE	Adalimumab + no steroid no IMM, 239 Dose: 160,80,40 mg every 2 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Malik, 2011[229] Royal Hospital Sick Children	Infliximab + steroid, 15	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Methotrexate	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malik, 2011[229] Royal Hospital Sick Children	Infliximab + no steroid, 13 Route: IV Dose: 5 mg/kg every 2 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Methotrexate	NR	NR
Malik, 2011[229] Royal Hospital Sick Children	Infliximab + Methotrexate, 21	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
Malik, 2011[229] Royal Hospital Sick Children	Infliximab + no MTX, 7	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
Mantzaris, 2009[88]	Hydrocortisone + Infliximab, 23 Route: IV Dose: 250 mg every 8 weeks + 5 mg/kg every 8 weeks	Male, %: 52.2 Race NR Smoking, % Smoker, 47.8 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 35 Min: 20 Max: 57	Severity NR Location, % Ileal: 30.4 Ileo-colonic: 47.8 Colonic: 21.7 Behavior, % Inflammatory: 100 CRP NR	CDAI Mean: 298	NR	5ASA: 91.3 Corticosteroids: 69.6 budesonide: 34.8 NO azathiprine: 26.1 topical ASA: 17.4 : 26.1	Infliximab: 100

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Mantzaris, 2009[88]	Azathioprine + Infliximab, 23 Route: Oral + IV Dose: 2.0-2.5 mg/kg every day + 5 mg/kg every 8 weeks	Male, %: 47.8 Race NR Smoking, % Smoker, 43.5 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 37 Min: 21 Max: 62	Severity NR Location, % Ileal: 26.1 Ileo-colonic: 56.5 Colonic: 17.4 Behavior, % Inflammatory: 100 CRP NR	CDAI Mean: 287	NR	5ASA: 87 Corticosteroids: 69.6 budesonide: 34.8 NO azathiprine: 100 topical ASA: 13 : 100	Infliximab: 100
Marehbian, 2009[168]	TNF-alpha Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	Thiopurine + TNF-alpha	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	Never user corticosteroids, azathioprine/6-MP/methotrexate, TNF-alpha inhibitor or combination of these drugs	Gender NR Race NR Smoking NR CD, %: Total sample NR, but n CD was 0	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Marehbian, 2009[168]	Corticosteroid Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	Thiopurine Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	TNF-alpha + Corticosteroid	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	Corticosteroid + TNF-alpha	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	Thiopurine + TNF-alpha Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Mortimore, 2001[174]	Infliximab + No concomitant immunosuppressive, 15 Route: IV + Unknown Dose: 5 mg/kg + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Mortimore, 2001[174]	Infliximab, 42 Route: IV Dose: 5 mg/kg	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Methotrexate: 21.4 Thiopurines: 81 Mycophenolate: 4.8	NR	NR
Moss, 2008[148]	Infliximab + Corticosteroid, 86 Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Moss, 2008[148]	Infliximab + No steroids, 201	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Moss, 2008[148]	Infliximab + No immunomodulator at initiation, 172 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Moss, 2008[148]	Infliximab + Thiopurine, 115 Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Moss, 2010[147]	Infliximab + 6-MP, 62 Route: IV	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
Moss, 2010[147]	Infliximab, 61 Route: IV	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
Moss, 2010[147]	Infliximab, 61 Route: IV	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
Moss, 2010[147]	Infliximab, 61 Route: IV	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Moss, 2010[147]	Infliximab, 61 Route: IV	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
Orlando, 2005[128]	Infliximab + Immunomodulator (unspecified), 211	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids	NR	NR
Orlando, 2005[128]	Infliximab + No concomitant immunomodulators, 362	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Antibiotics Corticosteroids	NR	NR
Present, 1999[44]	Infliximab, 32 Route: IV Dose: 10 mg/kg	Male, %: 37.5 Race, % W: 90.6 B: 9.4 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 11.5 Age at enrollment Mean: 35	Severity NR Location, % Ileal: 12.5 Ileo-colonic: 56.2 Colonic: 31.2 Behavior NR CRP NR	CDAI Mean: 184.9 Median: 203 Perianal DAI Median: 10	5ASA: 50 Antibiotics: 34.4 Corticosteroids: 31.2 Thiopurines: 53.1	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Present, 1999[44]	Infliximab, 31 Route: IV Dose: 5 mg/kg	Male, %: 48.4 Race, % W: 90.3 B: 9.7 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 13.6 Age at enrollment Mean: 41.2	Severity NR Location, % Ileal: 22.6 Ileo-colonic: 54.8 Colonic: 22.6 Behavior NR CRP NR	CDAI Mean: 184.4 Median: 163 Perianal DAI Median: 8	5ASA: 54.8 Antibiotics: 19.4 Corticosteroids: 38.7 Thiopurines: 38.7	NR	NR
Present, 1999[44]	Placebo, 31 Route: IV	Male, %: 54.8 Race, % W: 93.5 B: 6.5 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 12 Age at enrollment Mean: 35.4	Severity NR Location, % Ileal: 9.7 Ileo-colonic: 61.3 Colonic: 29 Behavior NR CRP NR	CDAI Mean: 192.9 Median: 162 Perianal DAI Median: 9	5ASA: 61.3 Antibiotics: 35.5 Corticosteroids: 35.5 Thiopurines: 29	NR	NR
Ricart, 2001[138]	Infliximab + Corticosteroid, 44 Route: IV + Unknown Dose: 5 mg/kg + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Methotrexate Thiopurines Immunomodulators	5ASA Antibiotics Corticosteroids Methotrexate Thiopurines Immunomodulators	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Ricart, 2001[138]	Infliximab + Never user corticosteroid, 56 Route: IV + Unknown Dose: 5 mg/kg + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Methotrexate Thiopurines Immunomodulators	5ASA Antibiotics Corticosteroids Methotrexate Thiopurines Immunomodulators	NR
Ricart, 2001[138]	Infliximab + Never user immunomodulators, 5 Route: IV + Unknown Dose: 5 mg/kg + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Corticosteroids	5ASA Antibiotics Corticosteroids Methotrexate Thiopurines Immunomodulators	NR
Ricart, 2001[138]	Infliximab + Immunomodulators, 95 Route: IV + Unknown Dose: 5 mg/kg + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Corticosteroids	5ASA Antibiotics Corticosteroids Methotrexate Thiopurines Immunomodulators	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Rudolph, 2008[175]	Infliximab + Never user immunomodulator at start of infliximab, 71	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	Corticosteroids Immunomodulators	NR
Rudolph, 2008[175]	Infliximab + Immunomudulator, 127	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Rutgeerts, 1999[85]	Infliximab, 37 Route: IV Dose: 10 mg/kg every 8 weeks	Male, %: 40.5 Race, % W: 100 Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 9.4 Min: 1.1 Max: 30.8 Age at enrollment Median: 34 Min: 20 Max: 64	Severity NR Location, % Ileal: 13.5 Ileo-colonic: 62.2 Colonic: 24.3 Behavior NR CRP Median: 0.5	CDAI Median: 175 IBDQ Median: 165	NR	NR	TNF-alpha inhibitors: 91.9

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Rutgeerts, 1999[85]	Placebo, 36 Route: Unknown Dose: NA every 8 weeks	Male, %: 63.9 Race, % W: 100 Smoking NR CD NR	Age at diagnosis NR Disease duration Median: 12.1 Min: 0.3 Max: 32.8 Age at enrollment Median: 39 Min: 20 Max: 65	Severity NR Location, % Ileal: 13.9 Ileo-colonic: 47.2 Colonic: 38.9 Behavior NR CRP Median: 0.4	CDAI Median: 170 IBDQ Median: 170	NR	NR	TNF-alpha inhibitors: 97.2
Russell, 2011[236]	Adalimumab + no IMM (Thio or MTX) +/- steroid, 24 Route: Unknown + Unknown Dose: 40 mg every 15 days + NR	Gender NR Race NR Smoking NR CD, %: 283.3	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines Immunomodulators	NR
Russell, 2011[236]	Adalimumab + IMM (Thio or MTX) +/- steroid, 46 Route: Unknown + Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines Immunomodulators	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 2005[33]	Natalizumab, 724 Route: IV Dose: 300 mg every 4 weeks	Male, %: 43 Race NR Smoking, % >10 cigarettes/day, 22.7 CD NR	Age at diagnosis NR Disease duration Mean: 10.1 Age at enrollment Mean: 38	Severity NR Location, % Ileal: 26.8 Ileo-colonic: 51.5 Colonic: 21.7 Behavior NR CRP Mean: 20 Median: 9 Min: 0 Max: 370	CDAI Mean: 302	5ASA: 47.4 Antibiotics: 5.9 Corticosteroids: 37.4 Methotrexate: 4.3 Thiopurines: 29.8 Prednisone: 27.2 Budesonide: 10.9 >/= 1 corticosteroids or immunomodulators: 56.2 Corticosteroids and immunosuppressants: 15.3	TNF-alpha inhibitors: 40.2	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 2005[33]	Placebo, 181 Route: IV Dose: NA every 4 weeks	Male, %: 40.3 Race NR Smoking, % >10 cigarettes/day, 24.3 CD NR	Age at diagnosis NR Disease duration Mean: 9.16 Age at enrollment Mean: 39	Severity NR Location, % Ileal: 26 Ileo-colonic: 46.4 Colonic: 27.1 Behavior NR CRP Mean: 23 Median: 12 Min: 0 Max: 127	CDAI Mean: 303	5ASA: 44.2 Antibiotics: 6.6 Corticosteroids: 38.7 Methotrexate: 3.3 Thiopurines: 25.4 Prednisone: 29.3 Budesonide: 11 >/= 1 corticosteroid or immunomodulators: 55.2 Corticosteroids and immunosuppressants: 12.2	TNF-alpha inhibitors: 38.1	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 2007[39]	Placebo, 328 Route: SC Dose: NA every 4 weeks	Male, %: 40 Race NR Smoking, % Current smoker, 33 CD NR	Age at diagnosis NR Disease duration Mean: 8 Median: 5 Min: 1 Max: 40 Age at enrollment Mean: 38 Min: 18 Max: 77	Severity NR Location, % Ileal: 27 Ileo-colonic: 51 Colonic: 23 Behavior NR CRP Mean: 9 Min: 2 Max: 244	CDAI Mean: 297 Min: 161 Max: 513	Corticosteroids: 23 Immunomodulators: 20 Glucocorticoids + immunomodulators: 17 Neither glucocorticoids nor immunomodulators: 40	infliximab: 26	NR
Sandborn, 2007[39]	Certolizumab pegol, 331 Route: SC Dose: 400 mg every 4 weeks	Male, %: 47 Race NR Smoking, % Current smoker, 31 CD NR	Age at diagnosis NR Disease duration Mean: 7 Median: 5 Min: 1 Max: 44 Age at enrollment Mean: 37 Min: 18 Max: 73	Severity NR Location, % Ileal: 29 Ileo-colonic: 45 Colonic: 26 Behavior NR CRP Mean: 8 Min: 2 Max: 205	CDAI Mean: 300 Min: 149 Max: 491	Corticosteroids: 22 Immunomodulators: 21 Glucocorticoids + immunomodulators: 17 Neither glucocorticoids nor immunomodulators: 40	infliximab: 30	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 2007[38]	Placebo, 166 Route: SC Dose: NA	Male, %: 39.2 Race NR Smoking, % Smoker, 33.7 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 37	Severity NR Location, % Ileal: 74.7 Colonic: 68.1 Perianal: 18.7 Behavior NR CRP Mean: 20	CDAI Mean: 313 IBDQ Mean: 124	5ASA: 36.1 Corticosteroids: 44 Immunomodulators: 51.2	NR	NR
Sandborn, 2007[38]	Adalimumab, 159 Route: SC	Male, %: 31.4 Race NR Smoking, % Smoker, 34.6 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 39	Severity NR Location, % Ileal: 70.4 Colonic: 66 Perianal: 17 Behavior NR CRP Mean: 19	CDAI Mean: 313 IBDQ Mean: 120	5ASA: 28.3 Corticosteroids: 34.6 Immonomodulator: 45.9	NR	NR
Sandborn, 2007[83]	Adalimumab, 18 Route: SC Dose: 40 mg every 1 week	Male, %: 50 Race NR Smoking, % Patients who smoked, 56 CD, %: 100	Age at diagnosis NR Disease duration Mean: 9.13 Age at enrollment Mean: 38	Severity NR Location NR Behavior NR CRP NR	IBDQ Mean: 191	5ASA: 67 Antibiotics: 0 Corticosteroids: 50 Methotrexate: 0 Thiopurines: 28 Immunomodulators: 28	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 2007[83]	Placebo, 18 Route: SC Dose: NA every 1 week	Male, %: 33 Race NR Smoking, % Patients who smoked, 67 CD, %: 100	Age at diagnosis NR Disease duration Mean: 8.24 Age at enrollment Mean: 36	Severity NR Location NR Behavior NR CRP NR	IBDQ Mean: 188	5ASA: 44 Antibiotics: 6 Corticosteroids: 56 Methotrexate: 6 Thiopurines: 11.1 Immunomodulators: 17	NR	TNF-alpha inhibitors: 100
Sandborn, 2007[83]	Adalimumab, 19 Route: SC Dose: 40 mg every 2 weeks	Male, %: 37 Race NR Smoking, % Patients who smoked, 68 CD NR	Age at diagnosis NR Disease duration Mean: 7.73 Age at enrollment Mean: 34	Severity NR Location NR Behavior NR CRP NR	IBDQ Mean: 187	5ASA: 74 Antibiotics: 0 Corticosteroids: 47 Methotrexate: 0 Thiopurines: 21 Immunomodulators: 21	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sandborn, 2011[42]	Certolizumab pegol, 223 Route: SC Dose: 400 mg every 2 weeks	Male, %: 47.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.5 Age at enrollment NR	Severity NR Location, % Ileal: 28.3 Ileo-colonic: 40.4 Colonic: 29.1 Behavior, % Inflammatory: 75.3 Stricturing: 14.8 Penetrating: 9 CRP Mean: 9.41	CDAI Mean: 262.1 HBI Mean: 9.8 IBDQ Mean: 126.5	Corticosteroids: 43.5 Immunomodulators: 34.5 corticosteroid or IMM: 62.3 corticosteroid and IMM: 15.7 neither corticosteroid nor IMM: 37.7	NR	NR
Sandborn, 2011[42]	Placebo, 215 Route: SC Dose: 400 mg every 2 weeks	Male, %: 41.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7 Age at enrollment Min: 18 Max: 70	Severity NR Location, % Ileal: 26.5 Ileo-colonic: 41.4 Colonic: 28.4 Behavior, % Inflammatory: 76.7 Stricturing: 15.8 Penetrating: 7.4 CRP Mean: 9.02	CDAI Mean: 292.7 HBI Mean: 9.7 IBDQ Mean: 122.1	Corticosteroids: 45.6 Immunomodulators: 31.2 corticosteroid or IMM: 62.3 corticosteroid and IMM: 14.4 neither corticosteroid nor IMM: 37.7	NR	NR
Sands, 2004[87]	Placebo, 99 Route: IV Dose: NA every 8 weeks	Male, %: 48 Race NR Smoking, % Current smoker, 38 CD, %: 100	Age at diagnosis NR Disease duration Median: 12.3 Min: 0.5 Max: 31.6 Age at enrollment Median: 36	Severity NR Location, % Ileal: 16 Ileo-colonic: 54 Colonic: 30 Behavior NR CRP Median: 0.7	IBDQ Median: 168	5ASA: 49 Antibiotics: 26 Corticosteroids: 30 Methotrexate: 2 Thiopurines: 35	Antibiotics: 93 Methotrexate: 8 Thiopurines: 64 cyclosporine or tacrolimus: 7	Infliximab: 100

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sands, 2004[87]	Infliximab, 96 Route: IV Dose: 5 mg/kg every 8 weeks	Male, %: 55 Race NR Smoking, % Current smoker, 45 CD, %: 100	Age at diagnosis NR Disease duration Median: 10.5 Min: 0.2 Max: 32.2 Age at enrollment Median: 37	Severity NR Location, % Ileal: 19 Ileo-colonic: 46 Colonic: 35 Behavior NR CRP Median: 0.6	IBDQ Median: 155	5ASA: 43 Antibiotics: 29 Corticosteroids: 26 Methotrexate: 1 Thiopurines: 30	Antibiotics: 96 Methotrexate: 5 Thiopurines: 72 cyclosporine or tacrolimus: 3	Infliximab: 100
Sands, 2007[35]	Placebo + Infliximab, 27 Route: IV + IV Dose: NA every 4 weeks + 5 mg/kg every 8 weeks	Male, %: 63 Race, % W: 85.2 B: 7.4 Other: 7.4 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10 Min: 0 Max: 36 Age at enrollment Mean: 38.9 Min: 19 Max: 72	Severity NR Location, % Ileal: 14.8 Ileo-colonic: 55.6 Colonic: 29.6 Behavior NR CRP Mean: 5.9 Min: 0 Max: 49	CDAI Mean: 243.6 Min: 150 Max: 366	5ASA: 37 Antibiotics: 18.5 Corticosteroids: 29.6 Azathioprine, 6-mercaptopurine, or methotrexate: 55.6	NR	NR
Sands, 2007[35]	Natalizumab + Infliximab, 52 Route: IV + IV Dose: 300 mg every 4 weeks + 5 mg/kg every 8 weeks	Male, %: 46.2 Race, % W: 94.2 B: 3.8 Other: 1.9 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 12.5 Age at enrollment Mean: 39.9 Min: 20 Max: 69	Severity NR Location, % Ileal: 21.2 Ileo-colonic: 53.8 Colonic: 25 Behavior NR CRP Mean: 6.5 Min: 0 Max: 71	CDAI Mean: 263.8 Min: 129 Max: 545	5ASA: 46.2 Antibiotics: 19.2 Corticosteroids: 26.9 Azathioprine, 6-mercaptopurine, or methotrexate: 50	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schneeweiss, 2009[230]	Corticosteroid, 7258 Route: Unknown Dose: NR	Male, %: 45.6 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 41.5	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA TNF-alpha inhibitors Methotrexate Thiopurines	5ASA Antibiotics TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines	NR
Schneeweiss, 2009[230]	Immunomodulator, 2883 Route: Unknown Dose: NR	Male, %: 46.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 38.6	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA TNF-alpha inhibitors Corticosteroids	5ASA Antibiotics TNF-alpha inhibitors Corticosteroids	NR
Schneeweiss, 2009[230]	Infliximab, 521 Route: Unknown Dose: NR	Male, %: 45.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids Methotrexate Thiopurines	5ASA Antibiotics TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schreiber, 2005[40]	Certolizumab pegol, 72 Route: SC Dose: 400 mg every 4 weeks	Male, %: 44.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.43 Min: 0.2 Max: 26.5 Age at enrollment Mean: 35.9 Min: 18 Max: 67	Severity NR Location, % Ileal: 77.8 Perianal: 29.2 Behavior NR CRP Mean: 7.7 Min: 0.4 Max: 128.2	IBDQ Mean: 126.5	5ASA: 38.9 Antibiotics: 8.3 Corticosteroids: 30.6 Methotrexate: 4.2 Immunomodulators: 37.5 Anti-diarrheals: 16.7 Codeine and derivatives: 2.8 Azathioprine: 30.6 6-MP: 2.8	TNF-alpha inhibitors: 16.7	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schreiber, 2005[40]	Certolizumab pegol, 74 Route: SC Dose: 100 mg every 4 weeks	Male, %: 47.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.73 Min: 0 Max: 31.8 Age at enrollment Mean: 33.5 Min: 18 Max: 56	Severity NR Location, % Ileal: 77 Perianal: 27 Behavior NR CRP Mean: 6.2 Min: 0.2 Max: 141	IBDQ Mean: 132.2	5ASA: 50 Antibiotics: 8.1 Corticosteroids: 32.4 Methotrexate: 5.4 Immunomodulators: 35.1 Anti-diarrheals: 25.7 Codeine and derivatives: 6.8 Azathioprine: 17.6 6-MP: 12.2	TNF-alpha inhibitors: 24.3	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schreiber, 2005[40]	Certolizumab pegol, 72 Route: SC Dose: 200 mg every 4 weeks	Male, %: 30.6 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.84 Min: 0 Max: 30.7 Age at enrollment Mean: 40.1 Min: 19 Max: 71	Severity NR Location, % Ileal: 70.8 Perianal: 31.9 Behavior NR CRP Mean: 6.5 Min: 0.2 Max: 127	IBDQ Mean: 122.9	5ASA: 44.4 Antibiotics: 9.7 Corticosteroids: 40.3 Methotrexate: 5.6 Thiopurines: 34.7 Immunomodulators: 40.3 Anti-diarrheals: 22.2 Codeine and derivatives: 6.9 Azathioprine: 31.9 6-MP: 2.8	TNF-alpha inhibitors: 23.6	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schreiber, 2005[40]	Placebo, 73 Route: SC Dose: NA every 4 weeks	Male, %: 32.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.95 Min: 0.1 Max: 27.6 Age at enrollment Mean: 35.8 Min: 19 Max: 64	Severity NR Location, % Ileal: 74 Perianal: 31.5 Behavior NR CRP Mean: 7.3 Min: 0.3 Max: 86.1	IBDQ Mean: 122.9	5ASA: 39.7 Antibiotics: 9.6 Corticosteroids: 39.7 Methotrexate: 6.8 Immunomodulators: 35.6 Anti-diarrheals: 13.7 Codeine and derivatives: 8.2 Azathioprine: 23.3 6-MP: 5.5	TNF-alpha inhibitors: 21.9	NR
Schreiber, 2007[84]	Certolizumab pegol, 216 Route: SC Dose: 400 mg every 4 weeks	Male, %: 43 Race NR Smoking, % Current smoker, 30 CD NR	Age at diagnosis NR Disease duration Mean: 9 Median: 7 Min: 1 Max: 33 Age at enrollment Mean: 38 Min: 18 Max: 67	Severity NR Location, % Ileal: 22 Ileo-colonic: 51 Colonic: 27 Behavior, % Inflammatory: 67.4 Stricturing: 11.6 Penetrating: 20.9 CRP Mean: 10 Min: 2 Max: 183	CDAI Mean: 306 Min: 179 Max: 504	Corticosteroids: 22 Immunomodulators: 27 Glucocorticoids + immunomodulators: 13 Neither glucocoricoids nor immunomodulators: 38	5ASA: 34.4 Corticosteroids: 49.3 Immunomodulators: 21.4 infliximab: 24	Certolizumab pegol: 100

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schreiber, 2007[84]	Placebo, 212 Route: SC Dose: NA every 4 weeks	Male, %: 52 Race NR Smoking, % Current smoker, 36 CD NR	Age at diagnosis NR Disease duration Mean: 7 Median: 5 Min: 1 Max: 43 Age at enrollment Mean: 38 Min: 18 Max: 69	Severity NR Location, % Ileal: 25 Ileo-colonic: 46 Colonic: 29 Behavior, % Inflammatory: 67.1 Stricturing: 9.5 Penetrating: 23.3 CRP Mean: 10 Min: 2 Max: 244	CDAI Mean: 301 Min: 183 Max: 583	Corticosteroids: 21 Immunomodulators: 25 Glucocorticoids + immunomodulators: 16 Neither glucocorticoids nor immunosuppressives: 38	5ASA: 34.3 Corticosteroids: 46.7 Immunomodulators: 20.5 infliximab: 24	Certolizumab pegol: 100
Schroder, 2006[47]	Methotrexate + Infliximab, 11 Route: IV + IV Dose: 20 mg every 1 week + 5 mg/kg every 2 weeks	Male, %: 54.5 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.2 Age at enrollment Mean: 31.6	Severity NR Location, % Ileal: 9.1 Ileo-colonic: 63.6 Colonic: 9.1 Behavior NR CRP NR	CDAI Mean: 251 IBDQ Mean: 113	5ASA: 18.2 Corticosteroids: 72.7	NR	NR
Schroder, 2006[47]	Infliximab, 8 Route: IV Dose: 5 mg/kg every 2 weeks	Male, %: 25 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 9.6 Age at enrollment Mean: 36.5	Severity NR Location, % Ileal: 12.5 Ileo-colonic: 62.5 Colonic: 12.5 Behavior NR CRP NR	CDAI Mean: 293 IBDQ Mean: 106	5ASA: 37.5 Corticosteroids: 87.5	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Seiderer, 2004[173]	Infliximab + 6-MP, 18	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids	NR	NR
Seiderer, 2004[173]	Infliximab + No azathioprine/6-MP at first infusion, 18	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids	NR	NR
Seiderer, 2004[173]	Infliximab + Corticosteroid, 42	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Thiopurines	NR	NR
Seiderer, 2004[173]	Infliximab + Thiopurine, 82	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids	NR	NR
Seiderer, 2004[173]	Infliximab + Azathioprine, 64	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sokol, 2010[129] MICISTA Registry--part of French group	Infliximab + Other immunwith azathioprine or methotrexate Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Sokol, 2010[129] MICISTA Registry--part of French group	Infliximab + No immunomod Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Sprakes, 2011[159] Leeds	Adalimumab + Corticosteroid, 25 Route: Unknown + Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Immunomodulators	TNF-alpha inhibitors	NR
Sprakes, 2011[159] Leeds	Adalimumab + Immunomodulants (Not specified), 21 Route: Unknown + Unknown	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	TNF-alpha inhibitors	Corticosteroids	NR
Sprakes, 2011[159] Leeds	Adalimumab + No steroids, 19 Route: Unknown	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	TNF-alpha inhibitors	Immunomodulators	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Sprakes, 2011[159] Leeds	Adalimumab + No IMM, 23 Route: Unknown Dose: 160 mg	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	TNF-alpha inhibitors	NR
Swoger, 2010[140] Mayo clinic	Adalimumab + Corticosteroid, 69 Route: Unknown + Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	5ASA TNF-alpha inhibitors Corticosteroids Thiopurines Immunomodulators	NR
Swoger, 2010[140] Mayo clinic	Adalimumab + Never user immunomodulator, 48 Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	NR
Swoger, 2010[140] Mayo clinic	Adalimumab + Never user corticosteroids, 49 Route: Unknown + Unknown Dose: NA	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	NR
Swoger, 2010[140] Mayo clinic	Adalimumab + Median age, years (range)a 35.7 (18β€“69) Corticosteroids/budesonide and AZA/6-MP/MTX, 42	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Swoger, 2010[140] Mayo clinic	Adalimumab + Corticosteroids/budesonide and aAZA/6-MP/MTX and infliximab, 10	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	NR
Swoger, 2010[140] Mayo clinic	Adalimumab + No therapy, monotherapy or 2 of Corticosteroids/budesonide and aAZA/6-MP/MTX and infliximab, 108	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	NR
Swoger, 2010[140] Mayo clinic	Adalimumab + no therapy or monotherapy with Corticosteroids/budesonide and AZA/6-MP/MTX, 76	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Swoger, 2010[140] Mayo clinic	Adalimumab + immunomodulator, 70 Route: Unknown + Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	5ASA TNF-alpha inhibitors Corticosteroids Immunomodulators	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Targan, 2007[32]	Placebo, 250 Route: IV Dose: NR every 4 weeks	Male, %: 41 Race, % W: 94 H: 1 B: 2 A: 1 not specified: 2 Smoking, % >10 cigarettes/day, 19 CD NR	Age at diagnosis NR Disease duration Mean: 10 Age at enrollment Mean: 37.7	Severity, % Severe disease: 28 Location, % Ileal: 26 Ileo-colonic: 48 Colonic: 26 Behavior NR CRP Mean: 23.4	CDAI Mean: 299.5 IBDQ Mean: 122.5	5ASA: 48 Antibiotics: 5 Corticosteroids: 38 Immunomodulators: 38	TNF-alpha inhibitors: 45	NR
Targan, 2007[32]	Natalizumab, 259 Route: IV Dose: 300 mg every 4 weeks	Male, %: 41 Race, % W: 95 H: 1 B: 1 A: 1 not specified: 3 Smoking, % >10 cigarettes/day, 22 CD NR	Age at diagnosis NR Disease duration Mean: 10.1 Age at enrollment Mean: 38.1	Severity, % Severe disease: 32 Location, % Ileal: 22 Ileo-colonic: 52 Colonic: 27 Behavior NR CRP Mean: 23	CDAI Mean: 303.9 IBDQ Mean: 123.6	5ASA: 49 Antibiotics: 7 Corticosteroids: 42 Immunomodulators: 37	TNF-alpha inhibitors: 50	NR
Thayu, 2010[199]	Placebo	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Thayu, 2010[199]	Infliximab	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Thayu, 2010[199]	Corticosteroid	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Thayu, 2010[199]	Methotrexate	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Tromm, 2011[74]	Mesalamine (Salofalk), 153 Route: Oral Dose: 3 x 1.5 g/day	Male, %: 50.3 Race, % W: 99.3 Smoking, % No smoking defintion abstracted, 25.5 CD NR	Age at diagnosis NR Disease duration Mean: 5.9 Age at enrollment Mean: 37.8	Severity NR Location NR Behavior NR CRP Mean: 16.6	CDAI Mean: 267.2	Thiopurines: 3.3	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Tromm, 2011[74]	Budesonide, 154 Route: Oral Dose: two administrations of 9mg total every 1 days	Male, %: 53.2 Race, % W: 99.4 Smoking, % No smoking defintion abstracted, 30.5 CD NR	Age at diagnosis NR Disease duration Mean: 6.1 Age at enrollment Mean: 36.8	Severity NR Location NR Behavior NR CRP Mean: 15.4	CDAI Mean: 265.6	Thiopurines: 3.2	NR	NR
Van Assche, 2008[89]	Infliximab, 40 Route: IV Dose: 5 mg/kg every 8 weeks	Male, %: 47.5 Race NR Smoking, % Smoker, 47.5 CD NR	Age at diagnosis NR Disease duration Median: 9 Min: 2 Max: 25 Age at enrollment Mean: 35.4	Severity NR Location, % Colonic: 12.5 Behavior NR CRP Median: 3.2	CDAI Mean: 138.1	TNF-alpha inhibitors: 100	TNF-alpha inhibitors: 100 Methotrexate Thiopurines	NR
Van Assche, 2008[89]	Infliximab + Immunomodulator, 40 Route: IV + Oral Dose: 5 mg/kg every 8 weeks + see below	Male, %: 42.5 Race NR Smoking, % Smoker, 45 CD NR	Age at diagnosis NR Disease duration Median: 9 Min: 1 Max: 36 Age at enrollment Mean: 35.6	Severity NR Location, % Colonic: 32.5 Behavior NR CRP Median: 3.4	CDAI Mean: 137.6	TNF-alpha inhibitors: 100 Methotrexate Thiopurines	TNF-alpha inhibitors: 100 Methotrexate Thiopurines	NR
Vermeire, 2007[154]	Infliximab + Methotrexate, 50 Route: IV + IM or SC Dose: NR + 15 mg every 1 week	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	Thiopurines	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Vermeire, 2007[154]	Infliximab + Thiopurine, 65 Route: IV + Unknown Dose: NR + See Comments every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Vermeire, 2007[154]	Infliximab + Thiopurine or methotrexate, 115	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Vermeire, 2007[154]	Infliximab + No concomitant methotrexate or azathioprine/6-MP, 59 Route: IV Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Vavricka, 2010[132] FACTS II	Certolizumab pegol + Budesonide, 5	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids Methotrexate Thiopurines budesonide: 100	NR	NR
Vavricka, 2010[132] FACTS II	Certolizumab pegol + No 5asa, 59	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 0 Corticosteroids Methotrexate Thiopurines	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Vavricka, 2010[132] FACTS II	Certolizumab pegol + No Budesonide, 55	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids Methotrexate Thiopurines budesonide: 0	NR	NR
Vavricka, 2010[132] FACTS II	Certolizumab pegol + Corticosteroid, 4	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids: 100	5ASA Corticosteroids Methotrexate Thiopurines	NR
Vavricka, 2010[132] FACTS II	Certolizumab pegol + No steroids, 56	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids: 0 Methotrexate Thiopurines	NR	NR
Vavricka, 2010[132] FACTS II	Certolizumab pegol + Thiopurine, 9	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids Methotrexate Thiopurines: 100	NR	NR
Vavricka, 2010[132] FACTS II	Certolizumab pegol + No Thio, 51	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Thiopurines: 100	5ASA Corticosteroids Methotrexate Thiopurines	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Vavricka, 2010[132] FACTS II	Certolizumab pegol + 5-ASA, 1 Route: SC Dose: 400 mg every 2 weeks	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 100 Corticosteroids Methotrexate Thiopurines	NR	NR
Winter, 2004[41]	Placebo, 25 Route: IV Dose: NA	Male, %: 24 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.74 Min: 0.1 Max: 21.9 Age at enrollment Mean: 32.1 Min: 18 Max: 56	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 40 Corticosteroids: 28 Immunomodulators: 44	TNF-alpha inhibitors: 13	NR
Winter, 2004[41]	Certolizumab pegol, 25 Route: IV Dose: 5 mg/kg	Male, %: 48 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.52 Min: 0.69 Max: 17.0 Age at enrollment Mean: 36.4 Min: 21 Max: 61	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 48 Corticosteroids: 24 Immunomodulators: 44	TNF-alpha inhibitors: 23	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Winter, 2004[41]	Certolizumab pegol, 17 Route: IV Dose: 10 mg/kg	Male, %: 35 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10.20 Min: 0.9 Max: 26.0 Age at enrollment Mean: 40.3 Min: 18 Max: 64	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 53 Corticosteroids: 35 Immunomodulators: 53	TNF-alpha inhibitors: 29	NR
Winter, 2004[41]	Certolizumab pegol, 23 Route: IV Dose: 20 mg/kg	Male, %: 44 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.94 Min: 1.3 Max: 18.9 Age at enrollment Mean: 33.3 Min: 19 Max: 60	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 39 Corticosteroids: 26 Immunomodulators: 44	TNF-alpha inhibitors: 30	NR
Winter, 2004[41]	Certolizumab pegol, 2 Route: IV Dose: 1.25 mg/kg	Male, %: 0 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 9.28 Min: 7.7 Max: 10.9 Age at enrollment Mean: 36.5 Min: 31 Max: 42	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA: 0 Corticosteroids: 50 Immunomodulators: 0	TNF-alpha inhibitors: 50	NR
Studies evaluating thiopurines								

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Beaugerie, 2009[130]	Thiopurine, 8676 Dose: NR	Male, %: 43 Race NR Smoking NR CD, %: 76.1	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location, % Ileal: 53.3 Colonic: 59.3 Perianal: 24.5 Behavior NR CRP NR	Disease activity index NR	TNF-alpha inhibitors: 10 Methotrexate: 7.5 Cyclosporin, mycophenolate mofetil, or cyclophosamide: 1.6	TNF-alpha inhibitors: 21.3 Methotrexate: 15.3	NR
Beaugerie, 2009[130]	Never user thiopurine, 10810 Dose: NA	Male, %: 47 Race NR Smoking NR CD, %: 48	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 42.3	Severity NR Location, % Ileal: 33.3 Colonic: 30.5 Perianal: 7.3 Behavior NR CRP NR	Disease activity index NR	TNF-alpha inhibitors: 0.6 Methotrexate: 0.4 Cyclosporin, mycophenolate mofetil, or cyclophosamide: 0.6	TNF-alpha inhibitors: 0.9 Methotrexate: 0.6	NR
Campbell, 2001[146]	Azathioprine, 56 Route: Unknown Dose: 1.8 mg/kg	Male, %: 53.6 Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 38	Severity NR Location, % Ileal: 26.8 Ileo-colonic: 26.8 Colonic: 46.4 Behavior NR CRP NR	Disease activity index NR	Corticosteroids: 25	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Campbell, 2001[146]	Azathioprine + 5-ASA, 48 Route: Unknown + Unknown Dose: 1.7 mg/kg + NR	Male, %: 31.2 Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 40	Severity NR Location, % Ileal: 16.7 Ileo-colonic: 18.8 Colonic: 64.6 Behavior NR CRP NR	Disease activity index NR	Corticosteroids: 20.8	NR	NR
Ewe, 1993[54]	Placebo + Prednisolone, 21 Dose: 60 mg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.3 Min: 18 Max: 48	Severity NR Location, % Ileal: 23.8 Ileo-colonic: 52.4 Colonic: 23.8 Behavior NR CRP NR	CDAI Mean: 285	NR	5ASA: 28.6 5-ASA + GCs: 38.1	NR
Ewe, 1993[54]	Azathioprine + Prednisolone, 21 Dose: 2.5 mg/kg every day + 60 mg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.4 Age at enrollment Mean: 27.3 Min: 18 Max: 43	Severity NR Location, % Ileal: 4.8 Ileo-colonic: 66.7 Colonic: 28.6 Behavior NR CRP NR	CDAI Mean: 290	NR	5ASA: 33.3 5-ASA + GCs: 57.1	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Farrell, 2000[231]	Immunomodulators, 238 Route: Unknown Dose: NR	Male, %: 44 Race NR Smoking NR CD, %: 46	Age at diagnosis NR Disease duration Mean: 9.4 Age at enrollment Mean: 39.8	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Farrell, 2000[231]	Never used immunomodulators, 544	Male, %: 49 Race NR Smoking NR CD, %: 28	Age at diagnosis NR Disease duration Mean: 10.3 Age at enrollment Mean: 46.1	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Fraser, 2002[232]	Never user azathioprine, 1578	Male, %: 47 Race NR Smoking NR CD, %: 37	Age at diagnosis Mean: 35.1 Disease duration Mean: 13.7 Age at enrollment NR	Severity NR Location, % Ileal: 17.7 Ileo-colonic: 18.6 Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Fraser, 2002[232]	Azathioprine, 626 Route: Unknown Dose: NR	Male, %: 46.6 Race NR Smoking NR CD, %: 43.3	Age at diagnosis Mean: 31.9 Disease duration Mean: 13.5 Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Govani, 2010[157]	Thiopurine + no steroid, 11 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Govani, 2010[157]	Thiopurine + Corticosteroid, 16 Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Never user immunomodulator, 2798 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Never user 5-aminosalicylate acid, 675	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Immunomodulator, 443 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hutfless, 2007[151]	Never user corticosteroid, 1073 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Corticosteroid, 2168 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	5-ASA, 2566 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Kane, 2008[141]	Never user immunnomodulators, 17 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Kane, 2008[141]	Immunomodulators, 23 Route: Unknown Dose: NR	Male, %: 0 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lees, 2009[144]	Immunomodulator, 105 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lees, 2009[144]	Never user immunomodulator, 234	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lemann, 2005[98]	Azathioprine, 40 Route: Oral Dose: as taken before enrollment every day	Male, %: 47 Race NR Smoking, % Smoker, 42 CD NR	Age at diagnosis NR Disease duration Mean: 11 Age at enrollment Mean: 40	Severity NR Location, % Ileal: 13 Ileo-colonic: 40 Colonic: 48 Perianal: 43 Behavior NR CRP Mean: 5.3	CDAI Mean: 41 CDEIS Mean: 2.5	Corticosteroids <10mg/day: 8	azathioprine: 100	NR
Lemann, 2005[98]	Placebo, 43 Route: Oral Dose: NA every day	Male, %: 42 Race NR Smoking, % Smoker, 42 CD NR	Age at diagnosis NR Disease duration Mean: 11 Age at enrollment Mean: 36	Severity NR Location, % Ileal: 9 Ileo-colonic: 51 Colonic: 40 Perianal: 44 Behavior NR CRP Mean: 6.9	CDAI Mean: 39 CDEIS Mean: 2.4	Corticosteroids <10mg/day: 5	azathioprine: 100	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lemann, 2006[46]	Placebo + Azathioprine or 6-MP, 56 Route: IV + Oral Dose: NA + stable mg/kg every day	Male, %: 42.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Min: 1 Max: 11 Age at enrollment Min: 22 Max: 36	Severity NR Location, % Ileal: 12.5 Ileo-colonic: 48.2 Colonic: 39.3 Perianal: 10.7 Behavior NR CRP Min: 4 Max: 35	CDAI Min: 42 Max: 262	NR	Thiopurines: 100	NR
Lemann, 2006[46]	Infliximab + Azathioprine or 6-MP, 57 Route: IV Dose: 5 mg/kg + stable	Male, %: 47.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Min: 1 Max: 10 Age at enrollment Min: 22 Max: 38	Severity NR Location, % Ileal: 28.1 Ileo-colonic: 50.9 Colonic: 21.1 Perianal: 33.3 Behavior NR CRP Min: 4 Max: 47	CDAI Min: 90 Max: 281	NR	Thiopurines: 100	NR
Lewis, 2001[136]	Never user mesalamine (NR), 7931 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lewis, 2001[136]	Never user corticosteroid, 11000 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Thiopurine, 837	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Never user azathioprine/6-MP, 5768	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Never user immunosuppressants (defined as either methotrexate, cyclosporine, tacrolimus or mycophenolate mofetil), 15087 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lewis, 2001[136]	Immunosuppressants (defined as either methotrexate, cyclosporine, tacrolimus or mycophenolate mofetil), 77 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Mesalamine (NR), 7233 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Corticosteroid, 4064 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lichtenstein, 2006[131]	No immunomodulators, 2526 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lichtenstein, 2006[131]	No reported prednisone usage, 2396 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lichtenstein, 2006[131]	Immunomodulator, 3764 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lichtenstein, 2006[131]	Infliximab, 3179 Route: IV	Male, %: 40.5 Race, % W: 88.8 H: 1.2 B: 7.2 A: 0.5 Other: 0.7 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10.7 Age at enrollment NR	Severity, % Mild-mod disease: 50.1 Mod-sev disease: 30.8 Severe disease: 2.5 Location, % Ileal: 25.1 Ileo-colonic: 43.2 Colonic: 28.2 Behavior NR CRP NR	Disease activity index NR	Prednisone: 27.4 Immunomodulator: 49.4 narcotic analgesic: 9.8	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lichtenstein, 2006[131]	Never user infliximab, 3111 Route: IV	Male, %: 40.8 Race, % W: 89.3 H: 1.4 B: 6.2 A: 0.3 Other: 0.6 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10.9 Age at enrollment NR	Severity, % Mild-mod disease: 47.9 Mod-sev disease: 10.3 Severe disease: 0.6 Location, % Ileal: 32.4 Ileo-colonic: 35.4 Colonic: 28 Behavior NR CRP NR	Disease activity index NR	Immunomodulators: 32.2 Prednisone: 16.1 Narcotic analgesics: 5.4	NR	NR
Lichtenstein, 2006[131]	Prednisone, 3894 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Maher, 2009[176]	Azathioprine, 16	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Antibiotics Corticosteroids	NR	NR
Maher, 2009[176]	Never user, 60	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Mantzaris, 2009[102]	Azathioprine, 38 Route: Oral Dose: 2.0-2.5 mg/kg every day	Male, %: 44.7 Race NR Smoking, % Smoker, 92.1 CD NR	Age at diagnosis NR Disease duration Mean: 1.8 Age at enrollment Median: 34.3 Min: 19 Max: 59	Severity, % Remission: 100 Location, % Ileo-colonic: 63.2 Colonic: 36.8 Behavior, % Inflammatory: 100 CRP NR	CDAI Mean: 132 CDEIS Mean: 7.2	NR	Corticosteroids: 100	Corticosteroids: 100
Mantzaris, 2009[102]	Budesonide, 39 Route: Oral Dose: 1-9 mg every day	Male, %: 43.6 Race NR Smoking, % Smoker, 92.3 CD NR	Age at diagnosis NR Disease duration Mean: 1.9 Age at enrollment Median: 34.5 Min: 19 Max: 62	Severity, % Remission: 100 Location, % Ileo-colonic: 66.7 Colonic: 33.3 Behavior, % Inflammatory: 100 CRP NR	CDAI Mean: 129 CDEIS Mean: 7.1	NR	Corticosteroids: 100	Corticosteroids: 100
Marehbian, 2009[168]	Thiopurine + TNF-alpha Route: Unknown + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	TNF-alpha Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Marehbian, 2009[168]	Thiopurine + TNF-alpha	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	Corticosteroid Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	Never user corticosteroids, azathioprine/6-MP/methotrexate, TNF-alpha inhibitor or combination of these drugs	Gender NR Race NR Smoking NR CD, %: Total sample NR, but n CD was 0	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	Thiopurine Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Marehbian, 2009[168]	TNF-alpha + Corticosteroid	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Marehbian, 2009[168]	Corticosteroid + TNF-alpha	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Markowitz, 2000[192]	6-MP + Prednisone, 27 Dose: 1.5 mg/kg every day + 40 mg every day	Male, %: 55.6 Race, % W: 93 Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13	Severity NR Location, % Ileal: 14.8 Ileo-colonic: 70.4 Colonic: 14.8 Behavior NR CRP NR	PCDAI Mean: 46.7 HBI Mean: 7.7 partial HB Mean: 6.6	NR	NR	NR
Markowitz, 2000[192]	Placebo + Prednisone, 28 Dose: 40 mg every day	Male, %: 64.3 Race, % W: 93 Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13.4	Severity NR Location, % Ileal: 3.6 Ileo-colonic: 78.6 Colonic: 17.9 Behavior NR CRP NR	PCDAI Mean: 44.7 HBI Mean: 7.4 partial HB Mean: 6.5	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
O'Donoghue, 1978[100]	Placebo, 27 Route: Oral Dose: NA	Male, %: 40.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.05 Min: 1.5 Max: 15 Age at enrollment Mean: 40.5 Min: 22 Max: 65	Severity, % Remission: 100 Location, % Ileal: 25.9 Ileo-colonic: 11.1 Colonic: 63 Behavior NR CRP NR	Unnamed clinical scoring system Mean: 2 Min: 0 Max: 7	Prednisolone and sulfasalazine collectively: 25.9	NR	Thiopurines: 100
O'Donoghue, 1978[100]	Azathioprine, 24 Route: Oral Dose: 2 mg/kg every 24 hours	Male, %: 45.8 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.25 Min: 1.5 Max: 20 Age at enrollment Mean: 40 Min: 21 Max: 78	Severity, % Remission: 100 Location, % Ileal: 12.5 Ileo-colonic: 41.7 Colonic: 45.8 Behavior NR CRP NR	Unnamed clinical scoring system Mean: 2.33 Min: 0 Max: 9	Corticosteroids and/or sulfasalazine: 33.3	NR	Thiopurines: 100
Reinisch, 2008[51]	Azathioprine + Prednisone, 52 Route: Oral + Oral Dose: 2.5 mg/kg every day + 1 mg/kg or >/= 40 mg every day	Male, %: 50 Race NR Smoking, % Smoker, 30.8 CD NR	Age at diagnosis NR Disease duration Median: 1.2 Min: 0 Max: 20.3 Age at enrollment Median: 38.5 Min: 19 Max: 74	Severity NR Location, % Ileal: 71.2 Colonic: 73.1 Behavior NR CRP NR	CDAI Median: 282 Min: 225 Max: 435 IBDQ Median: 126 Min: 46 Max: 198	NR	NR	Corticosteroids: 96.2

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Reinisch, 2008[51]	Placebo + Prednisone, 29 Route: Oral + Oral Dose: NA every day + 1mg/kg or >/= 40mg every day	Male, %: 55.2 Race NR Smoking, % Smoker, 34.5 CD NR	Age at diagnosis NR Disease duration Median: 0.6 Min: 0 Max: 14.9 Age at enrollment Median: 39.5 Min: 18 Max: 64	Severity NR Location, % Ileal: 82.8 Colonic: 58.6 Behavior NR CRP NR	CDAI Median: 280 Min: 230 Max: 432 IBDQ Median: 120 Min: 70 Max: 147	NR	NR	Corticosteroids: 96.6
Sandborn, 1999[59]	Azathioprine + Azathioprine, 51 Route: IV + Oral Dose: 40 mg/kg + 2 mg/kg every day	Male, %: 47.1 Race NR Smoking, % Smoker, 43.1 CD NR	Age at diagnosis NR Disease duration Median: 7.1 Min: 0 Max: 28 Age at enrollment Median: 33 Min: 19 Max: 63	Severity NR Location, % Ileal: 33.3 Ileo-colonic: 52.9 Colonic: 13.7 Behavior NR CRP NR	CDAI Median: 244 Min: 89 Max: 424 IBDQ Median: 127 Min: 73 Max: 183	NR	NR	NR
Sandborn, 1999[59]	Placebo + Azathioprine, 45 Route: Oral Dose: 2 mg/kg every day	Male, %: 55.6 Race NR Smoking, % Smoker, 35.6 CD NR	Age at diagnosis NR Disease duration Median: 6.6 Min: 0 Max: 35 Age at enrollment Median: 35 Min: 19 Max: 65	Severity NR Location, % Ileal: 17.8 Ileo-colonic: 60 Colonic: 22.2 Behavior NR CRP NR	CDAI Median: 245 Min: 142 Max: 476 IBDQ Median: 123 Min: 77 Max: 182	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schneeweiss, 2009[230]	Corticosteroid, 7258 Route: Unknown Dose: NR	Male, %: 45.6 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 41.5	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA TNF-alpha inhibitors Methotrexate Thiopurines	5ASA Antibiotics TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines	NR
Schneeweiss, 2009[230]	Immunomodulator, 2883 Route: Unknown Dose: NR	Male, %: 46.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 38.6	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA TNF-alpha inhibitors Corticosteroids	5ASA Antibiotics TNF-alpha inhibitors Corticosteroids	NR
Schneeweiss, 2009[230]	Infliximab, 521 Route: Unknown Dose: NR	Male, %: 45.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	5ASA Corticosteroids Methotrexate Thiopurines	5ASA Antibiotics TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Seksik, 2009[155]	Never user azathioprine, 61 Route: Unknown Dose: NR	Male, %: 41 Race NR Smoking NR CD, %: 67.2	Age at diagnosis NR Disease duration Mean: 12.6 Age at enrollment Mean: 40.8 Min: 21.4 Max: 76.8	Severity NR Location, % Ileal: 45.9 Ileo-colonic: 13.1 Colonic: 8.2 Behavior NR CRP NR	Disease activity index NR	5ASA: 77 Corticosteroids: 5 Azathioprine: 0 Infliximab: 0	NR	NR
Seksik, 2009[155]	Azathioprine, 169 Route: Unknown Dose: NR	Male, %: 42.6 Race NR Smoking NR CD, %: 71.6	Age at diagnosis NR Disease duration Mean: 13.1 Age at enrollment Mean: 37.7 Min: 17.8 Max: 71.8	Severity NR Location, % Ileal: 22.5 Ileo-colonic: 30.8 Colonic: 17.8 Behavior NR CRP NR	Disease activity index NR	5ASA: 0 Corticosteroids: 14 Azathioprine: 100 Infliximab: 4	NR	NR
Shah, 2008[156]	Azathioprine + Never user mesalamine, 95	Gender NR Race NR Smoking NR CD, %: 69.5	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Shah, 2008[156]	Azathioprine + Mesalamine (NR), 104	Gender NR Race NR Smoking NR CD, %: 53.8	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Azathioprine, 59 Route: Oral Dose: 2.5 mg/kg every 24 hours	Male, %: 52.5 Race, % W: 89.8 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.25 Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 40.7 Ileo-colonic: 44.1 Colonic: 15.3 Behavior NR CRP NR	CDAI Mean: 240.7	NR	Corticosteroids: 37.3 Sulfasalazine: 30.5	NR
Summers, 1979[56]	Prednisone, 85 Route: Oral Dose: If CDAI<150 then dose of prednisone is 1/4mg/kg, if CDAI = 150-300 then prednisone was dosed at 1/2mg/kg, if CDAI >300 then prednisone is 3/4mg/kg. every 24 hours	Male, %: 52.9 Race, % W: 92.9 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.48 Age at enrollment Mean: 31.8	Severity NR Location, % Ileal: 30.6 Ileo-colonic: 60 Colonic: 9.4 Behavior NR CRP NR	CDAI Mean: 243.4	NR	Corticosteroids: 24.7 Sulfasalazine: 30.6	NR
Summers, 1979[56]	Placebo, 77 Route: Oral Dose: NA	Male, %: 45.5 Race, % W: 93.5 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.97 Age at enrollment Mean: 33.7	Severity NR Location, % Ileal: 32.5 Ileo-colonic: 55.8 Colonic: 11.7 Behavior NR CRP NR	CDAI Mean: 241.9	NR	Corticosteroids: 37.7 sulfasalazine: 35.1	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Sulfasalazine, 74 Route: Oral Dose: 1g/15kgs every 24 hours	Male, %: 65.7 Race, % W: 93.2 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.42 Age at enrollment Mean: 29.6	Severity NR Location, % Ileal: 23 Ileo-colonic: 66.2 Colonic: 10.8 Behavior NR CRP NR	CDAI Mean: 256.2	NR	Corticosteroids: 38.4 sulfasalazine: 51.1	NR
Summers, 1979[56]	Placebo, 101 Route: Oral Dose: NA	Male, %: 53.5 Race, % W: 94.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.84 Age at enrollment Mean: 31.6	Severity, % Remission: 100 Location, % Ileal: 43 Ileo-colonic: 48 Colonic: 9 Behavior NR CRP NR	CDAI Mean: 83.5	NR	NR	Corticosteroids: 31.7
Summers, 1979[56]	Sulfasalazine, 58 Route: Oral Dose: 1/2 g/ 15 kg every 24 hours	Male, %: 53.4 Race, % W: 98.3 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.11 Age at enrollment Mean: 32.2	Severity, % Remission: 100 Location, % Ileal: 50 Ileo-colonic: 40 Colonic: 10 Behavior NR CRP NR	CDAI Mean: 89.4	NR	NR	Corticosteroids: 32.8

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Azathioprine, 54 Route: Oral Dose: 1 mg/kg every 24 hours	Male, %: 57.4 Race, % W: 94.4 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.99 Age at enrollment Mean: 31	Severity, % Remission: 100 Location, % Ileal: 37 Ileo-colonic: 56 Colonic: 7 Behavior NR CRP NR	CDAI Mean: 85.9	NR	NR	Corticosteroids: 31.5
Summers, 1979[56]	Prednisone, 61 Route: Oral Dose: 1-4 mg/kg every 24 hours	Male, %: 50.8 Race, % W: 95.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 4.37 Age at enrollment Mean: 32.6	Severity, % Remission: 100 Location, % Ileal: 46 Ileo-colonic: 43 Colonic: 11 Behavior NR CRP NR	CDAI Mean: 94.8	NR	NR	Corticosteroids: 34.4
Tay, 2003[233]	Any immunomodulator, 72 Route: Unknown	Male, %: 40.3 Race NR Smoking, % Smoker, 1.4 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Min: 19 Max: 51	Severity NR Location, % Ileal: 2.8 Ileo-colonic: 1.4 Colonic: 1.4 Behavior NR CRP NR	Disease activity index NR	Immunomodulators: 5.6	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Tay, 2003[233]	No immunomodulator, 28 Route: Unknown	Male, %: 46.4 Race NR Smoking, % Smoker, 7.1 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Min: 28 Max: 60	Severity NR Location, % Ileal: 14.3 Ileo-colonic: 10.7 Colonic: 3.6 Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
van Schaik, 2011[234] Netherlands claims database	5-ASA + Never user thiopurines, 973 Route: Unknown Dose: 1.2 g every 1 days	Male, %: 43 Race NR Smoking NR CD, %: 46	Age at diagnosis NR Disease duration Mean: 3 Age at enrollment Mean: 43	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
van Schaik, 2011[234] Netherlands claims database	Thiopurine + Never user asa, 314 Route: Unknown Dose: 50 mg every 1 days	Male, %: 42 Race NR Smoking NR CD, %: 39	Age at diagnosis NR Disease duration Mean: 2.8 Age at enrollment Mean: 42	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
van Schaik, 2011[234] Netherlands claims database	5-ASA + Thiopurine, 456 Route: Unknown + Unknown Dose: 1.2 g + 50 mg every 1 days	Male, %: 42 Race NR Smoking NR CD, %: 47	Age at diagnosis NR Disease duration Mean: 3.3 Age at enrollment Mean: 44	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
van Schaik, 2011[234] Netherlands claims database	Never user ASA or thiopurine or didn't meet dose/duration requirement, 835 Route: Unknown Dose: NR	Male, %: 43 Race NR Smoking NR CD, %: 43	Age at diagnosis NR Disease duration Mean: 2.9 Age at enrollment Mean: 43	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Studies evaluating methotrexate								
Feagan, 1995[63]	Placebo + Prednisone, 47 Route: IM + Oral Dose: NA every 1 week + every day	Male, %: 55 Race NR Smoking, % Cigarette smoker, 47 CD NR	Age at diagnosis NR Disease duration Mean: 98 Age at enrollment Mean: 36	Severity NR Location, % Ileal: 17 Ileo-colonic: 64 Colonic: 19 Behavior NR CRP NR	CDAI Mean: 190 IBDQ Mean: 159	Hydrocortisone ointment	NR	NR
Feagan, 1995[63]	Methotrexate + Prednisone, 94 Route: IM + Oral Dose: 25 mg every 1 week	Male, %: 54 Race NR Smoking, % Cigarette smoker, 49 CD NR	Age at diagnosis NR Disease duration Mean: 93 Age at enrollment Mean: 34	Severity NR Location, % Ileal: 32 Ileo-colonic: 52 Colonic: 16 Behavior NR CRP NR	CDAI Mean: 181 IBDQ Mean: 162	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Feagan, 2000[105]	Methotrexate, 40 Route: IM Dose: 15 mg every 1 week	Male, %: 40 Race NR Smoking, % Cigarette smoker, 50 CD NR	Age at diagnosis NR Disease duration Mean: 7.33 Age at enrollment Mean: 32	Severity, % Remission: 100 Location, % Ileal: 45 Ileo-colonic: 28 Colonic: 28 Behavior NR CRP NR	CDAI Mean: 94	NR	NR	Methotrexate: 100
Feagan, 2000[105]	Placebo, 36 Route: IM Dose: NA every 1 week	Male, %: 61 Race NR Smoking, % Cigarette smoker, 42 CD NR	Age at diagnosis NR Disease duration Mean: 84 Age at enrollment Mean: 34	Severity, % Remission: 100 Location, % Ileal: 31 Ileo-colonic: 44 Colonic: 25 Behavior NR CRP NR	CDAI Mean: 84	NR	Methotrexate: 100 Thiopurines: 3	Methotrexate: 100
Thayu, 2010[199]	Infliximab	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Thayu, 2010[199]	Placebo	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Thayu, 2010[199]	Corticosteroid	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Thayu, 2010[199]	Methotrexate	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Studies evaluating corticosteroids								
Alemzadeh, 2002[200]	Placebo, 108	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Alemzadeh, 2002[200]	Corticosteroid, 27	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Campieri, 1997[68]	Budesonide + Placebo, 61 Route: Oral + Oral Dose: 4.5 mg every 12 hours + NA every 24 hours	Male, %: 45.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 7.9 Min: 0 Max: 37 Age at enrollment Mean: 38 Min: 20 Max: 71	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 274 Min: 107 Max: 465	Corticosteroids: 100	NR	NR
Campieri, 1997[68]	Prednisolone + Placebo, 58 Route: Oral + Oral Dose: 40 mg every day + NA every 12 hours	Male, %: 39.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 6.7 Min: 0 Max: 27 Age at enrollment Mean: 36 Min: 19 Max: 70	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 279 Min: 202 Max: 458	Corticosteroids: 100	NR	NR
Campieri, 1997[68]	Budesonide + Placebo, 58 Route: Oral + Oral Dose: 9 mg every day + NA every 24 hours	Male, %: 36.2 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 8.3 Min: 0 Max: 30 Age at enrollment Mean: 36 Min: 17 Max: 71	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 277 Min: 121 Max: 476	Corticosteroids: 100	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Escher, 2004[190]	Budesonide, 22 Dose: 9 mg every day	Male, %: 31.8 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 0.6 Age at enrollment Mean: 13	Severity NR Location, % Ileal: 59.1 Ileo-colonic: 31.8 Colonic: 9.1 Behavior NR CRP NR	CDAI Mean: 239 PCDAI Mean: 39	NR	NR	NR
Escher, 2004[190]	Prednisolone, 26 Dose: 1 mg/kg every day	Male, %: 69.2 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 0.8 Age at enrollment Mean: 13	Severity NR Location, % Ileal: 26.9 Ileo-colonic: 65.4 Colonic: 3.8 Behavior NR CRP NR	CDAI Mean: 268 PCDAI Mean: 45	NR	NR	NR
Goldstein, 1967[142]	Corticosteroid, 430 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Goldstein, 1967[142]	Never user corticosteroids/ACTH, 124	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hutfless, 2007[151]	Corticosteroid, 2168 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Immunomodulator, 443 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Never user immunomodulator, 2798 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Never user 5-aminosalicylic acid, 675	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	5-ASA, 2566 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hutfless, 2007[151]	Never user corticosteroid, 1073 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Issenman, 1993[196]	Discontinued corticosteroids, 8	Male, %: 100 Race NR Smoking NR CD, %: 212.5	Age at diagnosis Mean: 13.2 Disease duration NR Age at enrollment Mean: 13.2	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Issenman, 1993[196]	Prednisone, 9 Route: Oral Dose: 2 mg/kg every day	Male, %: 100 Race NR Smoking NR CD NR	Age at diagnosis Mean: 14.5 Disease duration NR Age at enrollment Mean: 14.5	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 64.1	Corticosteroids: 100	5ASA	NR
Levine, 2002[198]	Budesonide, 62 Dose: 9 mg every day	Male, %: 59.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 14.1	Severity NR Location NR Behavior NR CRP NR	PCDAI Mean: 25.8	NR	immunosuppressives: 29	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Levine, 2002[198]	Prednisone, 58 Dose: 40 mg every day	Male, %: 60.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13.7	Severity NR Location NR Behavior NR CRP NR	PCDAI Mean: 29.6	NR	immunosuppressives: 20.6	NR
Levine, 2003[191]	Prednisone + Mesalamine, 14 Dose: 40 mg every day + 3-4 g every day	Male, %: 50 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 14.15	Severity NR Location NR Behavior NR CRP NR	PCDAI Mean: 28.9	NR	NR	NR
Levine, 2003[191]	Budesonide + Mesalamine, 19 Dose: 3 mg every 8 hours + 3-4 g every day	Male, %: 68.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13.8	Severity NR Location NR Behavior NR CRP NR	PCDAI Mean: 29.3	NR	NR	NR
Lewis, 2001[136]	Never user azathioprine/6-MP, 5768	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lewis, 2001[136]	Never user immunosuppressants (defined as either methotrexate, cyclosporine, tacrolimus or mycophenolate mofetil), 15087 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Immunosuppressants (defined as either methotrexate, cyclosporine, tacrolimus or mycophenolate mofetil), 77 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Thiopurine, 837	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Mesalamine (NR), 7233 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lewis, 2001[136]	Corticosteroid, 4064 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Never user corticosteroid, 11000 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Never user mesalamine (NR), 7931 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lichtenstein, 2006[131]	Infliximab, 3179 Route: IV	Male, %: 40.5 Race, % W: 88.8 H: 1.2 B: 7.2 A: 0.5 Other: 0.7 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10.7 Age at enrollment NR	Severity, % Mild-mod disease: 50.1 Mod-sev disease: 30.8 Severe disease: 2.5 Location, % Ileal: 25.1 Ileo-colonic: 43.2 Colonic: 28.2 Behavior NR CRP NR	Disease activity index NR	Prednisone: 27.4 Immunomodulator: 49.4 narcotic analgesic: 9.8	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lichtenstein, 2006[131]	No reported prednisone usage, 2396 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lichtenstein, 2006[131]	Prednisone, 3894 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lichtenstein, 2006[131]	No immunomodulators, 2526 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lichtenstein, 2006[131]	Immunomodulator, 3764 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lichtenstein, 2006[131]	Never user infliximab, 3111 Route: IV	Male, %: 40.8 Race, % W: 89.3 H: 1.4 B: 6.2 A: 0.3 Other: 0.6 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10.9 Age at enrollment NR	Severity, % Mild-mod disease: 47.9 Mod-sev disease: 10.3 Severe disease: 0.6 Location, % Ileal: 32.4 Ileo-colonic: 35.4 Colonic: 28 Behavior NR CRP NR	Disease activity index NR	Immunomodulators: 32.2 Prednisone: 16.1 Narcotic analgesics: 5.4	NR	NR
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 38 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 42.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.2	Severity NR Location, % Ileal: 23.7 Ileo-colonic: 52.6 Colonic: 23.7 Behavior NR CRP NR	CDAI Mean: 185.3	NR	NR	NR
Malchow, 1984[64]	(6)-Methylprednisolone, 38 Route: IV Dose: 48 mg every 24 hours	Male, %: 47.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 26.1	Severity NR Location, % Ileal: 31.6 Ileo-colonic: 57.9 Colonic: 10.5 Behavior NR CRP NR	CDAI Mean: 147.4	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Placebo, 42 Route: Oral Dose: NA	Male, %: 35.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.1	Severity NR Location, % Ileal: 23.8 Ileo-colonic: 52.4 Colonic: 23.8 Behavior NR CRP NR	CDAI Mean: 178.2	NR	NR	NR
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 74 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 41.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 32.4 Ileo-colonic: 46 Colonic: 21.6 Behavior NR CRP NR	CDAI Mean: 148.2	NR	Sulfasalazine: 83.8 Prednisolone: 59.5 Azathioprine: 6.8	NR
Malchow, 1984[64]	(6)-Methylprednisolone, 75 Route: Unknown Dose: 48 mg every 24 hours	Male, %: 50.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 32.5	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 159.9	NR	Sulfasalazine: 81.3 Prednisolone: 55.4 Azathioprine: 4	NR
Malchow, 1984[64]	Sulfasalazine, 75 Route: Oral Dose: 3 g every 24 hours	Male, %: 48 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 31.2	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 165.2	NR	sulfasalazine: 88 Prednisolone: 54.7 Azathioprine: 5.3	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Placebo, 68 Route: Oral Dose: NA	Male, %: 44.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.1	Severity NR Location, % Ileal: 33.8 Ileo-colonic: 45.6 Colonic: 20.6 Behavior NR CRP NR	CDAI Mean: 161.4	NR	sulfasalazine: 92.6 Prednisolone: 47.8 Azathioprine: 4.4	NR
Malchow, 1984[64]	Sulfasalazine, 42 Route: Oral Dose: 3 g every 24 hours	Male, %: 50 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 33.1	Severity NR Location, % Ileal: 62.4 Ileo-colonic: 113.3 Colonic: 62.4 Behavior NR CRP NR	CDAI Mean: 181.9	NR	NR	NR
Mantzaris, 2003[113]	Budesonide, 29 Route: Unknown Dose: 6 mg every day	Male, %: 44.8 Race NR Smoking, % Smoker, 86 CD NR	Age at diagnosis NR Disease duration Mean: 3.5 Age at enrollment Mean: 34.1 Min: 20 Max: 62	Severity NR Location, % Ileal: 52 Ileo-colonic: 38 Colonic: 10 Behavior NR CRP NR	CDAI Mean: 139 IBDQ Mean: 188	Corticosteroids: 100	Thiopurines: 41	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Mantzaris, 2003[113]	Mesalamine (Salofalk), 28 Route: Unknown Dose: 1 g every 8 hours	Male, %: 42.9 Race NR Smoking, % Smoker, 82 CD NR	Age at diagnosis NR Disease duration Mean: 3.2 Age at enrollment Mean: 31.8 Min: 19 Max: 65	Severity NR Location, % Ileal: 54 Ileo-colonic: 28 Colonic: 18 Behavior NR CRP NR	CDAI Mean: 138 IBDQ Mean: 186	Corticosteroids: 100	Thiopurines: 43	NR
Saha, 1998[197]	Prednisone	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Saha, 1998[197]	Placebo	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Schoon, 2005[185]	Budesonide, 137 Route: Oral Dose: 9 mg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Vitamin D: 12 Calcium: 46	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Schoon, 2005[185]	Prednisolone, 134 Route: Oral Dose: 40 mg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Vitamin D: 15 Calcium: 51	NR	NR
Siffledeen, 2007[127]	Never user corticosteroids during year before DXA scan, 107	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Siffledeen, 2007[127]	Corticosteroid, 109	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Singleton, 1979[75]	Placebo + Prednisone, 46 Route: Unknown + Oral Dose: NA + every day	Male, %: 46 Race, % W: 89 Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 31.9	Severity NR Location, % Ileo-colonic: 55 Colonic: 11 Behavior NR CRP NR	CDAI Mean: 236.3	NR	5ASA: 54 Corticosteroids: 52	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Singleton, 1979[75]	Sulfasalazine + Prednisone, 43 Route: Oral + Unknown Dose: 1g per 15kg body weight to 5g max every day + every day	Male, %: 47 Race, % W: 86 Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30	Severity NR Location, % Ileo-colonic: 56 Colonic: 9 Behavior NR CRP NR	CDAI Mean: 239	NR	5ASA: 51 Corticosteroids: 47	NR
Summers, 1979[56]	Placebo, 77 Route: Oral Dose: NA	Male, %: 45.5 Race, % W: 93.5 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.97 Age at enrollment Mean: 33.7	Severity NR Location, % Ileal: 32.5 Ileo-colonic: 55.8 Colonic: 11.7 Behavior NR CRP NR	CDAI Mean: 241.9	NR	Corticosteroids: 37.7 sulfasalazine: 35.1	NR
Summers, 1979[56]	Sulfasalazine, 74 Route: Oral Dose: 1g/15kgs every 24 hours	Male, %: 65.7 Race, % W: 93.2 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.42 Age at enrollment Mean: 29.6	Severity NR Location, % Ileal: 23 Ileo-colonic: 66.2 Colonic: 10.8 Behavior NR CRP NR	CDAI Mean: 256.2	NR	Corticosteroids: 38.4 sulfasalazine: 51.1	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Prednisone, 85 Route: Oral Dose: If CDAI<150 then dose of prednisone is 1/4mg/kg, if CDAI = 150-300 then prednisone was dosed at 1/2mg/kg, if CDAI >300 then prednisone is 3/4mg/kg. every 24 hours	Male, %: 52.9 Race, % W: 92.9 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.48 Age at enrollment Mean: 31.8	Severity NR Location, % Ileal: 30.6 Ileo-colonic: 60 Colonic: 9.4 Behavior NR CRP NR	CDAI Mean: 243.4	NR	Corticosteroids: 24.7 Sulfasalazine: 30.6	NR
Summers, 1979[56]	Azathioprine, 59 Route: Oral Dose: 2.5 mg/kg every 24 hours	Male, %: 52.5 Race, % W: 89.8 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.25 Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 40.7 Ileo-colonic: 44.1 Colonic: 15.3 Behavior NR CRP NR	CDAI Mean: 240.7	NR	Corticosteroids: 37.3 Sulfasalazine: 30.5	NR
Summers, 1979[56]	Azathioprine, 54 Route: Oral Dose: 1 mg/kg every 24 hours	Male, %: 57.4 Race, % W: 94.4 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.99 Age at enrollment Mean: 31	Severity, % Remission: 100 Location, % Ileal: 37 Ileo-colonic: 56 Colonic: 7 Behavior NR CRP NR	CDAI Mean: 85.9	NR	NR	Corticosteroids: 31.5

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Placebo, 101 Route: Oral Dose: NA	Male, %: 53.5 Race, % W: 94.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.84 Age at enrollment Mean: 31.6	Severity, % Remission: 100 Location, % Ileal: 43 Ileo-colonic: 48 Colonic: 9 Behavior NR CRP NR	CDAI Mean: 83.5	NR	NR	Corticosteroids: 31.7
Summers, 1979[56]	Sulfasalazine, 58 Route: Oral Dose: 1/2 g/ 15 kg every 24 hours	Male, %: 53.4 Race, % W: 98.3 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.11 Age at enrollment Mean: 32.2	Severity, % Remission: 100 Location, % Ileal: 50 Ileo-colonic: 40 Colonic: 10 Behavior NR CRP NR	CDAI Mean: 89.4	NR	NR	Corticosteroids: 32.8
Summers, 1979[56]	Prednisone, 61 Route: Oral Dose: 1-4 mg/kg every 24 hours	Male, %: 50.8 Race, % W: 95.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 4.37 Age at enrollment Mean: 32.6	Severity, % Remission: 100 Location, % Ileal: 46 Ileo-colonic: 43 Colonic: 11 Behavior NR CRP NR	CDAI Mean: 94.8	NR	NR	Corticosteroids: 34.4

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Thayu, 2010[199]	Methotrexate	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Thayu, 2010[199]	Infliximab	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Thayu, 2010[199]	Placebo	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Thayu, 2010[199]	Corticosteroid	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Tremaine, 2002[65]	Placebo, 41 Route: Oral Dose: NA every day	Male, %: 43.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10 Median: 8.2 Age at enrollment Mean: 37 Median: 36	Severity, % Mild-mod disease: 100 Location NR Behavior NR CRP NR	CDAI Mean: 271 Median: 253 Min: 197 Max: 425	NR	NR	NR
Tremaine, 2002[65]	Budesonide, 80 Route: Oral Dose: 9 mg every day	Male, %: 23.8 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 11.9 Median: 9.2 Age at enrollment Mean: 41 Median: 36	Severity, % Mild-mod disease: 100 Location NR Behavior NR CRP NR	CDAI Mean: 280 Median: 268 Min: 199 Max: 484	NR	NR	NR
Tremaine, 2002[65]	Budesonide, 79 Route: Oral Dose: 4.5 mg every 12 hours	Male, %: 44.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 10 Median: 7.1 Age at enrollment Mean: 39 Median: 38	Severity, % Mild-mod disease: 100 Location NR Behavior NR CRP NR	CDAI Mean: 279 Median: 270 Min: 166 Max: 437	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Studies evaluating 5-aminosalicylate acids								
Bernstein, 2011[235] University of Manitoba	5-ASA, 5787 Route: Oral Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Bernstein, 2011[235] University of Manitoba	Never user ASA, 2957 Route: Unknown Dose: NA	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Never user corticosteroid, 1073 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Immunomodulator, 443 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Hutfless, 2007[151]	Never user immunomodulator, 2798 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Never user 5-aminosalicylate acid, 675	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	5-ASA, 2566 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Hutfless, 2007[151]	Corticosteroid, 2168 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Never user mesalamine (NR), 7931 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lewis, 2001[136]	Never user corticosteroid, 11000 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Thiopurine, 837	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Never user azathioprine/6-MP, 5768	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Never user immunosuppressants (defined as either methotrexate, cyclosporine, tacrolimus or mycophenolate mofetil), 15087 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lewis, 2001[136]	Immunosuppressants (defined as either methotrexate, cyclosporine, tacrolimus or mycophenolate mofetil), 77 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Mesalamine (NR), 7233 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lewis, 2001[136]	Corticosteroid, 4064 Route: Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 74 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 41.9 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 32.4 Ileo-colonic: 46 Colonic: 21.6 Behavior NR CRP NR	CDAI Mean: 148.2	NR	Sulfasalazine: 83.8 Prednisolone: 59.5 Azathioprine: 6.8 : 59.5	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	(6)-Methylprednisolone, 75 Route: Unknown Dose: 48 mg every 24 hours	Male, %: 50.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 32.5	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 159.9	NR	Sulfasalazine: 81.3 Prednisolone: 55.4 Azathioprine: 4 : 55.4	NR
Malchow, 1984[64]	Sulfasalazine, 75 Route: Oral Dose: 3 g every 24 hours	Male, %: 48 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 31.2	Severity NR Location, % Ileal: 32 Ileo-colonic: 48 Colonic: 20 Behavior NR CRP NR	CDAI Mean: 165.2	NR	sulfasalazine: 88 Prednisolone: 54.7 Azathioprine: 5.3 : 54.7	NR
Malchow, 1984[64]	Sulfasalazine, 42 Route: Oral Dose: 3 g every 24 hours	Male, %: 50 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 33.1	Severity NR Location, % Ileal: 62.4 Ileo-colonic: 113.3 Colonic: 62.4 Behavior NR CRP NR	CDAI Mean: 181.9	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malchow, 1984[64]	Placebo, 68 Route: Oral Dose: NA	Male, %: 44.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 29.1	Severity NR Location, % Ileal: 33.8 Ileo-colonic: 45.6 Colonic: 20.6 Behavior NR CRP NR	CDAI Mean: 161.4	NR	sulfasalazine: 92.6 Prednisolone: 47.8 Azathioprine: 4.4 : 47.8	NR
Malchow, 1984[64]	Placebo, 42 Route: Oral Dose: NA	Male, %: 35.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.1	Severity NR Location, % Ileal: 23.8 Ileo-colonic: 52.4 Colonic: 23.8 Behavior NR CRP NR	CDAI Mean: 178.2	NR	NR	NR
Malchow, 1984[64]	Sulfasalazine + Prednisolone, 38 Route: Oral + Unknown Dose: 3 g every 24 hours + 48 mg every 24 hours	Male, %: 42.1 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30.2	Severity NR Location, % Ileal: 23.7 Ileo-colonic: 52.6 Colonic: 23.7 Behavior NR CRP NR	CDAI Mean: 185.3	NR	NR	NR
Malchow, 1984[64]	(6)-Methylprednisolone, 38 Route: IV Dose: 48 mg every 24 hours	Male, %: 47.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 26.1	Severity NR Location, % Ileal: 31.6 Ileo-colonic: 57.9 Colonic: 10.5 Behavior NR CRP NR	CDAI Mean: 147.4	NR	NR	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Sulfasalazine, 74 Route: Oral Dose: 1g/15kgs every 24 hours	Male, %: 65.7 Race, % W: 93.2 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.42 Age at enrollment Mean: 29.6	Severity NR Location, % Ileal: 23 Ileo-colonic: 66.2 Colonic: 10.8 Behavior NR CRP NR	CDAI Mean: 256.2	NR	Corticosteroids: 38.4 sulfasalazine: 51.1	NR
Summers, 1979[56]	Placebo, 77 Route: Oral Dose: NA	Male, %: 45.5 Race, % W: 93.5 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.97 Age at enrollment Mean: 33.7	Severity NR Location, % Ileal: 32.5 Ileo-colonic: 55.8 Colonic: 11.7 Behavior NR CRP NR	CDAI Mean: 241.9	NR	Corticosteroids: 37.7 sulfasalazine: 35.1	NR
Summers, 1979[56]	Prednisone, 85 Route: Oral Dose: If CDAI<150 then dose of prednisone is 1/4mg/kg, if CDAI = 150-300 then prednisone was dosed at 1/2mg/kg, if CDAI >300 then prednisone is 3/4mg/kg. every 24 hours	Male, %: 52.9 Race, % W: 92.9 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.48 Age at enrollment Mean: 31.8	Severity NR Location, % Ileal: 30.6 Ileo-colonic: 60 Colonic: 9.4 Behavior NR CRP NR	CDAI Mean: 243.4	NR	Corticosteroids: 24.7 Sulfasalazine: 30.6	NR

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Azathioprine, 59 Route: Oral Dose: 2.5 mg/kg every 24 hours	Male, %: 52.5 Race, % W: 89.8 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.25 Age at enrollment Mean: 29.8	Severity NR Location, % Ileal: 40.7 Ileo-colonic: 44.1 Colonic: 15.3 Behavior NR CRP NR	CDAI Mean: 240.7	NR	Corticosteroids: 37.3 Sulfasalazine: 30.5	NR
Summers, 1979[56]	Azathioprine, 54 Route: Oral Dose: 1 mg/kg every 24 hours	Male, %: 57.4 Race, % W: 94.4 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.99 Age at enrollment Mean: 31	Severity, % Remission: 100 Location, % Ileal: 37 Ileo-colonic: 56 Colonic: 7 Behavior NR CRP NR	CDAI Mean: 85.9	NR	NR	Corticosteroids: 31.5
Summers, 1979[56]	Placebo, 101 Route: Oral Dose: NA	Male, %: 53.5 Race, % W: 94.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 2.84 Age at enrollment Mean: 31.6	Severity, % Remission: 100 Location, % Ileal: 43 Ileo-colonic: 48 Colonic: 9 Behavior NR CRP NR	CDAI Mean: 83.5	NR	NR	Corticosteroids: 31.7

Evidence Table 13. Population characteristics of randomized controlled trials and observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Summers, 1979[56]	Sulfasalazine, 58 Route: Oral Dose: 1/2 g/ 15 kg every 24 hours	Male, %: 53.4 Race, % W: 98.3 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 3.11 Age at enrollment Mean: 32.2	Severity, % Remission: 100 Location, % Ileal: 50 Ileo-colonic: 40 Colonic: 10 Behavior NR CRP NR	CDAI Mean: 89.4	NR	NR	Corticosteroids: 32.8
Summers, 1979[56]	Prednisone, 61 Route: Oral Dose: 1-4 mg/kg every 24 hours	Male, %: 50.8 Race, % W: 95.1 Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 4.37 Age at enrollment Mean: 32.6	Severity, % Remission: 100 Location, % Ileal: 46 Ileo-colonic: 43 Colonic: 11 Behavior NR CRP NR	CDAI Mean: 94.8	NR	NR	Corticosteroids: 34.4

Abbreviations: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; A = Asian; B = African American; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; H = Hispanic; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; kg = kilogram; Max. = maximum; mg = milligram; Min. = minimum; NR = not reported; SC = subcutaneous; W = White

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2010[45]	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Infusion and injection-site rx (any adverse event that occurred during or within 1 hour after infusion) @ 54 wks	NR No No	Incidence 27 / 163 (17%)	Incidence 9 / 161 (6%) P: 0.002
Colombel, 2010[45]	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Mortality (NR) @ 54 wks	NR No Yes	Incidence 0 / 163 (0%)	Incidence 1 / 161 (1%)
Colombel, 2010[45]	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Other cancers (colon cancer) @ 54 wks	NR No No	Incidence 0 / 163 (0%)	Incidence 2 / 161 (1%)
Colombel, 2010[45]	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Other infections (serious and non-serious) @ 54 wks	NR No No	Incidence 75 / 163 (46%)	Incidence 73 / 161 (45%) P: 0.91
Colombel, 2010[45]	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Serious infections (sepsis) @ 54 wks	NR No No	Incidence 0 / 163 (0%)	Incidence 1 / 161 (1%)
Colombel, 2010[45]	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Serious infections (NR) @ 54 wks	NR No No	Incidence 8 / 163 (5%)	Incidence 9 / 161 (6%) P: 0.81
Colombel, 2010[45]	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	TB (NR) @ 54 wks	NR No No	Incidence 0 / 163 (0%)	Incidence 0 / 161 (0%)
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Infusion and injection-site rx (any adverse event that occurred during or within 1 hour after infusion) @ 54 wks	NR No No	Incidence 9 / 179 (5%)	Incidence 9 / 161 (6%) P: 1
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Mortality (NR) @ 54 wks	NR No Yes	Incidence 0 / 179 (0%)	Incidence 1 / 161 (1%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Other cancers (colon cancer) @ 54 wks	NR No No	Incidence 0 / 179 (0%)	Incidence 2 / 161 (1%)
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Other infections (serious and non-serious) @ 54 wks	NR No No	Incidence 75 / 179 (42%)	Incidence 73 / 161 (45%) P: 0.58
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Serious infections (sepsis) @ 54 wks	NR No No	Incidence 0 / 179 (0%)	Incidence 1 / 161 (1%)
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	Serious infections (NR) @ 54 wks	NR No No	Incidence 7 / 179 (4%)	Incidence 9 / 161 (6%) P: 0.61
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Azathioprine + Placebo Route: Oral + IV Dose: 2.5 mg/kg every 1 d + NA every 8 wks	TB (NR) @ 54 wks	NR No No	Incidence 1 / 179 (1%)	Incidence 0 / 161 (0%)
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Infusion and injection-site rx (any adverse event that occurred during or within 1 hour after infusion) @ 54 wks	NR No No	Incidence 9 / 179 (5%)	Incidence 27 / 163 (17%)
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Mortality (NR) @ 54 wks	NR No Yes	Incidence 0 / 179 (0%)	Incidence 0 / 163 (0%)
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Other cancers (colon cancer) @ 54 wks	NR No No	Incidence 0 / 179 (0%)	Incidence 0 / 163 (0%)
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Other infections (serious and non-serious) @ 54 wks	NR No No	Incidence 75 / 179 (42%)	Incidence 75 / 163 (46%) P: 0.45

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Serious infections (NR) @ 54 wks	NR No No	Incidence 7 / 179 (4%)	Incidence 8 / 163 (5%) P: 0.79
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	Serious infections (sepsis) @ 54 wks	NR No No	Incidence 0 / 179 (0%)	Incidence 0 / 163 (0%)
Colombel, 2010[45]	Azathioprine + Infliximab Route: Oral + IV Dose: 2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Infliximab + Placebo Route: IV + Oral Dose: 5 mg/kg every 8 wks + NA every 1 d	TB (NR) @ 54 wks	NR No No	Incidence 1 / 179 (1%)	Incidence 0 / 163 (0%)
Mantzaris, 2009[88]	Hydrocortisone + Infliximab Route: IV Dose: 250 mg every 8 wks + 5 mg/kg every 8 wks	Azathioprine + Infliximab Route: Oral + IV Dose: 2.0-2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Infusion and injection-site rx (NR)	NR No NA	Incidence 1 / 23 (4%)	Incidence 0 / 23 (0%)
Mantzaris, 2009[88]	Hydrocortisone + Infliximab Route: IV Dose: 250 mg every 8 wks + 5 mg/kg every 8 wks	Azathioprine + Infliximab Route: Oral + IV Dose: 2.0-2.5 mg/kg every 1 d + 5 mg/kg every 8 wks	Mortality (NR)	NR No NA	Incidence 0 / 23 (0%)	Incidence 0 / 23 (0%)
Beaugerie, 2009[130]	Thiopurine Dose: NR	Never user thiopurine Dose: NA	Lymphoma (lymphoproliferative disorder, including lymphoma) @ 156 wks	Passive No NA	Incidence 17 / 8676 (0%) RH: 5.26 (2.2 to 12.6) P: 0.0002 vs. main	Incidence 6 / 10810 (0%)
Beaugerie, 2009[130]	Thiopurine Dose: NR	Never user thiopurine Dose: NA	Mortality (NR) @ 156 wks	Passive No NA	Incidence 91 / 8676 (1%)	Incidence 95 / 10810 (1%)
Beaugerie, 2009[130]	Thiopurine Dose: NR	Never user thiopurine Dose: NA	Other cancers (NR) @ 156 wks	Passive No NA	Incidence 155 / 8676 (2%)	Incidence 134 / 10810 (1%)
Lees, 2009[144]	Immunomodulator Route: Unknown Dose: NR	Never user immunomodulator	Cervical cancer (cervical adenocarcinoma)	Passive No NA	Incidence 0 / 105 (0%)	Incidence 1 / 234 (0%)
Moss, 2010[147]	Infliximab + 6-MP Route: IV	Infliximab Route: IV	Infusion and injection-site rx (NR)	Passive No NA	OR: 0.3 (0.1 to 0.8) P: 0.02 vs. main	
Moss, 2010[147]	Infliximab + 6-MP Route: IV	Infliximab Route: IV	Infusion and injection-site rx (NR)	Passive No NA	OR: 0.3 (0.1 to 0.8) P: 0.02 vs. main	

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Moss, 2010[147]	Infliximab + 6-MP Route: IV	Infliximab Route: IV	Other cancers (NR)	Passive No NA	Incidence 1 / 62 (2%)	Incidence 0 / 61 (0%)
Moss, 2010[147]	Infliximab + 6-MP Route: IV	Infliximab Route: IV	Other cancers (NR)	Passive No NA	Incidence 1 / 62 (2%)	Incidence 0 / 61 (0%)
Moss, 2010[147]	Infliximab + 6-MP Route: IV	Infliximab Route: IV	Other infections (NR) @ 8 wks	Passive No No	Incidence 0 / 62 (0%)	Incidence 2 / 61 (3%)
Moss, 2010[147]	Infliximab + 6-MP Route: IV	Infliximab Route: IV	Other infections (NR) @ 8 wks	Passive No No	Incidence 0 / 62 (0%)	Incidence 2 / 61 (3%)
Marehbian, 2009[168]	Corticosteroid Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Lymphoma (ICD9 code available on request)	Passive No NA	Event rate 0 events / 379 pys	Event rate 64 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other cancers (solid tumors)	Passive No NR	Event rate 0 events / 379 pys RH: 1.07 (0.87 to 1.31) vs. main	Event rate 2115 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (sepsis)	Passive No NA	Event rate 72 events / 379 pys	Event rate 1833 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (opportunistic infection or candidiasis or TB)	Passive No NA	Event rate 25 events / 379 pys RH: 3.2 (2.12 to 4.84) vs. main	Event rate 305 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (Herpes zoster)	Passive No NA	Event rate 9 events / 379 pys	Event rate 123 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (herpes simplex)	Passive No NA	Event rate 3 events / 379 pys	Event rate 134 events / 15673 pys
Marehbian, 2009[168]	Thiopurine Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Lymphoma (ICD9 code available on request)	Passive No NA	Event rate 3 events / 911 pys	Event rate 64 events / 15673 pys
Marehbian, 2009[168]	Thiopurine Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other cancers (solid tumors)	Passive No NR	Event rate 3 events / 911 pys RH: 1.17 (0.99 to 1.38) vs. main	Event rate 2115 events / 15673 pys

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Marehbian, 2009[168]	Thiopurine Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (herpes simplex)	Passive No NA	Event rate 5 events / 911 pys	Event rate 134 events / 15673 pys
Marehbian, 2009[168]	Thiopurine Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (opportunistic infection or candidiasis or TB)	Passive No NA	Event rate 17 events / 911 pys RH: 1.06 (0.64 to 1.77) vs. main	Event rate 305 events / 15673 pys
Marehbian, 2009[168]	Thiopurine Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (sepsis)	Passive No NA	Event rate 95 events / 911 pys	Event rate 1833 events / 15673 pys
Marehbian, 2009[168]	Thiopurine Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (Herpes zoster)	Passive No NA	Event rate 6 events / 911 pys	Event rate 123 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Lymphoma (ICD9 code available on request)	Passive No NA	Event rate 2 events / 292 pys	Event rate 64 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other cancers (solid tumors)	Passive No NR	Event rate 2 events / 292 pys RH: 0.95 (0.7 to 1.29) vs. main	Event rate 2115 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (Herpes zoster)	Passive No NA	Event rate 3 events / 292 pys	Event rate 123 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (herpes simplex)	Passive No NA	Event rate 4 events / 292 pys	Event rate 134 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (sepsis)	Passive No NA	Event rate 48 events / 292 pys	Event rate 1833 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha Route: Unknown Dose: NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (opportunistic infection or candidiasis or TB)	Passive No NA	Event rate 11 events / 292 pys RH: 2.03 (1.1 to 3.77) vs. main	Event rate 305 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha + Corticosteroid	Never user of steroids, IMM, TNF, or combination of these drugs	Lymphoma (ICD9 code available on request)	Passive No NA	Event rate 0 events / 19 pys	Event rate 64 events / 15673 pys

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Marehbian, 2009[168]	TNF-alpha + Corticosteroid	Never user of steroids, IMM, TNF, or combination of these drugs	Other cancers (solid tumors)	Passive No NR	Event rate 0 events / 19 pys RH: 0.97 (0.66 to 1.43) vs. main	Event rate 2115 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha + Corticosteroid	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (sepsis)	Passive No NA	Event rate 6 events / 19 pys	Event rate 1833 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha + Corticosteroid	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (herpes simplex)	Passive No NA	Event rate 0 events / 19 pys	Event rate 134 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha + Corticosteroid	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (opportunistic infection or candidiasis or TB)	Passive No NA	Event rate 2 events / 19 pys RH: 4.75 (2.73 to 8.27) vs. main	Event rate 305 events / 15673 pys
Marehbian, 2009[168]	TNF-alpha + Corticosteroid	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (Herpes zoster)	Passive No NA	Event rate 0 events / 19 pys	Event rate 123 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Lymphoma (ICD9 code available on request)	Passive No NA	Event rate 0 events / 142 pys	Event rate 64 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Other cancers (solid tumors)	Passive No NR	Event rate 11 events / 142 pys RH: 0.32 (0.04 to 2.28) vs. main	Event rate 2115 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (opportunistic infection or candidiasis or TB)	Passive No NA	Event rate 2 events / 142 pys RH: 5.62 (1.38 to 22.9) vs. main	Event rate 305 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (sepsis)	Passive No NA	Event rate 27 events / 142 pys	Event rate 1833 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (herpes simplex)	Passive No NA	Event rate 1 events / 142 pys	Event rate 134 events / 15673 pys
Marehbian, 2009[168]	Corticosteroid + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (Herpes zoster)	Passive No NA	Event rate 3 events / 142 pys	Event rate 123 events / 15673 pys

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Marehbian, 2009[168]	Thiopurine + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Lymphoma (ICD9 code available on request)	Passive No NA	Event rate 1 events / 162 pys	Event rate 64 events / 15673 pys
Marehbian, 2009[168]	Thiopurine + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Other cancers (solid tumors)	Passive No NR	Event rate 20 events / 162 pys RH: 1.13 (0.72 to 1.78) vs. main	Event rate 2115 events / 15673 pys
Marehbian, 2009[168]	Thiopurine + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (sepsis)	Passive No NA	Event rate 23 events / 162 pys	Event rate 1833 events / 15673 pys
Marehbian, 2009[168]	Thiopurine + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (herpes simplex)	Passive No NA	Event rate 3 events / 162 pys	Event rate 134 events / 15673 pys
Marehbian, 2009[168]	Thiopurine + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (opportunistic infection or candidiasis or TB)	Passive No NA	Event rate 15 events / 162 pys RH: 0.71 (0.17 to 2.87) vs. main	Event rate 305 events / 15673 pys
Marehbian, 2009[168]	Thiopurine + TNF-alpha	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (Herpes zoster)	Passive No NA	Event rate 4 events / 162 pys	Event rate 123 events / 15673 pys
Marehbian, 2009[168]	Thiopurine + TNF-alpha Dose: NR + NR	Never user of steroids, IMM, TNF, or combination of these drugs	Lymphoma (ICD9 code available on request)	Passive No NA	Event rate 0 events / 31 pys	Event rate 64 events / 15673 pys
Marehbian, 2009[168]	Thiopurine + TNF-alpha Dose: NR + NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other cancers (solid tumors)	Passive No NR	Event rate 3 events / 31 pys RH: 0.89 (0.33 to 2.38) vs. main	Event rate 2115 events / 15673 pys
Marehbian, 2009[168]	Thiopurine + TNF-alpha Dose: NR + NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (Herpes zoster)	Passive No NA	Event rate 1 events / 31 pys	Event rate 123 events / 15673 pys
Marehbian, 2009[168]	Thiopurine + TNF-alpha Dose: NR + NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (herpes simplex)	Passive No NA	Event rate 0 events / 31 pys	Event rate 134 events / 15673 pys
Marehbian, 2009[168]	Thiopurine + TNF-alpha Dose: NR + NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (opportunistic infection or candidiasis or TB)	Passive No NA	Event rate 2 events / 31 pys RH: 3.61 (0.9 to 14.56) vs. main	Event rate 305 events / 15673 pys

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Marehbian, 2009[168]	Thiopurine + TNF-alpha Dose: NR + NR	Never user of steroids, IMM, TNF, or combination of these drugs	Other infections (sepsis)	Passive No NA	Event rate 9 events / 31 pys	Event rate 1833 events / 15673 pys
Schneeweiss, 2009[230]	Infliximab Route: Unknown Dose: NR	Immunomodulator Route: Unknown Dose: NR	Other infections (C.difficile)	Passive No NA	Event rate 0 events / 682.1 pys	Event rate 14 events / 3971.9 pys
Schneeweiss, 2009[230]	Infliximab Route: Unknown Dose: NR	Immunomodulator Route: Unknown Dose: NR	Other infections (bacteriaemia)	Passive No NA	Event rate 5 events / 678.1 pys RH: 1.41 (0.47 to 4.24) vs. main	Event rate 15 events / 3973.4 pys
Schneeweiss, 2009[230]	Infliximab Route: Unknown Dose: NR	Immunomodulator Route: Unknown Dose: NR	Serious infections (bacteriaemia/ septicaemia, pneumonia, osteomyelitis, pyelonephritis, meningitis, encephalitis or endocarditis)	Passive No NA	Event rate 6 events / pys	Event rate 27 events / 3963.8 pys
Schneeweiss, 2009[230]	Corticosteroid Route: Unknown Dose: NR	Immunomodulator Route: Unknown Dose: NR	Other infections (bacteriaemia)	Passive No NA	Event rate 17 events / 4077.3 pys RH: 1.12 (0.52 to 2.41) vs. main	Event rate 15 events / 3973.4 pys
Schneeweiss, 2009[230]	Corticosteroid Route: Unknown Dose: NR	Immunomodulator Route: Unknown Dose: NR	Other infections (C.difficile)	Passive No NA	Event rate 57 events / 4063.4 pys	Event rate 14 events / 3971.9 pys
Schneeweiss, 2009[230]	Corticosteroid Route: Unknown Dose: NR	Immunomodulator Route: Unknown Dose: NR	Serious infections (bacteriaemia/ septicaemia, pneumonia, osteomyelitis, pyelonephritis, meningitis, encephalitis or endocarditis)	Passive No NA	Event rate 32 events / 4065.8 pys	Event rate 27 events / 3963.8 pys
Schneeweiss, 2009[230]	Corticosteroid Route: Unknown Dose: NR	Infliximab Route: Unknown Dose: NR	Other infections (bacteriaemia)	Passive No NA	Event rate 17 events / 4077.3 pys	Event rate 5 events / 678.1 pys
Schneeweiss, 2009[230]	Corticosteroid Route: Unknown Dose: NR	Infliximab Route: Unknown Dose: NR	Other infections (C.difficile)	Passive No NA	Event rate 57 events / 4063.4 pys	Event rate 0 events / 682.1 pys

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Schneeweiss, 2009[230]	Corticosteroid Route: Unknown Dose: NR	Infliximab Route: Unknown Dose: NR	Serious infections (bacteriaemia/ septicaemia, pneumonia, osteomyelitis, pyelonephritis, meningitis, encephalitis or endocarditis)	Passive No NA	Event rate 32 events / 4065.8 pys	Event rate 6 events / pys
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Infusion and injection-site rx (NR) @ 52 wks	NA Yes	Incidence 67 / 260 (25.8%)	Incidence 36 / 261 (13.8%)
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Mortality (NR) @ 52 wks	NA Yes	Incidence 0 / 260 (0%)	Incidence 0 / 261 (0%)
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other cancers (malignant neoplasm) @ 52 wks	Active Yes	Incidence 0 / 260 (0%)	Incidence 1 / 261 (0.4%)
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (opportunistic infection) @ 52 wks	NA Yes	Incidence 1 / 260 (0.4%)	Incidence 5 / 261 (2%)
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (infectious adverse event) @ 52 wks	NA Yes	Incidence 153 / 260 (58.9%)	Incidence 148 / 261 (56.7%)
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (NR) @ 52 wks	NA Yes	Incidence 10 / 260 (3.9%)	Incidence 13 / 261 (5%)
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	TB (NR) @ 52 wks	NA Yes	Incidence 1 / 260 (0%)	Incidence 0 / 261 (0%)
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Infusion and injection-site rx (NR) @ 52 wks	NA Yes	Incidence 66 / 257 (25.7%)	Incidence 36 / 261 (13.8%) P: <0.001
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Mortality (NR) @ 52 wks	NA Yes	Incidence 0 / 257 (0%)	Incidence 0 / 261 (0%)
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Other cancers (malignant neoplasm) @ 52 wks	Active Yes	Incidence 0 / 257 (0%)	Incidence 1 / 261 (0.4%) P: NS

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (infectious adverse event) @ 52 wks	NA Yes	Incidence 161 / 257 (62.7%)	Incidence 148 / 261 (56.7%) P: NS
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (opportunistic infection) @ 52 wks	NA Yes	Incidence 5 / 257 (2%)	Incidence 5 / 261 (2%) P: NS
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (NR) @ 52 wks	NA Yes	Incidence 12 / 257 (4.7%)	Incidence 13 / 261 (5%) P: NS
Colombel, 2009[95]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	TB (NR) @ 52 wks	NA Yes	Incidence 1 / 257 (0%)	Incidence 0 / 261 (0%)
Seksik, 2009[155]	Azathioprine Route: Unknown Dose: NR	Never user azathioprine Route: Unknown Dose: NR	Other infections (upper respiratory tract infections)	Active Yes NA	Event rate 2.2 events / 1 pys	Event rate 2.1 events / 1 pys P: 0.77
Seksik, 2009[155]	Azathioprine Route: Unknown Dose: NR	Never user azathioprine Route: Unknown Dose: NR	Other infections (herpes-virus skin and genital lesions)	Active Yes NA	Incidence 29 / 169 (17.2%) Event rate 1 events / 1 pys	Incidence 2 / 61 (3.3%) Event rate 0.2 events / 1 pys P: 0.04
Maher, 2009[176]	Azathioprine	Never user	Other infections (CMV)	Active No NA	Event rate 2 events / 12 persons	Event rate 7 events / 60 persons
Clare, 2009[181]	Infliximab + Azathioprine Route: IV Dose: NR	Infliximab Route: IV Dose: NR	Infusion and injection-site rx (rash, breathlessness, wheeze, headache, dizziness, nausea, nonspecific symptoms of feeling unwell, drop in systolic, bronchospasm)	Active Yes NA		OR: 0.89 (0.27 to 2.97) P: 0.85 vs. comp

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Clare, 2009[181]	Infliximab + Immunomodulator	Infliximab Route: IV Dose: NR	Infusion and injection-site rx (rash, breathlessness, wheeze, headache, dizziness, nausea, nonspecific symptoms of feeling unwell, drop in systolic, bronchospasm)	Active Yes NA	OR: 1.41 (0.26 to 7.69) P: 0.69 vs. main	
Clare, 2009[181]	Infliximab + Methotrexate Route: IV Dose: NR	Infliximab + Azathioprine Route: IV Dose: NR	Infusion and injection-site rx (rash, breathlessness, wheeze, headache, dizziness, nausea, nonspecific symptoms of feeling unwell, drop in systolic, bronchospasm)	Active Yes NA	OR: 1.21 (0.49 to 3.03) P: 0.68 vs. main	
de Vries, 2008[227]	Infliximab + Corticosteroid	Infliximab + No corticosteroids	Other cancers (paper or electronic chart review: CRC basal cell carcinoma, melanoma, breast cancer, squamous cell carcinoma, carcinoid tumor and lymphangitis carcinomatosa)	Passive No NA	Incidence 4 / 102 (4%)	Incidence 5 / 45 (11%)
de Vries, 2008[227]	Infliximab + Corticosteroid	Infliximab + No corticosteroids	Serious infections (hospitalization for infection from paper and electronic medical records)	Passive No NA	Incidence 18 / 102 (18%)	Incidence 18 / 45 (40%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
de Vries, 2008[227]	Infliximab + No immunomodulator	Infliximab + No corticosteroids	Other cancers (paper or electronic chart review: CRC basal cell carcinoma, melanoma, breast cancer, squamous cell carcinoma, carcinoid tumor and lymphangitis carcinomatosa)	Passive No NA	Incidence 2 / 54 (4%)	Incidence 5 / 45 (11%)
de Vries, 2008[227]	Infliximab + No immunomodulator	Infliximab + No corticosteroids	Serious infections (hospitalization for infection from paper and electronic medical records)	Passive No NA	Incidence 18 / 54 (33%)	Incidence 18 / 45 (40%)
de Vries, 2008[227]	Infliximab + Immunomodulator	Infliximab + No corticosteroids	Other cancers (paper or electronic chart review: CRC basal cell carcinoma, melanoma, breast cancer, squamous cell carcinoma, carcinoid tumor and lymphangitis carcinomatosa)	Passive No NA	Incidence 7 / 93 (8%)	Incidence 5 / 45 (11%)
de Vries, 2008[227]	Infliximab + Immunomodulator	Infliximab + No corticosteroids	Serious infections (hospitalization for infection from paper and electronic medical records)	Passive No NA	Incidence 18 / 93 (19%)	Incidence 18 / 45 (40%)
de Vries, 2008[227]	Infliximab + No immunomodulator	Infliximab + Corticosteroid	Other cancers (paper or electronic chart review: CRC basal cell carcinoma, melanoma, breast cancer, squamous cell carcinoma, carcinoid tumor and lymphangitis carcinomatosa)	Passive No NA	Incidence 2 / 54 (4%)	Incidence 4 / 102 (4%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
de Vries, 2008[227]	Infliximab + No immunomodulator	Infliximab + Corticosteroid	Serious infections (hospitalization for infection from paper and electronic medical records)	Passive No NA	Incidence 18 / 54 (33%)	Incidence 18 / 102 (18%)
de Vries, 2008[227]	Infliximab + Immunomodulator	Infliximab + Corticosteroid	Other cancers (paper or electronic chart review: CRC basal cell carcinoma, melanoma, breast cancer, squamous cell carcinoma, carcinoid tumor and lymphangitis carcinomatosa)	Passive No NA	Incidence 7 / 93 (8%)	Incidence 4 / 102 (4%)
de Vries, 2008[227]	Infliximab + Immunomodulator	Infliximab + Corticosteroid	Serious infections (hospitalization for infection from paper and electronic medical records)	Passive No NA	Incidence 18 / 93 (19%)	Incidence 18 / 102 (18%)
de Vries, 2008[227]	Infliximab + Immunomodulator	Infliximab + No immunomodulator	Other cancers (paper or electronic chart review: CRC basal cell carcinoma, melanoma, breast cancer, squamous cell carcinoma, carcinoid tumor and lymphangitis carcinomatosa)	Passive No NA	Incidence 7 / 93 (8%)	Incidence 2 / 54 (4%)
de Vries, 2008[227]	Infliximab + Immunomodulator	Infliximab + No immunomodulator	Serious infections (hospitalization for infection from paper and electronic medical records)	Passive No NA	Incidence 18 / 93 (19%)	Incidence 18 / 54 (33%)
Mantzaris, 2009[102]	Azathioprine Route: Oral Dose: 2.0-2.5 mg/kg every 1 d	Budesonide Route: Oral Dose: 09-Jun mg every 1 d	Other infections (NR)	NR No NA	Incidence 25 / 38 (66%)	Incidence 14 / 39 (36%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Caspersen, 2008[225]	Infliximab + Azathioprine Route: IV Dose: NR	Infliximab Route: IV Dose: NR	Infusion and injection-site rx (NR)	Passive No NA	Event rate 63 events / 2079 other denominator	Event rate 83 events / 1272 other denominator
Caspersen, 2008[225]	Infliximab + Corticosteroid	Infliximab Route: IV Dose: NR	Infusion and injection-site rx (NR)	Passive No NA	Event rate 33 events / 611 other denominator	Event rate 83 events / 1272 other denominator
Caspersen, 2008[225]	Infliximab + Corticosteroid	Infliximab + Azathioprine Route: IV Dose: NR	Infusion and injection-site rx (NR)	Passive No NA	Event rate 33 events / 611 other denominator	Event rate 63 events / 2079 other denominator
Fidder, 2009[153]	Infliximab Route: IV Dose: NR	Never user infliximab	Infusion and injection-site rx (acute infusion reaction)	Passive No NA	Incidence 115 / 682 (17%)	
Fidder, 2009[153]	Infliximab Route: IV Dose: NR	Never user infliximab	Infusion and injection-site rx (delayed-type hypersensitivity reaction)	Passive No NA	Incidence 50 / 682 (7%)	
Fidder, 2009[153]	Infliximab Route: IV Dose: NR	Never user infliximab	Lymphoma (chart review)	Passive No NA	Incidence 3 / 743 (0%)	Incidence 5 / 666 (1%)
Fidder, 2009[153]	Infliximab Route: IV Dose: NR	Never user infliximab	Mortality (chart review)	Passive No NA	Incidence 12 / 743 (2%) Event rate 12 events / 743 persons	Incidence 16 / 666 (2%) Event rate 16 events / 666 persons OR: 1.33 (0.56 to 3) P: 0.45 vs. comp
Fidder, 2009[153]	Infliximab Route: IV Dose: NR	Never user infliximab	Other cancers (malignancies, non-melanoma skin cancers)	Passive No NA	Incidence 21 / 734 (3%) Event rate 23 events / 3775 pys OR: 0.97 (0.56 to 1.65) P: 0.91 vs. main	Incidence 30 / 666 (5%) Event rate 42 events / 6704 pys
Fidder, 2009[153]	Infliximab Route: IV Dose: NR	Never user infliximab	Serious infections (chart review -- requiring hospitalization, prolonged hospitalization, fatal, life-threatening or led to significant disability)	Passive No NA	Incidence 48 / 743 (6%) Event rate 59 events / 743 persons	Incidence 62 / 666 (9%) Event rate 77 events / 666 persons

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Reinisch, 2008[51]	Azathioprine + Prednisone Route: Oral + Oral Dose: 2.5 mg/kg every 1 d + 1 mg/kg or ≥40 mg every 1 d	Placebo + Prednisone Route: Oral + Oral Dose: NA every 1 d + 1mg/kg or ≥ 40mg every 1 d	Mortality (NR) @ 28 wks	NR No No	Incidence 0 / 52 (0%)	Incidence 0 / 28 (0%)
Reinisch, 2008[51]	Azathioprine + Prednisone Route: Oral + Oral Dose: 2.5 mg/kg every 1 d + 1 mg/kg or ≥ 40 mg every 1 d	Placebo + Prednisone Route: Oral + Oral Dose: NA every 1 d + 1mg/kg or ≥ 40mg every 1 d	Other infections (perianal abscess) @ 28 wks	NR No NA	Incidence 0 / 52 (0%)	Incidence 3 / 28 (11%)
Reinisch, 2008[51]	Azathioprine + Prednisone Route: Oral + Oral Dose: 2.5 mg/kg every 1 d + 1 mg/kg or ≥ 40 mg every 1 d	Placebo + Prednisone Route: Oral + Oral Dose: NA every 1 d + 1mg/kg or ≥ 40mg every 1 d	Other infections (perianal abscess) @ 28 wks	NR No No	Incidence 0 / 52 (0%)	Incidence 3 / 28 (11%)
Reinisch, 2008[51]	Azathioprine + Prednisone Route: Oral + Oral Dose: 2.5 mg/kg every 1 d + 1 mg/kg or ≥ 40 mg every 1 d	Placebo + Prednisone Route: Oral + Oral Dose: NA every 1 d + 1mg/kg or ≥ 40mg every 1 d	Other infections (Nasopharyngitis) @ 28 wks	NR No No	Incidence 7 / 52 (13%)	Incidence 3 / 28 (11%)
Moss, 2008[148]	Infliximab + Corticosteroid Dose: NR + NR	Infliximab + No immunomodulator at initiation Route: Unknown Dose: NR	Infusion and injection-site rx (Development of new symptoms within 1-2 h of an infusion (acute), or in the 14 d after (delayed) an infusion)	Passive No NA	Incidence 18 / 86 (21%)	Incidence 38 / 172 (22%)
Moss, 2008[148]	Infliximab + Thiopurine Dose: NR + NR	Infliximab + No immunomodulator at initiation Route: Unknown Dose: NR	Infusion and injection-site rx (Development of new symptoms within 1-2 h of an infusion (acute), or in the 14 d after (delayed) an infusion)	Passive No NA	Incidence 13 / 115 (11%) OR: 0.3 (0.2 to 0.9) P: 0.007 vs. main	Incidence 38 / 172 (22%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Moss, 2008[148]	Infliximab + No steroids	Infliximab + No immunomodulator at initiation Route: Unknown Dose: NR	Infusion and injection-site rx (Development of new symptoms within 1-2 h of an infusion (acute), or in the 14 d after (delayed) an infusion)	Passive No NA	Incidence 33 / 201 (16%)	Incidence 38 / 172 (22%)
Moss, 2008[148]	Infliximab + Thiopurine Dose: NR + NR	Infliximab + Corticosteroid Dose: NR + NR	Infusion and injection-site rx (Development of new symptoms within BE 1-2 h of an infusion (acute), or in the 14 d after (delayed) an infusion)	Passive No NA	Incidence 13 / 115 (11%)	Incidence 18 / 86 (21%)
Moss, 2008[148]	Infliximab + No steroids	Infliximab + Corticosteroid Dose: NR + NR	Infusion and injection-site rx (Development of new symptoms within BE 1-2 h of an infusion (acute), or in the 14 d after (delayed) an infusion)	Passive No NA	Incidence 33 / 201 (16%)	Incidence 18 / 86 (21%)
Moss, 2008[148]	Infliximab + No steroids	Infliximab + Thiopurine Dose: NR + NR	Infusion and injection-site rx (Development of new symptoms within BE 1-2 h of an infusion (acute), or in the 14 d after (delayed) an infusion)	Passive No NA	Incidence 33 / 201 (16%)	Incidence 13 / 115 (11%)
Van Assche, 2008[89]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Infliximab + Immunomodulator Route: IV + Oral Dose: 5 mg/kg every 8 wks	Infusion and injection-site rx (NR) @ 104 wks	NR Yes NR	Incidence 1 / 40 (2%)	Incidence 1 / 40 (3%)
Van Assche, 2008[89]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Infliximab + Immunomodulator Route: IV + Oral Dose: 5 mg/kg every 8 wks	Mortality (sudden cardiac death) @ 104 wks	NR Yes NR	Incidence 1 / 40 (2%)	Incidence 0 / 40 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Van Assche, 2008[89]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Infliximab + Immunomodulator Route: IV + Oral Dose: 5 mg/kg every 8 wks	Other cancers (renal cell carcinoma) @ 104 wks	NR Yes NR	Incidence 0 / 40 (0%)	Incidence 1 / 40 (2%)
Van Assche, 2008[89]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Infliximab + Immunomodulator Route: IV + Oral Dose: 5 mg/kg every 8 wks	Other infections (NR) @ 104 wks	NR Yes NR	Incidence 4 / 40 (10%)	Incidence 5 / 40 (12%)
Shah, 2008[156]	Azathioprine + Mesalamine (NR)	Azathioprine + Never user mesalamine	Other infections (NR)	Passive No NA	Event rate 2 events / 104 persons	Event rate 2 events / 95 persons
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone Route: Oral + Oral Dose: 9 mg every 1 d + 32 mg every 1 d	Infliximab + Azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Other infections (vaginal infections)	NA NA	Incidence 7 / 64 (11%)	Incidence 7 / 65 (11%) P: 1
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone Route: Oral + Oral Dose: 9 mg every 1 d + 32 mg every 1 d	Infliximab + Azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Other infections (gastrointestinal infection)	NA NA	Incidence 13 / 64 (20%)	Incidence 12 / 65 (18%) P: 0.83
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone Route: Oral + Oral Dose: 9 mg every 1 d + 32 mg every 1 d	Infliximab + Azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Other infections (upper respiratory tract infection)	NA NA	Incidence 20 / 64 (31%)	Incidence 22 / 65 (34%) P: 0.85
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone Route: Oral + Oral Dose: 9 mg every 1 d + 32 mg every 1 d	Infliximab + Azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Other infections (urinary tract infections)	NA NA	Incidence 6 / 64 (9%)	Incidence 6 / 65 (9%) P: 1
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone Route: Oral + Oral Dose: 9 mg every 1 d + 32 mg every 1 d	Infliximab + Azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Other infections (eye infections)	NA NA	Incidence 3 / 64 (5%)	Incidence 4 / 65 (6%) P: 1

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone Route: Oral + Oral Dose: 9 mg every 1 d + 32 mg every 1 d	Infliximab + Azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Other infections (common cold)	NR NA	Incidence 31 / 64 (48%)	Incidence 26 / 65 (40%) P: 0.38
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone Route: Oral + Oral Dose: 9 mg every 1 d + 32 mg every 1 d	Infliximab + Azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Serious infections (pneumonia)	NA NA	Incidence 0 / 64 (0%)	Incidence 1 / 65 (2%) P: 1
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone Route: Oral + Oral Dose: 9 mg every 1 d + 32 mg every 1 d	Infliximab + Azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Serious infections (perianal abscess or fistula)	NA NA	Incidence 7 / 64 (11%)	Incidence 3 / 65 (5%) P: 0.21
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone Route: Oral + Oral Dose: 9 mg every 1 d + 32 mg every 1 d	Infliximab + Azathioprine Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Serious infections (Hepatitis C)	NA NA	Incidence 1 / 64 (2%)	Incidence 0 / 65 (0%) P: 0.5
Hutfless, 2007[151]	ASA Route: Unknown Dose: NR	Never user 5-aminosalicylate acid	Mortality (All-cause mortality)	Passive No NA	Incidence 175 / 2566 (7%) OR: 0.7 (0.5 to 1.1) vs. main	Incidence 56 / 675 (8%)
Hutfless, 2007[151]	Immunomodulator Route: Unknown Dose: NR	Never user immunomodulator Route: Unknown Dose: NR	Mortality (All-cause mortality)	Passive No NA	Incidence 37 / 443 (8%) OR: 1.3 (0.9 to 1.9) vs. main	Incidence 194 / 2798 (7%)
Hutfless, 2007[151]	Corticosteroid Route: Unknown Dose: NR	Never user corticosteroid Route: Unknown Dose: NR	Mortality (All-cause mortality)	Passive No NA	Incidence 157 / 2168 (7%) OR: 1 (0.7 to 1.4) vs. main	Incidence 74 / 1073 (7%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Infusion and injection-site rx (Any adverse event occurring within 2 hrs of the infusion) @ 48 wks	Active Yes Yes	Incidence 14 / 214 (7%)	Incidence 18 / 214 (8%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Lymphoma (NR) @ 48 wks	Active Yes Yes	Incidence 0 / 214 (0%)	Incidence 0 / 214 (0%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Mortality (NR) @ 48 wks	Active Yes Yes	Incidence 0 / 214 (0%)	Incidence 0 / 214 (0%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Other cancers (Basal cell carcinoma) @ 48 wks	Active Yes Yes	Incidence 1 / 214 (0%)	Incidence 1 / 214 (0%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Other infections (NR) @ 48 wks	Active Yes Yes	Incidence 132 / 214 (62%)	Incidence 119 / 214 (56%)
Feagan, 2007[81]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Serious infections (abscesses, sepsis, pneumonia, meningitis, gastroenteritis) @ 48 wks	Active Yes Yes	Incidence 6 / 214 (3%)	Incidence 5 / 214 (2%)
Kane, 2008[141]	Immunomodulators Route: Unknown Dose: NR	Never user immunnomodulators Route: Unknown Dose: NR	Cervical cancer (Glandular or squamous carcinoma of the cervix)	Passive NA	Incidence 0 / 23 (0%)	Incidence 0 / 17 (0%)
Rudolph, 2008[175]	Infliximab + Immunomudulator	Infliximab + Never user immunomodulator at start of infliximab	Infusion and injection-site rx (occurring within 1 h after infusion)	Passive No NA	Event rate 6 events	Event rate 9 events
Rudolph, 2008[175]	Infliximab + Immunomudulator	Infliximab + Never user immunomodulator at start of infliximab	Serious infections (NR)	Passive No NA	Event rate 1 events	Event rate 0 events
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Infusion and injection-site rx (NR) @ 18 wks	Active Yes Yes	Incidence 6 / 216 (3%)	Incidence 31 / 212 (15%) P: 0.003
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Mortality (NR) @ 18 wks	Active Yes NA	Incidence 0 / 216 (0%)	Incidence 0 / 212 (0%)
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Other cancers (any neoplasm) @ 18 wks	Active Yes NA	Incidence 0 / 216 (0%)	Incidence 0 / 212 (0%)
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Serious infections (NR) @ 18 wks	Active Yes NA	Incidence 6 / 216 (3%)	Incidence 2 / 212 (1%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Schreiber, 2007[84]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	TB (NR) @ 18 wks	Active Yes Yes	Incidence 1 / 216 (0%)	Incidence 0 / 212 (0%)
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Cervical cancer (cervical carcinoma, stage 0) @ 26 wks	Active Yes Yes	Incidence 0 / 331 (0%)	Incidence 1 / 329 (0%)
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Infusion and injection-site rx (occurred at injection site and temporally related to injection) @ 26 wks	Active Yes Yes	Incidence 9 / 331 (3%)	Incidence 47 / 329 (14%)
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Lymphoma (Hodgkin's lymphoma) @ 26 wks	Active Yes Yes	Incidence 0 / 331 (0%)	Incidence 1 / 329 (0%)
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Mortality (NR) @ 26 wks	Passive Yes Yes	Incidence 1 / 331 (0%)	Incidence 0 / 329 (0%)
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Other cancers (any neoplasm (benign, malignant, or unspecified, including cysts and polyps)) @ 26 wks	Active Yes Yes	Incidence 2 / 331 (1%)	Incidence 0 / 329 (0%)
Sandborn, 2007[39]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Serious infections (NR) @ 26 wks	Active Yes Yes	Incidence 7 / 331 (2%) Event rate 9 events	Incidence 3 / 329 (1%)
Targan, 2007[32]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NR every 4 wks	Infusion and injection-site rx (Hypersensitivity reactions within 24 hrs of infusion)	Passive Yes No	Incidence 10 / 260 (4%)	Incidence 1 / 250 (2%)
Targan, 2007[32]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NR every 4 wks	Infusion and injection-site rx (occurring within 2 hrs of infusion)	Active No No	Incidence 23 / 260 (9%)	Incidence 17 / 250 (7%)
Targan, 2007[32]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NR every 4 wks	Lymphoma (B cell lymphoma)	Active Yes NA		

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Targan, 2007[32]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NR every 4 wks	Mortality (NR) @ 12 wks	Active Yes Yes	Incidence 0 / 260 (0%)	Incidence 0 / 250 (0%)
Targan, 2007[32]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NR every 4 wks	Other cancers (Basal cell carcinoma)	Active No No	Incidence 1 / 260 (1%)	Incidence 0 / 250 (0%)
Targan, 2007[32]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NR every 4 wks	Other infections (occur in > 2% of patients in either treatment groups)	Active No No	Incidence 9 / 260 (35%)	Incidence 75 / 250 (30%)
Targan, 2007[32]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NR every 4 wks	Serious infections (NR) @ 12 wks	Active No No	Incidence 13 / 260 (5%)	Incidence 24 / 250 (10%)
Siffledeen, 2007[127]	Corticosteroid	Never user corticosteroids during year before DXA scan	Fractures (Height reduction >20% and a loss of surface area >10%, in the presence of a biconcave, crush, or wedge deformity as measured by DXA scan)	Active No NA	Incidence 25 / 105 (24%)	Incidence 17 / 102 (17%)
Sandborn, 2007[38]	Adalimumab Route: SC	Placebo Route: SC Dose: NA	Infusion and injection-site rx (NR)	Active No NA	Incidence 17 / 159 (11%)	Incidence 17 / 166 (10%)
Sandborn, 2007[38]	Adalimumab Route: SC	Placebo Route: SC Dose: NA	Mortality (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 159 (0%)	Incidence 0 / 166 (0%)
Sandborn, 2007[38]	Adalimumab Route: SC	Placebo Route: SC Dose: NA	Other cancers (Solid tumors or hematologic cancer) @ 4 wks	Active Yes Yes	Incidence 0 / 159 (0%)	Incidence 0 / 166 (0%)
Sandborn, 2007[38]	Adalimumab Route: SC	Placebo Route: SC Dose: NA	Other infections (NR)	Active NA	Incidence 26 / 159 (16%)	Incidence 39 / 166 (23%)
Sandborn, 2007[38]	Adalimumab Route: SC	Placebo Route: SC Dose: NA	Serious infections (NR)	Active No NA	Incidence 0 / 159 (0%)	Incidence 4 / 166 (2%)
Sandborn, 2007[38]	Adalimumab Route: SC	Placebo Route: SC Dose: NA	TB (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 159 (0%)	Incidence 0 / 166 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	Infusion and injection-site rx (NR) @ 52 wks	Active Yes Yes	Incidence 1 / 19 (5%)	Incidence 2 / 18 (12%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	Lymphoma (NR) @ 52 wks	NA Yes	Incidence 0 / 19 (0%)	Incidence 0 / 18 (0%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	Mortality (NR) @ 52 wks	NA Yes	Incidence 0 / 19 (0%)	Incidence 0 / 18 (0%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	Other cancers (squamous cell carcinoma) @ 52 wks	Active Yes Yes	Incidence 0 / 19 (0%)	Incidence 1 / 18 (5%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	Other infections (nasopharyngitis) @ 52 wks	Active Yes Yes	Incidence 5 / 19 (26%)	Incidence 7 / 18 (39%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	Other infections (sinusitis) @ 52 wks	Active Yes Yes	Incidence 4 / 19 (21%)	Incidence 1 / 18 (6%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	Other infections (treatment-emergent infectious adverse events) @ 52 wks	Active Yes Yes	Incidence 14 / 19 (74%)	Incidence 15 / 18 (83%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	Serious infections (NR) @ 52 wks	Active Yes Yes	Incidence 0 / 19 (0%)	Incidence 0 / 18 (0%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 1 wks	TB (NR) @ 52 wks	NA Yes	Incidence 0 / 19 (0%)	Incidence 0 / 18 (0%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	Infusion and injection-site rx (NR) @ 52 wks	Active Yes Yes	Incidence 0 / 18 (0%)	Incidence 2 / 18 (12%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	Lymphoma (NR) @ 52 wks	NA Yes	Incidence 0 / 18 (0%)	Incidence 0 / 18 (0%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	Mortality (NR) @ 52 wks	NA Yes	Incidence 0 / 18 (0%)	Incidence 0 / 18 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	Other cancers (squamous cell carcinoma) @ 52 wks	Active Yes Yes	Incidence 0 / 19 (0%)	Incidence 1 / 18 (5%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	Other infections (nasopharyngitis) @ 52 wks	Active Yes Yes	Incidence 2 / 18 (11%)	Incidence 7 / 18 (39%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	Other infections (sinusitis) @ 52 wks	Active Yes Yes	Incidence 1 / 18 (6%)	Incidence 1 / 18 (6%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	Other infections (treatment-emergent infectious adverse events) @ 52 wks	Active Yes Yes	Incidence 6 / 18 (33%)	Incidence 15 / 18 (83%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	Serious infections (NR) @ 52 wks	Active Yes Yes	Incidence 0 / 18 (0%)	Incidence 0 / 18 (0%)
Sandborn, 2007[83]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 1 wks	TB (NR) @ 52 wks	NA Yes	Incidence 0 / 18 (0%)	Incidence 0 / 18 (0%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (abscess) @ 52 wks	Active Yes NA	Incidence 3 / 260 (1.2%)	Incidence 5 / 261 (1.9%)
Colombel, 2007[82]	Adalimumab Route: SC Dose: 40 mg every 1 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (abscess) @ 52 wks	Active Yes NA	Incidence 5 / 257 (1.9%)	Incidence 5 / 261 (1.9%) P: NS
Vermeire, 2007[154]	Infliximab + Methotrexate Route: IV + IM or SC Dose: NR + 15 mg every 1 wks	Infliximab + No concomitant methotrexate or thiopurine Route: IV Dose: NR	Infusion and injection-site rx (NR)	Passive No NA	Incidence 7 / 50 (14%)	Incidence 24 / 59 (40%)
Vermeire, 2007[154]	Infliximab + Thiopurine Route: IV + Unknown Dose: NR + See Comments every 1 d	Infliximab + No concomitant methotrexate or thiopurine Route: IV Dose: NR	Infusion and injection-site rx (NR)	Passive No NA	Incidence 12 / 65 (18%)	Incidence 24 / 59 (40%)
Vermeire, 2007[154]	Infliximab + Thiopurine or methotrexate	Infliximab + No concomitant methotrexate or thiopurine Route: IV Dose: NR	Infusion and injection-site rx (NR)	Passive No NA	Incidence 18 / 115 (16%)	Incidence 24 / 59 (40%) P: 0.04

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Vermeire, 2007[154]	Infliximab + Thiopurine Route: IV + Unknown Dose: NR + See Comments every 1 d	Infliximab + Methotrexate Route: IV + IM or SC Dose: NR + 15 mg every 1 wks	Infusion and injection-site rx (NR)	Passive No NA	Incidence 12 / 65 (18%)	Incidence 7 / 50 (14%) P: >0.05
Vermeire, 2007[154]	Infliximab + Thiopurine or methotrexate	Infliximab + Methotrexate Route: IV + IM or SC Dose: NR + 15 mg every 1 wks	Infusion and injection-site rx (NR)	Passive No NA	Incidence 18 / 115 (16%)	Incidence 7 / 50 (14%)
Vermeire, 2007[154]	Infliximab + Thiopurine or methotrexate	Infliximab + Thiopurine Route: IV + Unknown Dose: NR + See Comments every 1 d	Infusion and injection-site rx (NR)	Passive No NA	Incidence 18 / 115 (16%)	Incidence 12 / 65 (18%)
Sands, 2007[35]	Natalizumab + Infliximab Route: IV + IV Dose: 300 mg every 4 wks + 5 mg/kg every 8 wks	Placebo + Infliximab Route: IV + IV Dose: NA every 4 wks + 5 mg/kg every 8 wks	Lymphoma (NR) @ 20 wks	Active Yes Yes	Incidence 0 / 52 (0%)	Incidence 0 / 27 (0%)
Sands, 2007[35]	Natalizumab + Infliximab Route: IV + IV Dose: 300 mg every 4 wks + 5 mg/kg every 8 wks	Placebo + Infliximab Route: IV + IV Dose: NA every 4 wks + 5 mg/kg every 8 wks	Other infections (upper resp. tract infection)	NR No NR	Incidence 3 / 52 (6%)	Incidence 1 / 27 (4%)
Sands, 2007[35]	Natalizumab + Infliximab Route: IV + IV Dose: 300 mg every 4 wks + 5 mg/kg every 8 wks	Placebo + Infliximab Route: IV + IV Dose: NA every 4 wks + 5 mg/kg every 8 wks	Other infections (nasopharyngitis)	NR NR	Incidence 5 / 52 (10%)	Incidence 3 / 27 (11%)
Lichtenstein, 2006[131]	Infliximab Route: IV	Never user infliximab Route: IV	Mortality (NR)	Passive Yes NA	Incidence 29 / 3179 (1%) OR: 1.015 (0.531 to 1.942) P: 0.96 vs. main	Incidence 26 / 3111 (1%)
Lichtenstein, 2006[131]	Infliximab Route: IV	Never user infliximab Route: IV	Mortality (NR)	Passive Yes NA	Event rate 0.53 events / 100 pys RR: 1.24 (0.729 to 2.102) P: 0.43 vs. main	Event rate 0.43 events / 100 pys
Lichtenstein, 2006[131]	Infliximab Route: IV	Never user infliximab Route: IV	Serious infections (NR)	Active Yes NA	Event rate 1.37 events / 100 pys RR: 2.15 (1.442 to 3.21) vs. main	Event rate 0.65 events / 100 pys

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Lichtenstein, 2006[131]	Infliximab Route: IV	Never user infliximab Route: IV	Serious infections (NR)	Active Yes NA	Incidence 69 / 2933 (2%) OR: 0.991 (0.641 to 1.535) P: 0.97 vs. main	Incidence 37 / 3320 (1%)
Lichtenstein, 2006[131]	No reported prednisone usage Route: Unknown Dose: NR	Prednisone Route: Unknown Dose: NR	Mortality (NR)	NR Yes NA	Incidence 23 / 3894 (1%)	Incidence 30 / 2396 (1%) OR: 2.096 (1.147 to 3.832) P: 0.016 vs. comp
Lichtenstein, 2006[131]	No reported prednisone usage Route: Unknown Dose: NR	Prednisone Route: Unknown Dose: NR	Serious infections (NR)	Active Yes NA	Incidence 45 / 4111 (1%)	Incidence 61 / 2142 (3%) OR: 2.212 (1.464 to 3.342) vs. comp
Lichtenstein, 2006[131]	No immunomodulators Route: Unknown Dose: NR	Immunomodulator Route: Unknown Dose: NR	Mortality (NR)	Passive Yes NA	Incidence 26 / 2526 (1%)	Incidence 27 / 3764 (1%) OR: 0.731 (0.398 to 1.34) P: 0.31 vs. comp
Lichtenstein, 2006[131]	No immunomodulators Route: Unknown Dose: NR	Immunomodulator Route: Unknown Dose: NR	Serious infections (NR)	Active Yes NA	Incidence 48 / 2775 (2%)	Incidence 58 / 3478 (2%) OR: 0.782 (0.519 to 1.179) P: 0.24 vs. comp
Lemann, 2006[46]	Infliximab + Azathioprine or 6-MP Route: IV Dose: 5 mg/kg + stable	Placebo + Azathioprine or 6-MP Route: IV + Oral Dose: NA + stable mg/kg every 1 d	Mortality (NR) @ 52 wks	Active Yes Yes	Incidence 0 / 57 (0%)	Incidence 0 / 56 (0%)
Lemann, 2006[46]	Infliximab + Azathioprine or 6-MP Route: IV Dose: 5 mg/kg + stable	Placebo + Azathioprine or 6-MP Route: IV + Oral Dose: NA + stable mg/kg every 1 d	Other cancers (NR) @ 52 wks	Active Yes Yes	Incidence 0 / 57 (0%)	Incidence 0 / 56 (0%)
Lemann, 2006[46]	Infliximab + Azathioprine or 6-MP Route: IV Dose: 5 mg/kg + stable	Placebo + Azathioprine or 6-MP Route: IV + Oral Dose: NA + stable mg/kg every 1 d	Other infections (infections) @ 24 wks	NR No NR	Event rate 18 events	Event rate 16 events

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Infusion and injection-site rx (NR) @ 4 wks	NA Yes	Incidence 19 / 74 (26%)	Incidence 12 / 74 (16%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Lymphoma (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 74 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Mortality (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 74 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (pneumonia) @ 4 wks	Active Yes Yes	Incidence 0 / 74 (0%)	Incidence 1 / 74 (1%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (NR) @ 4 wks	Active Yes Yes	Incidence 8 / 74 (10%)	Incidence 12 / 74 (16%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (opportunistic infections) @ 4 wks	Active Yes Yes	Incidence 0 / 74 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (pneumonia) @ 4 wks	Active Yes Yes	Incidence 0 / 74 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (abscess) @ 4 wks	Active Yes Yes	Incidence 0 / 74 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 74 (0%)	Incidence 0 / 74 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 40 mg then 20 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	TB (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 74 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Infusion and injection-site rx (NR) @ 4 wks	NA Yes	Incidence 18 / 75 (24%)	Incidence 12 / 74 (16%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Lymphoma (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 75 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Mortality (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 75 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (opportunistic infections) @ 4 wks	Active Yes Yes	Incidence 0 / 75 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (pneumonia) @ 4 wks	Active Yes Yes	Incidence 0 / 75 (0%)	Incidence 1 / 74 (1%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (NR) @ 4 wks	Active Yes Yes	Incidence 13 / 75 (17%)	Incidence 12 / 74 (16%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (abscess) @ 4 wks	Active Yes Yes	Incidence 0 / 75 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (pneumonia) @ 4 wks	Active Yes Yes	Incidence 0 / 75 (0%)	Incidence 0 / 74 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 75 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 80 mg then 40 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	TB (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 75 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Infusion and injection-site rx (NR) @ 4 wks	NA Yes	Incidence 29 / 76 (38%)	Incidence 12 / 74 (16%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Lymphoma (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 76 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Mortality (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 76 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (opportunistic infections) @ 4 wks	Active Yes Yes	Incidence 0 / 76 (0%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (pneumonia) @ 4 wks	Active Yes Yes	Incidence 2 / 76 (3%)	Incidence 1 / 74 (1%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Other infections (NR) @ 4 wks	Active Yes Yes	Incidence 16 / 76 (21%)	Incidence 12 / 74 (16%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (NR) @ 4 wks	Active Yes Yes	Incidence 2 / 76 (3%)	Incidence 0 / 74 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (abscess) @ 4 wks	Active Yes Yes	Incidence 1 / 76 (1%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	Serious infections (pneumonia) @ 4 wks	Active Yes Yes	Incidence 1 / 76 (1%)	Incidence 0 / 74 (0%)
Hanauer, 2006[37]	Adalimumab Route: SC Dose: 160 mg then 80 mg every 2 wks	Placebo Route: SC Dose: NA every 2 wks	TB (NR) @ 4 wks	Active Yes Yes	Incidence 0 / 76 (0%)	Incidence 0 / 74 (0%)
Schroder, 2006[47]	Methotrexate + Infliximab Route: IV + IV Dose: 20 mg every 1 wks + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	Other cancers (NR) @ 48 wks	Active Yes Yes	Incidence 0 / 11 (0%)	Incidence 0 / 8 (0%)
Schroder, 2006[47]	Methotrexate + Infliximab Route: IV + IV Dose: 20 mg every 1 wks + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	Other infections (NR) @ 48 wks	Active Yes Yes	Incidence 2 / 11 (18%)	Incidence 1 / 8 (12%) P: 1
Schroder, 2006[47]	Methotrexate + Infliximab Route: IV + IV Dose: 20 mg every 1 wks + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	Other infections (respiratory tract infections) @ 48 wks	Active Yes Yes	Incidence 4 / 11 (36%)	Incidence 1 / 8 (12%) P: 0.34
Schroder, 2006[47]	Methotrexate + Infliximab Route: IV + IV Dose: 20 mg every 1 wks + 5 mg/kg every 2 wks	Infliximab Route: IV Dose: 5 mg/kg every 2 wks	Serious infections (NR) @ 48 wks	Active Yes Yes	Incidence 0 / 11 (0%)	Incidence 0 / 8 (0%)
Sandborn, 2005[33]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Infusion and injection-site rx (occurring within 2 hrs of infusion) @ 12 wks	Active Yes Yes	Incidence 83 / 723 (11%)	Incidence 14 / 181 (8%)
Sandborn, 2005[33]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Lymphoma (NR) @ 12 wks	Active Yes Yes	Incidence 0 / 724 (0%)	Incidence 0 / 181 (0%)
Sandborn, 2005[33]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Mortality (NR) @ 12 wks	Active Yes Yes	Incidence 2 / 724 (0%)	Incidence 0 / 181 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Sandborn, 2005[33]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Other infections (influenza, sinusitis, candidiasis, viral infections and herpes zoster / others) @ 12 wks	Active Yes Yes	Incidence 352 / 723 (49%)	Incidence 78 / 181 (43%)
Sandborn, 2005[33]	Natalizumab Route: IV Dose: 300 mg every 4 wks	Placebo Route: IV Dose: NA every 4 wks	Serious infections (abscess, sepsis, pneumonia, meningitis, gastroenteritis) @ 12 wks	Active Yes Yes	Incidence 12 / 723 (2%)	Incidence 4 / 181 (2%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 100 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Infusion and injection-site rx (NR)	NR No NR	Incidence 5 / 74 (6.8%)	Incidence 2 / 73 (2.7%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 100 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Lymphoma (NR) @ 12 wks	Active No Yes	Incidence 0 / 74 (0%)	Incidence 0 / 73 (0%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 100 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Mortality (NR) @ 12 wks	Active No Yes	Incidence 0 / 74 (0%)	Incidence 0 / 73 (0%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 100 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	TB (NR) @ 12 wks	Active No Yes	Incidence 0 / 74 (0%)	Incidence 0 / 73 (0%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 200 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Infusion and injection-site rx (NR)	NR No NR	Incidence 4 / 72 (5.6%)	Incidence 2 / 73 (2.7%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 200 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Lymphoma (NR) @ 12 wks	Active No Yes	Incidence 0 / 72 (0%)	Incidence 0 / 73 (0%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 200 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Mortality (NR) @ 12 wks	Active No Yes	Incidence 0 / 72 (0%)	Incidence 0 / 73 (0%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 200 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	TB (NR) @ 12 wks	Active No Yes	Incidence 0 / 72 (0%)	Incidence 0 / 73 (0%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Infusion and injection-site rx (NR)	NR No NR	Incidence 2 / 72 (2.7%)	Incidence 2 / 73 (2.7%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Lymphoma (NR) @ 12 wks	Active No Yes	Incidence 0 / 72 (0%)	Incidence 0 / 73 (0%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	Mortality (NR) @ 12 wks	Active No Yes	Incidence 0 / 72 (0%)	Incidence 0 / 73 (0%)
Schreiber, 2005[40]	Certolizumab pegol Route: SC Dose: 400 mg every 4 wks	Placebo Route: SC Dose: NA every 4 wks	TB (NR) @ 12 wks	Active No Yes	Incidence 0 / 72 (0%)	Incidence 0 / 73 (0%)
Biancone, 2006[149]	Infliximab Route: IV	Never user infliximab	Lymphoma (non-Hodgkin's lymphoma from chart review)	Passive No NA	Incidence 0 / 404 (0%)	Incidence 1 / 404 (0%)
Biancone, 2006[149]	Infliximab Route: IV	Never user infliximab	Other cancers (from charts: cholagiocarcinoma, anal carcinoma, breast cancer, leukemia, non-Hodgkin's lymphoma, baslioma, laryngeal carcinoma, adenocarcinoma cecum, spinaloma,)	Passive No NA	Incidence 9 / 404 (2%) OR: 1.33 (0.46 to 3.84) P: 0.4 vs. main	Incidence 7 / 404 (2%)
Biancone, 2006[149]	Infliximab + No immunomodulators	Never user infliximab	Other cancers (from charts: cholagiocarcinoma, anal carcinoma, breast cancer, leukemia, non-hod lymphoma, baslioma, laryngeal carcinoma, adenocarcinoma cecum, spinaloma,)	Passive No NA	Incidence 2 / 191 (1%)	Incidence 7 / 404 (2%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Biancone, 2006[149]	Infliximab + No immunomodulators	Certolizumab pegol + 6-MP/azathioprine/methotrexate	Other cancers (from charts: cholagiocarcinoma, anal carcinoma, breast cancer, leukemia, non-hod lymphoma, baslioma, laryngeal carcinoma, adenocarcinoma cecum, spinaloma,)	Passive No NA	Incidence 2 / 191 (1%)	Incidence 7 / 213 (3%)
Biancone, 2006[149]	No infliximab + 6-MP/azathioprine/methotrexate	Certolizumab pegol + 6-MP/azathioprine/methotrexate	Other cancers (from charts: cholagiocarcinoma, anal carcinoma, breast cancer, leukemia, non-hod lymphoma, baslioma, laryngeal carcinoma, adenocarcinoma cecum, spinaloma,)	Passive No NA	Incidence 3 / 218 (1%)	Incidence 7 / 213 (3%)
Biancone, 2006[149]	No infliximab + 6-MP/azathioprine/methotrexate	Certolizumab pegol + 6-MP/azathioprine/methotrexate	Other cancers (from charts: cholagiocarcinoma, anal carcinoma, breast cancer, leukemia, non-hod lymphoma, baslioma, laryngeal carcinoma, adenocarcinoma cecum, spinaloma,)	Passive No NA	Incidence 4 / 186 (2%)	Incidence 7 / 213 (3%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Biancone, 2006[149]	No infliximab + 6-MP/azathioprine/methotrexate	Infliximab + No immunomodulators	Other cancers (from charts: cholagiocarcinoma, anal carcinoma, breast cancer, leukemia, non-hod lymphoma, baslioma, laryngeal carcinoma, adenocarcinoma cecum, spinaloma,)	Passive No NA	Incidence 3 / 218 (1%)	Incidence 2 / 191 (1%)
Biancone, 2006[149]	No infliximab + 6-MP/azathioprine/methotrexate	Infliximab + No immunomodulators	Other cancers (from charts: cholagiocarcinoma, anal carcinoma, breast cancer, leukemia, non-hod lymphoma, baslioma, laryngeal carcinoma, adenocarcinoma cecum, spinaloma,)	Passive No NA	Incidence 4 / 186 (2%)	Incidence 2 / 191 (1%)
Lemann, 2005[98]	Azathioprine Route: Oral Dose: as taken before enrollment every 1 d	Placebo Route: Oral Dose: NA every 1 d	Mortality (NR) @ 48 wks	NR No Yes	Incidence 1 / 40 (2%)	Incidence 0 / 43 (0%)
Orlando, 2005[128]	Infliximab + Immunomodulator (unspecified)	Infliximab + No concomitant immunomodulators	Mortality (within 12 wks (of first or last infusion--unclear))	NR No NA	Incidence 0 / 211 (0%)	Incidence 0 / 362 (0%)
Orlando, 2005[128]	Infliximab + Immunomodulator (unspecified)	Infliximab + No concomitant immunomodulators	Other cancers (anal adenocarcinoma, breast adenocarcinoma, laryngeal carcinoma, leukemia, biliary duct carcinoma, skin carcinoma)	NR No NA	Incidence 6 / 211 (3%)	Incidence 2 / 362 (1%)
Schoon, 2005[185]	Prednisolone Route: Oral Dose: 40 mg every 1 d	Budesonide Route: Oral Dose: 9 mg every 1 d	Fractures (traumatic and atraumatic fractures at all sites) @ 104 wks	Active Yes Yes	Event rate 3 events	Event rate 3 events

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 1.25 mg/kg	Placebo Route: IV Dose: NA	Infusion and injection-site rx (NR) @ 12 wks	Active Yes No	Incidence 0 / 2 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 1.25 mg/kg	Placebo Route: IV Dose: NA	Mortality (NR) @ 12 wks	Active Yes No	Incidence 0 / 2 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 1.25 mg/kg	Placebo Route: IV Dose: NA	Other infections (Opportunistic infections) @ 12 wks	Passive Yes No	Incidence 0 / 2 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 1.25 mg/kg	Placebo Route: IV Dose: NA	Other infections (NR) @ 12 wks	Active Yes No	Incidence 13 / 68 (19.1%)	Incidence 3 / 24 (12.5%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 1.25 mg/kg	Placebo Route: IV Dose: NA	Other infections (NR) @ 4 wks	Active Yes No	Incidence 8 / 68 (11.8%)	Incidence 2 / 24 (8.3%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 1.25 mg/kg	Placebo Route: IV Dose: NA	Serious infections (perianal abscess) @ 12 wks	Active Yes No	Incidence 0 / 2 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 1.25 mg/kg	Placebo Route: IV Dose: NA	TB (NR) @ 12 wks	Active Yes No	Incidence 0 / 2 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	Infusion and injection-site rx (NR) @ 12 wks	Active Yes No	Incidence 0 / 26 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	Mortality (NR) @ 12 wks	Active Yes No	Incidence 0 / 26 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	Other infections (Opportunistic infections) @ 12 wks	Passive Yes No	Incidence 0 / 26 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	Serious infections (perianal abscess) @ 12 wks	Active Yes No	Incidence 0 / 26 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 5 mg/kg	Placebo Route: IV Dose: NA	TB (NR) @ 12 wks	Active Yes No	Incidence 0 / 26 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	Infusion and injection-site rx (NR) @ 12 wks	Active Yes No	Incidence 0 / 17 (0%)	Incidence 0 / 24 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	Mortality (NR) @ 12 wks	Active Yes No	Incidence 0 / 17 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	Other infections (Opportunistic infections) @ 12 wks	Passive Yes No	Incidence 0 / 17 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	Serious infections (perianal abscess) @ 12 wks	Active Yes No	Incidence 0 / 17 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 10 mg/kg	Placebo Route: IV Dose: NA	TB (NR) @ 12 wks	Active Yes No	Incidence 0 / 17 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	Infusion and injection-site rx (NR) @ 12 wks	Active Yes No	Incidence 0 / 23 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	Mortality (NR) @ 12 wks	Active Yes No	Incidence 0 / 23 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	Other infections (Opportunistic infections) @ 12 wks	Passive Yes No	Incidence 0 / 23 (0%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	Serious infections (perianal abscess) @ 12 wks	Active Yes No	Incidence 1 / 23 (4%)	Incidence 0 / 24 (0%)
Winter, 2004[41]	Certolizumab pegol Route: IV Dose: 20 mg/kg	Placebo Route: IV Dose: NA	TB (NR) @ 12 wks	Active Yes No	Incidence 0 / 23 (0%)	Incidence 0 / 24 (0%)
Seiderer, 2004[173]	Infliximab + Azathioprine	Infliximab + No azathioprine/6-MP at first infusion	Infusion and injection-site rx (NR)	Active No NA	Incidence 2 / 64 (3%)	Incidence 0 / 18 (0%)
Seiderer, 2004[173]	Infliximab + Azathioprine	Infliximab + No azathioprine/6-MP at first infusion	Mortality (from chart review)	Passive No NA	Incidence 0 / 64 (0%)	Incidence 0 / 18 (0%)
Seiderer, 2004[173]	Infliximab + Azathioprine	Infliximab + No azathioprine/6-MP at first infusion	Other cancers (malignancy from medical record review)	Passive No NA	Incidence 0 / 64 (0%)	Incidence 0 / 18 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Seiderer, 2004[173]	Infliximab + Azathioprine	Infliximab + No azathioprine/6-MP at first infusion	Other infections (varicella-zoster, bacterial uncomplicated pneumonia, E coli, sepsis)	Passive No NA	Incidence 3 / 64 (5%)	Incidence 0 / 18 (0%)
Seiderer, 2004[173]	Infliximab + 6-MP	Infliximab + No azathioprine/6-MP at first infusion	Infusion and injection-site rx (NR)	Active No NA	Incidence 0 / 18 (0%)	Incidence 0 / 18 (0%)
Seiderer, 2004[173]	Infliximab + 6-MP	Infliximab + No azathioprine/6-MP at first infusion	Mortality (from chart review)	Passive No NA	Incidence 0 / 18 (0%)	Incidence 0 / 18 (0%)
Seiderer, 2004[173]	Infliximab + 6-MP	Infliximab + No azathioprine/6-MP at first infusion	Other cancers (malignancy from medical record review)	Passive No NA	Incidence 0 / 18 (0%)	Incidence 0 / 18 (0%)
Seiderer, 2004[173]	Infliximab + 6-MP	Infliximab + No azathioprine/6-MP at first infusion	Other infections (varicella-zoster, bacterial uncomplicated pneumonia, E coli, sepsis)	Passive No NA	Incidence 1 / 18 (6%)	Incidence 0 / 18 (0%)
Seiderer, 2004[173]	Infliximab + Thiopurine	Infliximab + No azathioprine/6-MP at first infusion	Infusion and injection-site rx (NR)	Active No NA	Incidence 2 / 82 (2%)	Incidence 0 / 18 (0%)
Seiderer, 2004[173]	Infliximab + Thiopurine	Infliximab + No azathioprine/6-MP at first infusion	Mortality (from chart review)	Passive No NA	Incidence 0 / 82 (0%)	Incidence 0 / 18 (0%)
Seiderer, 2004[173]	Infliximab + Thiopurine	Infliximab + No azathioprine/6-MP at first infusion	Other cancers (malignancy from medical record review)	Passive No NA	Incidence 0 / 82 (0%)	Incidence 0 / 18 (0%)
Seiderer, 2004[173]	Infliximab + Thiopurine	Infliximab + No azathioprine/6-MP at first infusion	Other infections (varicella-zoster, bacterial uncomplicated pneumonia, E coli, sepsis)	Passive No NA	Incidence 4 / 82 (5%)	Incidence 0 / 18 (0%)
Mantzaris, 2003[113]	Mesalamine (Salofalk) Route: Unknown Dose: 1 g every 8 hrs	Budesonide Route: Unknown Dose: 6 mg every 1 d	Other infections (NR) @ 52 wks	Active No NA	Event rate 16 events	Event rate 19 events
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Infusion and injection-site rx (NR) @ 54 wks	Active Yes Yes	Incidence 22 / 138 (16%)	Incidence 24 / 144 (17%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Mortality (NR) @ 40 wks	Active Yes Yes	Incidence 0 / 139 (0%)	Incidence 0 / 143 (0%)
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Other cancers (Any cancer) @ 40 wks	Active Yes Yes	Incidence 0 / 139 (0%)	Incidence 0 / 143 (0%)
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Other infections (infections requiring antimicrobial treatment) @ 40 wks	Active Yes Yes	Incidence 47 / 138 (34%)	Incidence 39 / 144 (27%) P: 0.2
Sands, 2004[87]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Serious infections (NR) @ 40 wks	Active Yes Yes	Incidence 4 / 138 (3%)	Incidence 9 / 144 (6%) P: 0.18
Tay, 2003[233]	Any immunomodulator Route: Unknown	No immunomodulator Route: Unknown	Serious infections (IASC) @ 44 wks	Active Yes NA	Incidence 4 / 72 (6%)	Incidence 4 / 28 (14%) P: 0.1
Kinney, 2003[162]	Infliximab + Thiopurine Dose: NR + NR	Infliximab Route: Unknown Dose: NR	Mortality (NR)	Passive No NA	Incidence 0 / 58 (0%)	Incidence 1 / 36 (3%)
Kinney, 2003[162]	Infliximab + Methotrexate Dose: NR + NR	Infliximab Route: Unknown Dose: NR	Mortality (NR)	Passive No NA	Incidence 0 / 23 (0%)	Incidence 1 / 36 (3%)
Kinney, 2003[162]	Infliximab + Methotrexate Dose: NR + NR	Infliximab + Thiopurine Dose: NR + NR	Mortality (NR)	Passive No NA	Incidence 0 / 23 (0%)	Incidence 0 / 58 (0%)
Fraser, 2002[232]	Azathioprine Route: Unknown Dose: NR	Never user azathioprine	Lymphoma (Histology described)	Passive No NA	Incidence 3 / 626 (0%)	Incidence 5 / 1578 (0%)
Fraser, 2002[232]	Azathioprine Route: Unknown Dose: NR	Never user azathioprine	Other cancers (NR)	Passive No NA	Event rate 31 events	Event rate 77 events
Fraser, 2002[232]	Azathioprine Route: Unknown Dose: NR	Never user azathioprine	Other cancers (NR)	Passive No NA	Incidence 30 / 626 (5%)	Incidence 70 / 1578 (4%)
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 9 mg every 1 d	Placebo Route: Oral Dose: NA every 1 d	Other infections (respiratory infection)	Active Yes No	Incidence 8 / 80 (10%)	Incidence 5 / 41 (13%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Tremaine, 2002[65]	Budesonide Route: Oral Dose: 4.5 mg every 12 hrs	Placebo Route: Oral Dose: NA every 1 d	Other infections (respiratory infection)	Active Yes No	Incidence 2 / 79 (2%)	Incidence 5 / 41 (13%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Infusion and injection-site rx (NR) @ 52 wks	Active Yes Yes	Incidence 44 / 193 (23%)	Incidence 17 / 188 (9%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Lymphoma (natural-killer-cell lymphoma) @ 52 wks	Active No Yes	Incidence 0 / 193 (0%)	Incidence 1 / 188 (1%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Mortality (NR) @ 52 wks	Active Yes Yes	Incidence 3 / 193 (2%)	Incidence 0 / 188 (0%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Other cancers (any type of cancer) @ 52 wks	Active Yes Yes	Incidence 3 / 193 (2%)	Incidence 2 / 188 (1%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Other infections (infection requiring antimicrobial treatment) @ 52 wks	Active Yes Yes	Incidence 64 / 193 (33%)	Incidence 70 / 188 (37%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Serious infections (NR) @ 52 wks	Active Yes Yes	Incidence 8 / 193 (4%)	Incidence 8 / 188 (4%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 5 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	TB (NR) @ 52 wks	Active Yes Yes	Incidence 1 / 193 (1%)	Incidence 0 / 188 (0%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Infusion and injection-site rx (NR) @ 52 wks	Active Yes Yes	Incidence 36 / 192 (19%)	Incidence 17 / 188 (9%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Lymphoma (natural-killer-cell lymphoma) @ 52 wks	Active No Yes	Incidence 0 / 192 (0%)	Incidence 1 / 188 (1%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Mortality (NR) @ 52 wks	Active Yes Yes	Incidence 0 / 192 (0%)	Incidence 0 / 188 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Other cancers (any type of cancer) @ 52 wks	Active Yes Yes	Incidence 1 / 192 (1%)	Incidence 2 / 188 (1%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Other infections (infection requiring antimicrobial treatment) @ 52 wks	Active Yes Yes	Incidence 52 / 192 (27%)	Incidence 70 / 188 (37%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	Serious infections (NR) @ 52 wks	Active Yes Yes	Incidence 6 / 192 (3%)	Incidence 8 / 188 (4%)
Hanauer, 2002[86]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: IV Dose: NA every 8 wks	TB (NR) @ 52 wks	Active Yes Yes	Incidence 0 / 192 (0%)	Incidence 0 / 188 (0%)
Campbell, 2001[146]	Azathioprine + ASA Dose: 1.7 mg/kg + NR	Azathioprine Route: Unknown Dose: 1.8 mg/kg	Other cancers (NR)	Passive No NA	Incidence 1 / 48 (2%)	Incidence 0 / 56 (0%)
Lewis, 2001[136]	Thiopurine	Never user azathioprine/6-MP	Lymphoma (ICD code verified by physician questionnaire in most cases)	Passive No NA		
Lewis, 2001[136]	Thiopurine	Never user azathioprine/6-MP	Lymphoma (ICD code verified by physician questionnaire in most cases)	Passive No NA	Incidence 0 / 837 (0%)	Incidence 7 / 5768 (0%)
Lewis, 2001[136]	Never user corticosteroid Route: Unknown Dose: NR	Corticosteroid Route: Unknown Dose: NR	Lymphoma (ICD code verified by physician questionnaire in most cases)	Passive No NA	Incidence 11 / 11000 (0%)	Incidence 4 / 4064 (0%)
Lewis, 2001[136]	Never user mesalamine (NR) Route: Unknown Dose: NR	Mesalamine (NR) Route: Unknown Dose: NR	Lymphoma (ICD code verified by physician questionnaire in most cases)	Passive No NA	Incidence 8 / 7931 (0%)	Incidence 7 / 7233 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Lewis, 2001[136]	Never user immunosuppresants (defined as either methotrexate, cyclosporine, tacrolimus or mycophenolate mofetil) Route: Unknown Dose: NR	Immunosuppresants (defined as either methotrexate, cyclosporine, tacrolimus or mycophenolate mofetil) Route: Unknown Dose: NR	Lymphoma (ICD code verified by physician questionnaire in most cases)	Passive No NA	Incidence 14 / 15087 (0%)	Incidence 1 / 77 (1%)
Mortimore, 2001[174]	Infliximab + No concomitant immunosuppressive Route: IV + Unknown Dose: 5 mg/kg + NR	Infliximab Route: IV Dose: 5 mg/kg	Serious infections (Pneumocystis carinii pneumonia)	Passive No NA	Incidence 1 / 15 (7%)	Incidence 0 / 42 (0%)
Ricart, 2001[138]	Infliximab + Corticosteroid Route: IV + Unknown Dose: 5 mg/kg + NR	Infliximab + Never user corticosteroid Route: IV + Unknown Dose: 5 mg/kg + NR	Serious infections (Either pneumonia, varicella or candida esophagitis)	Active No NA	Incidence 2 / 44 (5%)	Incidence 4 / 56 (7%)
Ricart, 2001[138]	Infliximab + Immunomodulators Route: IV + Unknown Dose: 5 mg/kg + NR	Infliximab + Never user immunomodulators Route: IV + Unknown Dose: 5 mg/kg + NR	Infusion and injection-site rx (NR)	Active No NA	Incidence 18 / 95 (19%)	Incidence 1 / 5 (20%)
Ricart, 2001[138]	Infliximab + Immunomodulators Route: IV + Unknown Dose: 5 mg/kg + NR	Infliximab + Never user immunomodulators Route: IV + Unknown Dose: 5 mg/kg + NR	Serious infections (Either pneumonia, varicella or candida esophagitis)	Active No NA	Incidence 5 / 95 (5%)	Incidence 1 / 5 (20%)
Farrell, 2000[231]	Immunomodulators Route: Unknown Dose: NR	Never used immunomodulators	Lymphoma (Non-Hodgkins Lymphoma)	Passive No NA	Incidence 4 / 238 (2%)	Incidence 0 / 544 (0%) P: 0.002
Farrell, 2000[231]	Immunomodulators Route: Unknown Dose: NR	Never used immunomodulators	Other cancers (colorectal cancer, skin cancers, lymphoma and 'Other' Cancers)	Passive No NA	Incidence 14 / 238 (6%)	Incidence 16 / 544 (3%)
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	Lymphoma (B cell lymphoma) @ 36 wks	Active Yes No	Incidence 0 / 37 (0%)	Incidence 1 / 36 (3%)
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	Mortality (NR) @ 36 wks	Active No Yes	Incidence 0 / 37 (0%)	Incidence 1 / 36 (3%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	Other infections (Bronchitis) @ 36 wks	Active Yes Yes	Incidence 6 / 37 (16.2%)	Incidence 3 / 36 (8.3%)
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	Other infections (pharyngitis) @ 36 wks	Active Yes No	Incidence 7 / 37 (18.9%)	Incidence 1 / 36 (2.8%)
Rutgeerts, 1999[85]	Infliximab Route: IV Dose: 10 mg/kg every 8 wks	Placebo Route: Unknown Dose: NA every 8 wks	Other infections (Upper respiratory infections)	Active Yes Yes	Incidence 9 / 37 (24.3%)	Incidence 6 / 36 (16.7%)
Sandborn, 1999[59]	Azathioprine + Azathioprine Route: IV + Oral Dose: 40 mg/kg + 2 mg/kg every 1 d	Placebo + Azathioprine Route: Oral Dose: 2 mg/kg every 1 d	Infusion and injection-site rx (NR)	Active Yes Yes	Incidence 11 / 51 (22%)	Incidence 1 / 45 (2%) P: 0.005
Sandborn, 1999[59]	Azathioprine + Azathioprine Route: IV + Oral Dose: 40 mg/kg + 2 mg/kg every 1 d	Placebo + Azathioprine Route: Oral Dose: 2 mg/kg every 1 d	Other infections (pneumonia)	Active Yes Yes	Incidence 0 / 51 (0%)	Incidence 2 / 45 (4%) P: 0.217
Sandborn, 1999[59]	Azathioprine + Azathioprine Route: IV + Oral Dose: 40 mg/kg + 2 mg/kg every 1 d	Placebo + Azathioprine Route: Oral Dose: 2 mg/kg every 1 d	Other infections (viral lower respiratory infection)	Active Yes Yes	Incidence 6 / 51 (12%)	Incidence 6 / 45 (13%) P: 1
Campieri, 1997[68]	Budesonide + Placebo Route: Oral + Oral Dose: 4.5 mg every 12 hrs + NA every 24 hrs	Prednisolone + Placebo Route: Oral + Oral Dose: 40 mg every 1 d + NA every 12 hrs	Weight (kg) @ 8 wks	Active Yes Yes	B: Mean, 63 F-B: Mean, 0 G1-G2: 2.1	B: Mean, 61 F-B: Mean, 2.1 G1-G2: 2.1
Campieri, 1997[68]	Budesonide + Placebo Route: Oral + Oral Dose: 9 mg every 1 d + NA every 24 hrs	Prednisolone + Placebo Route: Oral + Oral Dose: 40 mg every 1 d + NA every 12 hrs	Weight (kg) @ 8 wks	Active Yes Yes	B: Mean, 63 F-B: Mean, 1 G1-G2: 1.1	B: Mean, 61 F-B: Mean, 2.1 G1-G2: 1.1
Feagan, 1995[63]	Methotrexate + Prednisone Route: IM + Oral Dose: 25 mg every 1 wks	Placebo + Prednisone Route: IM + Oral Dose: NA every 1 wks + every 1 d	Other infections (influenza like illness or pneumonia probably due to mycoplasma)	NR No Yes	Incidence 11 / 94 (12%)	Incidence 6 / 47 (13%)
Malchow, 1984[64]	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (NR) @ 104 wks	NR No No	Incidence 0 / 117 (0%)	Incidence 0 / 110 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Malchow, 1984[64]	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Placebo Route: Oral Dose: NA	Serious infections (abscesses) @ 6 wks	NA No	Incidence 1 / 75 (1%)	Incidence 1 / 68 (1%)
Malchow, 1984[64]	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Placebo Route: Oral Dose: NA	Serious infections (abscesses) @ 104 wks	NA No	Incidence 3 / 75 (4%)	Incidence 1 / 68 (1%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (NR) @ 104 wks	NR No No	Incidence 2 / 113 (2%)	Incidence 0 / 110 (0%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	Serious infections (abscesses) @ 6 wks	NA No	Incidence 0 / 75 (0%)	Incidence 1 / 68 (1%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	Serious infections (abscesses) @ 104 wks	NA No	Incidence 0 / 75 (0%)	Incidence 1 / 68 (1%)
Malchow, 1984[64]	Sulfasalazine + Prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (NR) @ 104 wks	NR No No	Incidence 0 / 112 (0%)	Incidence 0 / 110 (0%)
Malchow, 1984[64]	Sulfasalazine + Prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	Serious infections (abscesses) @ 104 wks	NA No	Incidence 2 / 74 (3%)	Incidence 1 / 68 (1%)
Malchow, 1984[64]	Sulfasalazine + Prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Placebo Route: Oral Dose: NA	Serious infections (abscesses) @ 6 wks	NA No	Incidence 1 / 74 (1%)	Incidence 1 / 68 (1%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Mortality (NR) @ 104 wks	NR No No	Incidence 2 / 113 (2%)	Incidence 0 / 117 (0%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Serious infections (abscesses) @ 6 wks	NA No	Incidence 0 / 75 (0%)	Incidence 1 / 75 (1%)
Malchow, 1984[64]	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Serious infections (abscesses) @ 104 wks	NA No	Incidence 0 / 75 (0%)	Incidence 3 / 75 (4%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Malchow, 1984[64]	Sulfasalazine + Prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Mortality (NR) @ 104 wks	NR No No	Incidence 0 / 112 (0%)	Incidence 0 / 117 (0%)
Malchow, 1984[64]	Sulfasalazine + Prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Serious infections (abscesses) @ 104 wks	NA No	Incidence 2 / 74 (3%)	Incidence 3 / 75 (4%)
Malchow, 1984[64]	Sulfasalazine + Prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	Sulfasalazine Route: Oral Dose: 3 g every 24 hrs	Serious infections (abscesses) @ 6 wks	NA No	Incidence 1 / 74 (1%)	Incidence 1 / 75 (1%)
Malchow, 1984[64]	Sulfasalazine + Prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Mortality (NR) @ 104 wks	NR No No	Incidence 0 / 112 (0%)	Incidence 2 / 113 (2%)
Malchow, 1984[64]	Sulfasalazine + Prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Serious infections (abscesses) @ 104 wks	NA No	Incidence 2 / 74 (3%)	Incidence 0 / 75 (0%)
Malchow, 1984[64]	Sulfasalazine + Prednisolone Route: Oral + Unknown Dose: 3 g every 24 hrs + 48 mg every 24 hrs	(6)-Methylprednisolone Route: Unknown Dose: 48 mg every 24 hrs	Serious infections (abscesses) @ 6 wks	NA No	Incidence 1 / 74 (1%)	Incidence 0 / 75 (0%)
Singleton, 1979[75]	Sulfasalazine + Prednisone Route: Oral + Unknown Dose: 1g per 15kg body weight to 5g max every 1 d + every 1 d	Placebo + Prednisone Route: Unknown + Oral Dose: NA + every 1 d	Other infections (NR) @ 8 wks	Active No NR	Incidence 19 / 43 (44%)	Incidence 33 / 46 (72%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (NR) @ 104 wks	Active Yes No	Event rate 0 events	Event rate 0 events

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (NR) @ 17 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (Perianal abscess) @ 104 wks	NA No	Incidence 3 / 74 (4%)	Incidence 5 / 77 (6%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (Other abscess) @ 104 wks	Active Yes NA	Incidence 0 / 74 (0%)	Incidence 0 / 77 (0%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 3 / 74 (4%)	Incidence 5 / 77 (6%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (Infections) @ 17 wks	NA No	Incidence 10 / 74 (14%)	Incidence 10 / 77 (13%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (NR) @ 104 wks	Active Yes No	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (NR) @ 17 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 2 / 85 (2%)	Incidence 5 / 77 (6%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (Infections) @ 17 wks	NA No	Incidence 27 / 85 (32%)	Incidence 10 / 77 (13%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (Perianal abscess) @ 104 wks	NA No	Incidence 1 / 85 (1%)	Incidence 5 / 77 (6%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (Other abscess) @ 104 wks	Active Yes NA	Incidence 1 / 85 (1%)	Incidence 0 / 77 (0%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (NR) @ 104 wks	Active Yes No	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (NR) @ 17 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (Other abscess) @ 104 wks	Active Yes NA	Incidence 2 / 59 (3%)	Incidence 0 / 77 (0%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (Perianal abscess) @ 104 wks	NA No	Incidence 2 / 59 (3%)	Incidence 5 / 77 (6%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (Infections) @ 17 wks	NA No	Incidence 5 / 59 (8%)	Incidence 10 / 77 (13%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 4 / 59 (7%)	Incidence 5 / 77 (6%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Mortality (NR) @ 104 wks	Active Yes No	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Mortality (NR) @ 17 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Other infections (Perianal abscess) @ 104 wks	NA No	Incidence 1 / 85 (1%)	Incidence 3 / 74 (4%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Other infections (Infections) @ 17 wks	NA No	Incidence 27 / 85 (32%)	Incidence 10 / 74 (14%)
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Other infections (Other abscess) @ 104 wks	Active Yes NA	Incidence 1 / 85 (1%)	Incidence 0 / 74 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 2 / 85 (2%)	Incidence 3 / 74 (4%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Mortality (NR) @ 17 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Mortality (NR) @ 104 wks	Active Yes No	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Other infections (Infections) @ 17 wks	NA No	Incidence 5 / 59 (8%)	Incidence 10 / 74 (14%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 4 / 59 (7%)	Incidence 3 / 74 (4%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Other infections (Other abscess) @ 104 wks	Active Yes NA	Incidence 2 / 59 (3%)	Incidence 0 / 74 (0%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: 1g/15kgs every 24 hrs	Other infections (Perianal abscess) @ 104 wks	NA No	Incidence 2 / 59 (3%)	Incidence 3 / 74 (4%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Mortality (NR) @ 17 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Mortality (NR) @ 104 wks	Active Yes No	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Other infections (Other abscess) @ 104 wks	Active Yes NA	Incidence 2 / 59 (3%)	Incidence 1 / 85 (1%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Other infections (Perianal abscess) @ 104 wks	NA No	Incidence 2 / 59 (3%)	Incidence 1 / 85 (1%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Other infections (Infections) @ 17 wks	NA No	Incidence 5 / 59 (8%)	Incidence 27 / 85 (32%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 2.5 mg/kg every 24 hrs	Prednisone Route: Oral Dose: If CDAI<150 then 1/4mg/kg, if CDAI = 150-300 1/2mg/kg, if CDAI >300 then 3/4mg/kg every 24 hrs	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 4 / 59 (7%)	Incidence 2 / 85 (2%)
O'Donoghue, 1978[100]	Azathioprine Route: Oral Dose: 2 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (Not defined) @ 52 wks	NR No Yes	Incidence 1 / 24 (4%)	Incidence 0 / 27 (0%)
Goldstein, 1967[142]	Corticosteroid Route: Unknown Dose: NR	Never user corticosteroids/ACTH	Fractures (NR)	NR No NA	Incidence 6 / 430 (1%)	Incidence 0 / 124 (0%)
Goldstein, 1967[142]	Corticosteroid Route: Unknown Dose: NR	Never user corticosteroids/ACTH	Mortality (Suicide)	NR No NA	Incidence 4 / 430 (1%)	Incidence 0 / 124 (0%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Goldstein, 1967[142]	Corticosteroid Route: Unknown Dose: NR	Never user corticosteroids/ACTH	Other infections (NR)	NR No NA	Incidence 95 / 430 (22%)	Incidence 17 / 124 (14%)
Keshavarzian, 2007[182]	Immunomodulators + Infliximab	Never user immunomodulators + Infliximab Route: Unknown Dose: NR	Infusion and injection-site rx	Passive No NA	Incidence 57 / 322 (18%) OR: 0.65 (0.4 to 1.07) P: 0.118 vs. main	Incidence 31 / 125 (25%) P: 0.118
Keshavarzian, 2007[182]	Immunomodulators + Infliximab	Never user immunomodulators + Infliximab Route: Unknown Dose: NR	Infusion and injection-site rx	Passive No NA	Event rate 91 events OR: 0.39 (0.3 to 0.52) vs. main	Event rate 135 events
Feagan, 2000[105]	Methotrexate Route: IM Dose: 15 mg every 1 wks	Placebo Route: IM Dose: NA every 1 wks	Other infections (serious or not infections including viral respiratory infection and influenza like illness) @ 40 wks	Active No Yes	Incidence 2 / 40 (5%)	Incidence 3 / 36 (8%)
Present, 1999[44]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV	Infusion and injection-site rx (during infusion or within 2 hrs of infusion: dizziness, fever, headache, chest pain with flushing)	Active Yes	Incidence 4 / 63 (6%)	Incidence 0 / 31 (0%)
Present, 1999[44]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV	Mortality (All-cause mortality) @ 18 wks	Active No NA	Incidence 0 / 31 (0%)	Incidence 0 / 31 (0%)
Present, 1999[44]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV	Other infections (pneumonia, abscess or upper respiratory infection) @ 18 wks	Active No Yes	Incidence 3 / 31 (10%)	Incidence 3 / 31 (10%)
Present, 1999[44]	Infliximab Route: IV Dose: 5 mg/kg	Placebo Route: IV	Serious infections (Either pneumonia or abscess formation) @ 18 wks	Active No NA	Incidence 2 / 31 (6%)	Incidence 1 / 31 (3%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Present, 1999[44]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV	Infusion and injection-site rx (during infusion or within 2 hrs of infusion: dizziness, fever, headache, chest pain with flushing)	Active Yes		Incidence 0 / 31 (0%)
Present, 1999[44]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV	Mortality (All-cause mortality) @ 18 wks	Active No NA	Incidence 0 / 32 (0%)	Incidence 0 / 31 (0%)
Present, 1999[44]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV	Other infections (pneumonia, abscess or upper respiratory infection) @ 18 wks	Active No Yes	Incidence 11 / 32 (34%)	Incidence 3 / 31 (10%)
Present, 1999[44]	Infliximab Route: IV Dose: 10 mg/kg	Placebo Route: IV	Serious infections (Either pneumonia or abscess formation) @ 18 wks	Active No NA	Incidence 6 / 32 (19%)	Incidence 1 / 31 (3%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Placebo Route: Oral Dose: NA	Mortality (NR) @ 104 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Placebo Route: Oral Dose: NA	Other infections (other abscess) @ 104 wks	Active Yes NA	Incidence 0 / 58 (0%)	Incidence 1 / 101 (1%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Placebo Route: Oral Dose: NA	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 2 / 58 (3%)	Incidence 1 / 101 (1%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Placebo Route: Oral Dose: NA	Other infections (Infection) @ 104 wks	Active Yes No	Incidence 17 / 58 (29%)	Incidence 19 / 101 (19%)
Summers, 1979[56]	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Placebo Route: Oral Dose: NA	Serious infections (Perianal abscess) @ 104 wks	Active Yes No	Incidence 2 / 58 (3%)	Incidence 0 / 101 (0%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Placebo Route: Oral Dose: NA	Mortality (NR) @ 104 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Placebo Route: Oral Dose: NA	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 3 / 61 (5%)	Incidence 1 / 101 (1%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Placebo Route: Oral Dose: NA	Other infections (other abscess) @ 104 wks	Active Yes NA	Incidence 2 / 61 (3%)	Incidence 1 / 101 (1%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Placebo Route: Oral Dose: NA	Other infections (Infection) @ 104 wks	Active Yes No	Incidence 8 / 61 (13%)	Incidence 19 / 101 (19%) P: NS
Summers, 1979[56]	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Placebo Route: Oral Dose: NA	Serious infections (Perianal abscess) @ 104 wks	Active Yes No	Incidence 1 / 61 (2%)	Incidence 0 / 101 (0%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Mortality (NR) @ 104 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (other abscess) @ 104 wks	Active Yes NA	Incidence 1 / 54 (2%)	Incidence 1 / 101 (1%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 2 / 54 (4%)	Incidence 1 / 101 (1%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Other infections (Infection) @ 104 wks	Active Yes No	Incidence 17 / 54 (31%)	Incidence 19 / 101 (19%) P: NS
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Placebo Route: Oral Dose: NA	Serious infections (Perianal abscess) @ 104 wks	Active Yes No	Incidence 1 / 54 (2%)	Incidence 0 / 101 (0%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Mortality (NR) @ 104 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 3 / 61 (5%)	Incidence 2 / 58 (3%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Other infections (other abscess) @ 104 wks	Active Yes NA	Incidence 2 / 61 (3%)	Incidence 0 / 58 (0%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Other infections (Infection) @ 104 wks	Active Yes No	Incidence 8 / 61 (13%)	Incidence 17 / 58 (29%)
Summers, 1979[56]	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Serious infections (Perianal abscess) @ 104 wks	Active Yes No	Incidence 1 / 61 (2%)	Incidence 2 / 58 (3%)

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn's disease (KQ3)

Author, year	Group1	Group2	Outcome (definition)	Adverse event collection / ITT	Results, Group 1	Results, Group 2
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Mortality (NR) @ 104 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Other infections (Infection) @ 104 wks	Active Yes No	Incidence 17 / 54 (31%)	Incidence 17 / 58 (29%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 2 / 54 (4%)	Incidence 2 / 58 (3%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Other infections (other abscess) @ 104 wks	Active Yes NA	Incidence 1 / 54 (2%)	Incidence 0 / 58 (0%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Sulfasalazine Route: Oral Dose: .5 g/ 15 kg every 1 d	Serious infections (Perianal abscess) @ 104 wks	Active Yes No	Incidence 1 / 54 (2%)	Incidence 2 / 58 (3%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Mortality (NR) @ 104 wks	Active Yes Yes	Event rate 0 events	Event rate 0 events
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Other infections (total abscess) @ 104 wks	Active Yes NA	Incidence 2 / 54 (4%)	Incidence 3 / 61 (5%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Other infections (other abscess) @ 104 wks	Active Yes NA	Incidence 1 / 54 (2%)	Incidence 2 / 61 (3%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Other infections (Infection) @ 104 wks	Active Yes No	Incidence 17 / 54 (31%)	Incidence 8 / 61 (13%)
Summers, 1979[56]	Azathioprine Route: Oral Dose: 1 mg/kg every 24 hrs	Prednisone Route: Oral Dose: 1-4 mg/kg every 1 d	Serious infections (Perianal abscess) @ 104 wks	Active Yes No	Incidence 1 / 54 (2%)	Incidence 1 / 61 (2%)

Abbreviations: 95% CI = 95% Confidence Interval; 6-MP = 6-Mercaptopurine; @ = at; AE = adverse events; AP = Acute Phase; ASA = Aminosalicylates; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity; d= day; DXA Scan = bone density test also called densitometry; EQ-5D VAS = EuroQol (EQ-5D), a generic health index comprises a five-part questionnaire and a visual analogue self-rating scale; FACIT = functional assessment of chronic illness therapy; g = gram; g/kgs = gram/kilograms; h = hour; HBI = Harvey-Bradshaw Index; HR QoL= Health-related Quality of Life; hrs = hours; IBDQ = Inflammatory Bowel Disease Questionnaire; ICD = International Code of Diseases; ICD9 = International Code of Diseases Version 9; IFX= Infliximab; IM = intramuscular; IMM = Immunomodulator; IV= intravenous; IQR= inter-quartile range; ITT = intention to treat; kg = kilogram; Max. = maximum; MCS = Mental Component Score; mg = milligram; mg/d = milligram/day; mg/kg = milligram/kilogram; mg/mo = milligram/month; Min. = minimum; Mo/mos= month(s); NA = Not Applicable; NR= Not Reported; NS = not significant; OR: Odds Ratio; PCS = Physical Component Score; PGWB = Psychological General Well-Being; P = p-value; pt = point; pys = person years; QALY = Quality-Adjusted Life Year; RH = relative hazard; rx = reaction; SC = subcutaneous; SD = standard deviation; SE= standard error; SES-CD = Simplified Endoscopic Activity Score for Crohn's Disease; SF = Short Form;

Evidence Table 14. Safety of pharmacologic therapies for the management of Crohn’s disease (KQ3)

Steroid free = steroid-free remission; TNF = tumor necrosis factor alpha inhibitor; TPMT= thiopurine methyltransferase; UTD = unable to determine; VAS = visual analog scale; and wks = weeks; WPAI:CD = Work Productivity and Activity Impairment: Crohn's Disease.

Evidence Table 15. Quality of randomized controlled trials reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Randomized controlled trials evaluating biologics								
Colombel, 2007[82]	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Colombel, 2009[95]	Yes	Yes	No	Yes	No	Yes	Yes	Poor
Colombel, 2010[45]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Good
D'Haens, 2008[48]	Yes	Yes	No	Yes	Yes	Yes	No	Fair
Feagan, 2007[81]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Fair
Hanauer, 2002[86]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Fair
Hanauer, 2006[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Lemann, 2006[46]	Yes	Yes	Yes	Yes	Yes	Yes	UTD	Good
Mantzaris, 2009[88]	Unclear	No	No	Yes	Yes	No	NA	Fair
Present, 1999[44]	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Rutgeerts, 1999[85]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Fair
Sandborn, 2005[33]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Sandborn, 2007[39]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Sandborn, 2007[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Sandborn, 2007[83]	Yes	Yes	No	Yes	Unclear	Yes	Yes	Fair
Sands, 2004[87]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Sands, 2007[35]	Unclear	Unclear	Yes	Yes	Yes	Yes	UTD	Good
Schreiber, 2005[40]	Yes	Yes	No	Yes	Yes	Yes	UTD	Good
Schreiber, 2007[84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Schroder, 2006[47]	Unclear	Unclear	Unclear	No	Yes	No	NA	Fair

Evidence Table 15. Quality of randomized controlled trials reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Targan, 2007[32]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Good
Van Assche, 2008[89]	Unclear	Yes	No	Yes	Yes	No	NA	Good
Winter, 2004[41]	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Poor
Randomized controlled trials evaluating thiopurines								
Ewe, 1993[54]	Unclear	Unclear	Unclear	Yes	Yes	Yes	UTD	Poor
Lemann, 2005[98]	Yes	Yes	Yes	Yes	Yes	Yes	UTD	Good
Lemann, 2006[46]	Yes	Yes	Yes	Yes	Yes	Yes	UTD	Good
Mantzaris, 2009[102]	Yes	Yes	No	No	Yes	UTD	NA	Fair
Markowitz, 2000[192]	Yes	Yes	Yes	Yes	Yes	No	NA	Good
O'Donoghue, 1978[100]	Unclear	Unclear	Yes	Yes	Yes	UTD	NA	Good
Reinisch, 2008[51]	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Fair
Sandborn, 1999[59]	Yes	Yes	Yes	Unclear	Yes	UTD	NA	Fair
Summers, 1979[56]	Yes	Yes	No	Yes	No	Yes	NA	Fair
Summers, 1979[56]	Yes	Yes	Unclear	Yes	Unclear	No	NA	Poor
Randomized controlled trials evaluating methotrexate								
Feagan, 1995[63]	Unclear	Unclear	Yes	Yes	Unclear	Yes	No	Fair
Feagan, 2000[105]	Yes	Yes	Yes	No	No	Yes	No	Fair
Randomized controlled trials evaluating corticosteroids								
Campieri, 1997[68]	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Fair
Escher, 2004[190]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Levine, 2003[191]	Unclear	Unclear	Unclear	Unclear	Unclear	UTD	NA	Poor
Malchow, 1984[64]	Unclear	Yes	Yes	No	No	Yes	UTD	Fair
Mantzaris, 2003[113]	Unclear	Unclear	No	Yes	Yes	UTD	NA	Fair

Evidence Table 15. Quality of randomized controlled trials reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Schoon, 2005[185]	Yes	Yes	No	Yes	No	Yes	Yes	Poor
Singleton, 1979[75]	Unclear	Unclear	Yes	Yes	Yes	No	NA	Good
Summers, 1979[56]	Yes	Yes	No	Yes	No	Yes	NA	Fair
Summers, 1979[56]	Yes	Yes	Unclear	Yes	Unclear	No	NA	Poor
Tremaine, 2002[65]	Yes	Yes	Yes	No	No	Yes	Yes	Poor
Randomized controlled trials evaluating 5-aminosalicylate acids								
Malchow, 1984[64]	Unclear	Yes	Yes	No	No	Yes	UTD	Fair
Summers, 1979[56]	Yes	Yes	No	Yes	No	Yes	NA	Fair
Summers, 1979[56]	Yes	Yes	Unclear	Yes	Unclear	No	NA	Poor

Abbreviations: NA = not applicable; UTD = unable to determine

*Study Quality Criteria: Criteria for a judgment of "GOOD" (i.e. low risk of bias): These studies have the least bias and results are considered valid- A study that adheres mostly to the commonly held concepts of high quality including the following: a) A formal randomized controlled study; b)Clear description of the population, setting, interventions, and comparison groups; c) Appropriate measurements of outcomes; d) Appropriate statistical and analytic methods and reporting; e) No reporting errors; f) Low dropout rate; and g) Clear reporting of dropouts. Criteria for a judgment of "FAIR": a) These studies are susceptible to some bias, but it is not sufficient to invalidate the results; b) do not meet all the criteria required for a rating of good qualities because they have some deficiencies, but no flaw is likely to cause major bias; and c) The study may be missing information, making it difficult to assess limitations and potential problems. Criteria for a judgment of "POOR" (i.e. high risk of bias): a) These studies have significant flaws that imply biases of various types that may invalidate the results; b) Have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Evidence Table 16. Quality of observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Main outcomes / Patient characteristics / Interventions described	Distribution of confounders described	Study groups from same population	Losses to followup accounted for	Adequate adjustment for confounding	Overall study quality*	Pharmaceutical support / Company involvement in design, conduct or reporting
Cohort studies evaluating biologics							
Biancone, 2006[149]	No / Yes / No	Yes	Yes	No	Yes	Poor	No / NA
Caspersen, 2008[225]	Yes / Yes / Yes	Yes	Yes	No	No	Poor	Yes / UTD
Clare, 2009[181]	Yes / Yes / No	Yes	Yes	No	No	Poor	UTD / NA
Colombel, 2004[137]	Yes / No / Yes	No	Yes	No	No	Poor	Yes / UTD
de Vries, 2008[227]	Yes / Yes / No	No	Yes	No	No	Poor	Yes / No
Domenech, 2010[228]	Yes / Yes / Yes	Yes	Yes	No	No	Poor	Yes / No
Fidder, 2009[153]	Yes / Yes / No	Yes	No	UTD	UTD	Poor	No / NA
Fidder, 2009[153]	Yes / Yes / Yes	Yes	No	No	No	Poor	No / NA
Keshavarzian, 2007[182]	Yes / Yes / Yes	No	Yes	No	No	Poor	Yes / Yes
Kinney, 2003[162]	Yes / No / Yes	No	Yes	No	No	Poor	UTD / NA
Lees, 2009[145]	No / No / No	No	No	No	No	Poor	Yes / No
Lichtenstein, 2006[131]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	Yes / Yes
Lichtenstein, 2006[131]	No / No / No	Yes	No	Yes	Yes	Poor	Yes / Yes
Marehbian, 2009[168]	No / No / Yes	No	Yes	Yes	No	Poor	Yes / Yes
Mortimore, 2001[174]	No / Yes / Yes	No	Yes	No	No	Poor	UTD / NA
Moss, 2008[148]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	Yes / No
Moss, 2010[147]	No / No / No	No	Yes	No	UTD	Poor	Yes / No
Orlando, 2005[128]	No / Yes / No	No	Yes	No	No	Poor	No / NA
Ricart, 2001[138]	No / Yes / Yes	Yes	Yes	No	No	Poor	Yes / No
Rudolph, 2008[175]	No / Yes / Yes	Yes	Yes	Yes	Yes	Fair	UTD / NA
Rudolph, 2008[175]	No / Yes / Yes	Yes	Yes	Yes	No	Fair	UTD / NA
Schneeweiss, 2009[230]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	Yes / No

Evidence Table 16. Quality of observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Main outcomes / Patient characteristics / Interventions described	Distribution of confounders described	Study groups from same population	Losses to followup accounted for	Adequate adjustment for confounding	Overall study quality*	Pharmaceutical support / Company involvement in design, conduct or reporting
Seiderer, 2004[173]	No / Yes / Yes	No	Yes	No	No	Poor	UTD / NA
Thayu, 2010[199]	Yes / Yes / UTD	Yes	UTD	Yes	Yes	Fair	No / NA
Vermeire, 2007[154]	No / Yes / Yes	No	Yes	Yes	No	Poor	Yes / No
Cohort studies evaluating thiopurines							
Beaugerie, 2009[130]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	Yes / No
Campbell, 2001[146]	No / No / Yes	Yes	UTD	No	No	Poor	UTD
Farrell, 2000[231]	No / No / Yes	No	Yes	No	No	Poor	UTD / NA
Fraser, 2002[232]	No / No / No	Yes	Yes	UTD	UTD	Poor	UTD / NA
Hutfless, 2007[151]	Yes / Yes / Yes	Yes	Yes	UTD	Yes	Good	UTD / NA
Kane, 2008[141]	Yes / No / Yes	Yes	No	No	No	Poor	No / NA
Lees, 2009[144]	Yes / Yes / Yes	Yes	Yes	No	No	Poor	Yes / UTD
Lewis, 2001[136]	Yes / Yes / Yes	Yes	Yes	Yes	No	Poor	Yes / UTD
Lichtenstein, 2006[131]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	Yes / Yes
Lichtenstein, 2006[131]	No / No / No	Yes	No	Yes	Yes	Poor	Yes / Yes
Maher, 2009[176]	Yes / No / No	No	UTD	No	No	Poor	UTD / NA
Marehbian, 2009[168]	No / No / Yes	No	Yes	Yes	No	Poor	Yes / Yes
Schneeweiss, 2009[230]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	Yes / No
Seksik, 2009[155]	No / Yes / Yes	Yes	UTD	Yes	No	Poor	No / NA
Shah, 2008[156]	No / No / Yes	No	Yes	No	No	Poor	No / NA
Tay, 2003[233]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	UTD / NA
Cohort studies evaluating methotrexate							
Thayu, 2010[199]	Yes / Yes / UTD	Yes	UTD	Yes	Yes	Fair	No / NA
Cohort studies evaluating corticosteroids							
Alemzadeh, 2002[200]	Yes / Yes / Yes	No	UTD	UTD	No	Poor	No / NA

Evidence Table 16. Quality of observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Author, year	Main outcomes / Patient characteristics / Interventions described	Distribution of confounders described	Study groups from same population	Losses to followup accounted for	Adequate adjustment for confounding	Overall study quality*	Pharmaceutical support / Company involvement in design, conduct or reporting
Goldstein, 1967[142]	No / No / Yes	No	No	No	No	Poor	UTD / NA
Hutfless, 2007[151]	Yes / Yes / Yes	Yes	Yes	UTD	Yes	Good	UTD / NA
Levine, 2002[198]	Yes / Yes / Yes	Yes	Yes	UTD	Yes	Fair	No / NA
Lewis, 2001[136]	Yes / Yes / Yes	Yes	Yes	Yes	No	Poor	Yes / UTD
Lichtenstein, 2006[131]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	Yes / Yes
Lichtenstein, 2006[131]	No / No / No	Yes	No	Yes	Yes	Poor	Yes / Yes
Saha, 1998[197]	Yes / Yes / Yes	No	Yes	UTD	UTD	Poor	No / NA
Siffledeen, 2007[127]	Yes / Yes / Yes	Yes	Yes	UTD	No	Poor	Yes / UTD
Thayu, 2010[199]	Yes / Yes / UTD	Yes	UTD	Yes	Yes	Fair	No / NA
Cohort studies evaluating 5-aminosalicylate acids							
Hutfless, 2007[151]	Yes / Yes / Yes	Yes	Yes	UTD	Yes	Good	UTD / NA
Lewis, 2001[136]	Yes / Yes / Yes	Yes	Yes	Yes	No	Poor	Yes / UTD

Evidence Table 16. Quality of observational studies reporting on the safety of pharmacologic therapies for the management of moderate to severe Crohn's disease (KQ3)

Case-control studies							
Armstrong, 2010[133]	Yes / Yes / Yes	Yes	Yes	No	Yes	Poor	No / NA
Bernstein, 2003[186]	Yes / Yes / Yes	Yes	No	No	No	Poor	UTD / NA
Gupta, 2006[135]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	No / No
Hutfless, 2008[152]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	No / NA
Lashner, 1992[143]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	UTD / UTD
Lewis, 2001[136]	Yes / Yes / Yes	Yes	Yes	Yes	No	Poor	Yes / UTD
Long, 2010[170]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	No / NA
Tang, 2010[172]	Yes / Yes / Yes	No	No	No	No	Poor	Yes / UTD
Terdiman, 2007[171]	No / No / No	No	UTD	Yes	No	Poor	Yes / UTD
Toruner, 2008[139]	Yes / Yes / Yes	Yes	Yes	Yes	Yes	Good	UTD / NA

Abbreviations: NA = not applicable; UTD = unable to determine

*Overall study quality: *Good indicates all "YES" responses in reporting, selection bias, and confounding domains of questionnaire. Fair indicates mostly "YES" for Reporting and all "YES" for Selection Bias and Confounding bias. Poor indicates at least 1 "NO" or "Unable to determine" for selection or confounding bias.*

Evidence Table 17. Study design characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies to prevent post-operative recurrence in Crohn's disease in terms of patient-reported outcomes (KQ4)

Author, year	Study design1	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Myrelid, 2006[189]	Prospective cohort	Start year: 1989 Median followup duration: 84.7 months	Europe Single center	NA	CD only, previous surgery , previous use of azathioprine or 6-MP, other criteria
Reinisch, 2010[188]	RCT, parallel arms	Start year: 2002 Duration of assigned treatment: 52 weeks	Europe, Asia Multicenter	Yes No	Adults, CD only, previous surgery (resection of terminal ileum and partial colectomy with ileoclonic anastomosis), CDAI (<200), in remission for >1 weeks, no use of antibiotics, TNF-alpha inhibitors, corticosteroids, immunomodulators, NSAIDs other than paracetamol or low-dose aspirin, moderate-severe disease, no short bowel syndrome, smokers and non smokers, other criteria

Abbreviations: 6-MP = 6-mercaptopurine; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; NA = not applicable; NSAID = non-steroidal anti-inflammatory drug; RCT = randomized controlled trial; TNF = tumor necrosis factor

Evidence Table 18. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies to prevent post-operative recurrence in Crohn's disease in terms of patient-reported outcomes (KQ4)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Myrelid, 2006[189]	Azathioprine, 28 Route: Unknown Dose: NR	Male, %: 35.7 Race NR Smoking, % Smoker, 10.7 CD NR	Age at diagnosis NR Disease duration Median: 13 Min: 0 Max: 34 Age at enrollment Median: 34.5 Min: 17 Max: 71	Severity NR Location, % Ileal: 7.1 Ileo-colonic: 71.4 Colonic: 21.4 Perianal: 50 Behavior NR CRP NR	Disease activity index NR	Thiopurines: 100	NR	NR
Myrelid, 2006[189]	azathioprine or 6-MP intolerant group, 14	Male, %: 35.7 Race NR Smoking, % Smoker, 0 CD NR	Age at diagnosis NR Disease duration Median: 12.5 Min: 0 Max: 36 Age at enrollment Median: 38 Min: 19 Max: 64	Severity NR Location, % Ileal: 28.6 Ileo-colonic: 57.1 Colonic: 14.3 Perianal: 42.9 Behavior NR CRP NR	Disease activity index NR	NR	Immunomodulators: 100	NR
Reinisch, 2010[188]	Mesalamine (Salofalk), 37 Route: Oral Dose: 4 g every day	Male, %: 54.1 Race NR Smoking, % Smoker, 54.1 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 36	Severity NR Location NR Behavior, % Inflammatory: 16.2 Stricturing: 40.5 Penetrating: 43.2 CRP NR	CDAI Mean: 102 Median: 93 Min: -10 Max: 204 Screening Rutgeerts score Mean: 2.97 IBDQ Mean: 175.2	NSAIDs: 27	5ASA: 73 TNF-alpha inhibitors: 2.7 Corticosteroids: 78.3 Thiopurines: 21.6 other	NR

Evidence Table 18. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies to prevent post-operative recurrence in Crohn's disease in terms of patient-reported outcomes (KQ4)

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Reinisch, 2010[188]	Azathioprine, 41 Route: Oral Dose: 2.0-2.5 mg/kg every day	Male, %: 58.5 Race NR Smoking, % Smoker, 41.5 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 35.5	Severity NR Location NR Behavior, % Inflammatory: 9.8 Stricturing: 24.4 Penetrating: 65.9 CRP Mean: 0.59	CDAI Mean: 70 Median: 72 Min: -29 Max: 209 Screening Rutgeerts Score Mean: 3.17 IBDQ Mean: 191.2	NSAIDS: 29.3	5ASA: 78 TNF-alpha inhibitors: 4.9 Corticosteroids: 78 Thiopurines: 14.6 other	NR

Abbreviations: 5-ASA = 5-aminosalicylic acid; CD = Crohn's disease; CRP = C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; Max. = maximum; Min. = minimum; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drug; TNF = tumor necrosis factor

Evidence Table 19. Effectiveness of pharmacologic therapies to prevent post-operative recurrence in Crohn's disease in terms of patient-reported outcomes (KQ4)

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Reinisch, 2010[188]	Azathioprine Route: Oral Dose: 2.0-2.5 mg/kg every 1 days	Mesalamine (Salofalk) Route: Oral Dose: 4 g every 1 days	HR QoL (IBDQ) @ 52 weeks	NA Yes	F-B: Mean, 9 (SD, 17.7) G1-G2: -4	F-B: Mean, 5 (SD, 27.4) P: 0.4565 G1-G2: -4
Myrelid, 2006[189]	Azathioprine Route: Unknown Dose: NR	Azathioprine or 6-MP intolerant group	HR QoL (Patients' perceived health assessed by visual analogue scale) @ 21.3 weeks	Active No NA	F: Mean, 65.4 (95% CI, 0 to 99.4)	F: Mean, 55.5 (95% CI, 14.6 to 98.6) P: NS

6-MP = 6-mercaptopurine; AE = adverse events; CI = confidence interval; F-B = change score; g = grams; G1-G2 = change score in group 1 minus the change score in group 2; HR QoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intention-to-treat analysis; mg/kg = milligrams per kilogram; NA = not applicable; NR = not reported; NS = not significant; SD = standard deviation

Evidence Table 20. Quality of randomized controlled trials reporting on the effectiveness of pharmacologic therapies to prevent post-operative recurrence in Crohn's disease in terms of patient-reported outcomes (KQ4)

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Reinisch, 2010[188]	Yes	Yes		Yes	Yes	No	NA	Good

Abbreviations: NA = not applicable

*Study Quality Criteria: Criteria for a judgment of "GOOD" (i.e. low risk of bias): These studies have the least bias and results are considered valid- A study that adheres mostly to the commonly held concepts of high quality including the following: a) A formal randomized controlled study; b)Clear description of the population, setting, interventions, and comparison groups; c) Appropriate measurements of outcomes; d) Appropriate statistical and analytic methods and reporting; e) No reporting errors; f) Low dropout rate; and g) Clear reporting of dropouts. Criteria for a judgment of "FAIR": a) These studies are susceptible to some bias, but it is not sufficient to invalidate the results; b) do not meet all the criteria required for a rating of good qualities because they have some deficiencies, but no flaw is likely to cause major bias; and c) The study may be missing information, making it difficult to assess limitations and potential problems. Criteria for a judgment of "POOR" (i.e. high risk of bias): a) These studies have significant flaws that imply biases of various types that may invalidate the results; b) Have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Evidence Table 21. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for the comparative effectiveness and safety of therapies among pediatrics

Number of Studies (Participants)	Domains Pertaining to Strength of Evidence					Strength of Evidence
	Risk of Bias	Consistency	Directness	Precision	Other concerns	
INDUCTION OF REMISSION						
Combination of a 6-mercaptopurine and prednisone versus prednisone alone						
1[192] (55)	Moderate	NA	Direct	Imprecise		Low
Budesonide versus prednisolone						
1[190] (48)	Low	NA	Direct	Imprecise		Moderate
Prednisone and mesalamine versus budesonide and mesalamine						
1[191] (33)	High	NA	Direct	Imprecise		Low
MAINTAIN REMISSION						
Mesalamine versus placebo						
1[194] (122)	High	NA	Direct	Imprecise		Low
SERIOUS INFECTIONS						
6-Mercaptopurine and prednisone versus prednisone alone						
1[192] (55)	Moderate	NA	Direct	Imprecise		Low
OTHER INFECTIONS						
Prednisone versus budesonide						
1[198] (120)	High	NA	Direct	Imprecise		Low
Budesonide versus prednisolone						
1[190] (48)	Low	NA	Direct	Imprecise		Moderate
Prednisone and mesalamine versus budesonide and mesalamine						
1[191] (33)	High	NA	Direct	Imprecise		Low
HEIGHT CHANGE						
6-mercaptopurine versus placebo						
1[192] (55)	Moderate	NA	Direct	Imprecise		Low
Prednisone versus placebo						
4[196 197 199 200] (277)	High	NA	Direct	Imprecise		Low
Prednisone versus budesonide						
1[198] (120)	High	NA	Direct	Imprecise		Low
WEIGHT CHANGE						
Infliximab versus placebo						
1[199] (78)	High	NA	Direct	Imprecise		Low
Methotrexate versus placebo						
1[199] (78)	High	NA	Direct	Imprecise		Low
Corticosteroids versus placebo						
1[199] (78)	High	NA	Direct	Imprecise		Low
Prednisone versus budesonide						
1[198] (120)	High	NA	Direct	Imprecise		Low

RCT = randomized controlled trial; NA = not applicable, consistency is not applicable when a single study reported comparison and outcome

Evidence Table 21. Number of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for the comparative effectiveness and safety of therapies among pediatrics

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.
N=total N for all studies in each comparison. This is not necessarily the N for analysis because the N for analysis often was not stated for each outcome.

Evidence Table 22. Study design characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Study design1	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Alemzadeh, 2002[200]	Retrospective cohort	Start year: NR Followup duration: NR	Europe Single center	NA	Pediatrics, CD only, other criteria
Beaugerie, 2009[130]	Prospective cohort	Start year: 2004 Median followup duration: 35 months	Europe Multicenter	NA	Pediatrics, adults, IBD, other criteria
Candy, 1995[53]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 weeks	Africa Single center	No	Pediatrics, adults, CD only, no previous surgery (extensive surgery for Crohn's disease), CDAI (>200), not pregnant, not nursing, other criteria
Cezard, 2009[194]	RCT, parallel arms	Start year: 1991 Duration of assigned treatment: 1 years	Europe Multicenter	No	Pediatrics, CD only, HBI (>5), no use of 5-aminosalicylate acids, thiopurines, methotrexate, active disease, other criteria
Crombe, 2011[226] EPIMAD	Retrospective cohort	Start year: 1988 Median followup duration: 32 months	Europe Multicenter	NA	Pediatrics, CD only, previous use of infliximab, other criteria
de Vries, 2008[227]	Other study design	Start year: 1999 Median followup duration: 9 years	Europe Single center	NA	Pediatrics, adults, IBD, no use of infliximab
D'Haens, 2008[48]	RCT, parallel arms	Start year: 2001 Duration of assigned treatment: 2 years	Europe Multicenter	Yes Yes	Pediatrics, adults, CD only, CDAI (>200), no use of corticosteroids, antimetabolites, biological agents, active disease, not pregnant, no obstructive symptoms with strictures, no history of TB, no cancer, other criteria
Escher, 2004[190]	RCT, parallel arms	Start year: 1998 Duration of	Europe Multicenter	No	Pediatrics, CD only, CDAI (>200), no use of corticosteroids, thiopurines, active disease, other criteria

Evidence Table 22. Study design characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Study design1	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
		assigned treatment: 12 weeks			
Griffiths, 1993[221]	RCT, crossover	Start year: 1988 Duration of assigned treatment: 8 weeks	North America Single center	No	Pediatrics, CD only, HBI (>4), other criteria
Issenman, 1993[196]	Prospective cohort	Start year: NR Mean followup duration: 2 years	North America Single center	NA	Pediatrics, CD only, males, active disease
Lees, 2009[145]	Retrospective cohort	Start year: 1999 Median followup duration: 2.4 years	Europe Multicenter	NA	Pediatrics, adults, IBD, not pregnant, other criteria
Levine, 2002[198]	Case-control study	Start year: NR Followup duration: NR	Israel Multicenter	NA	Pediatrics, CD only, PCDAI (12.5-40), no use of thiopurines, mild-moderate disease, other criteria
Levine, 2003[191]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 12 weeks	Israel Multicenter	No	Pediatrics, CD only, no previous surgery (in past 6 weeks), PCDAI (12.5-40), no use of corticosteroids, thiopurines, active disease, other criteria
Malik, 2011[229] Royal Hospital Sick Children	Retrospective cohort	Start year: 2003 Mean followup duration: 12 months	Europe Single center	NA	Pediatrics, CD only, other criteria
Markowitz, 2000[192]	RCT, parallel arms	Start year: NR Duration of assigned treatment: 18 months	US Multicenter	No	Pediatrics, CD only, moderate-severe disease, other criteria

Evidence Table 22. Study design characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Study design1	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
Mate-Jimenez, 2000[52]	RCT, parallel arms	Start year: 1994 Duration of assigned treatment: 26.5 months	Europe Single center	No	Pediatrics, adults, IBD, no previous surgery (extensive surgery), previous use of corticosteroids, not pregnant, not nursing, using adequate contraception, no abscess, other criteria
Present, 1980[60]	RCT, parallel arms, crossover	Start year: NR Duration of assigned treatment: 1 years	US Single center	Yes No	Pediatrics, adults, CD only, active disease, other criteria
Rhodes, 1971[61]	RCT, crossover	Start year: NR Duration of assigned treatment: 2 months	Location: NR Number of centers NR	Yes No	Pediatrics, adults, CD only
Russell, 2011[236]	Prospective cohort	Start year: 2008 Median followup duration: 0.8 years	Europe Multicenter	NA	Pediatrics, IBD, other criteria
Saha, 1998[197]	Prospective cohort	Start year: 1982 Followup duration: NR	Europe Single center	NA	Pediatrics, IBD
Thayu, 2010[199]	Case-control study	Start year: NR Mean followup duration: 43 months	US Single center	NA	Pediatrics, CD only, no use of any medications affecting growth and development, other criteria
Thayu, 2010[237] CHOP	Prospective cohort	Start year: NR	US Single center	NA	Pediatrics, CD only, other criteria
Thomson, 1990[224]	RCT, parallel arms	Start year: NR Duration of assigned	North America, Europe, Africa Multicenter	Yes Yes	Pediatrics, CD only, CDAI (<150), no use of azathioprine, metronidazole, no ostomy, no obstructive symptoms with strictures, other criteria

Evidence Table 22. Study design characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Study design1	Start year of enrollment / Length of followup	Location / Multicenter	Adherence reported / Adherence >80% in each study arm	Inclusion criteria
		treatment: 12 months			
Van Assche, 2008[89]	RCT, parallel arms	Start year: 2004 Duration of assigned treatment: 2 years	Europe Multicenter	No	Pediatrics, adults, CD only, previous use of methotrexate, infliximab, immunosuppressives (azathioprine/6-MP or methotrexate), perianal fistulizing, not pregnant, not nursing, other criteria

Abbreviations: 6-MP = 6-mercaptopurine; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; HBI = Harvey-Bradshaw Index; IBD = irritable bowel disease; PCDAI = Pediatric Crohn's Disease Activity Index; NR = not reported; RCT = randomized controlled trial; TB = tuberculosis; US = United States

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Alemzadeh, 2002[200]	Placebo, 108	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Alemzadeh, 2002[200]	Corticosteroid, 27	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Beaugerie, 2009[130]	Never user thiopurine, 10810 Dose: NA	Male, %: 47 Race NR Smoking NR CD, %: 48	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 42.3	Severity NR Location, % Ileal: 33.3 Colonic: 30.5 Perianal: 7.3 Behavior NR CRP NR	Disease activity index NR	TNF-alpha inhibitors: 0.6 Methotrexate: 0.4 Cyclosporin, mycophenolate mofetil, or cyclophosamide: 0.6	TNF-alpha inhibitors: 0.9 Methotrexate: 0.6	NR
Beaugerie, 2009[130]	Thiopurine, 8676 Dose: NR	Male, %: 43 Race NR Smoking NR CD, %: 76.1	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location, % Ileal: 53.3 Colonic: 59.3 Perianal: 24.5 Behavior NR CRP NR	Disease activity index NR	TNF-alpha inhibitors: 10 Methotrexate: 7.5 Cyclosporin, mycophenolate mofetil, or cyclophosamide: 1.6	TNF-alpha inhibitors: 21.3 Methotrexate: 15.3	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Candy, 1995[53]	Azathioprine + Prednisolone, 33 Route: Oral + Oral Dose: 2.5 mg/kg every day + 1 mg/kg every day	Male, %: 21 Race NR Smoking, % Smoker, 67 CD NR	Age at diagnosis NR Disease duration Median: 2.6 Min: 0.1 Max: 19.3 Age at enrollment Median: 33.9 Min: 15 Max: 60	Severity, % Severe disease: 52 Location, % Ileal: 24.2 Ileo-colonic: 60.6 Colonic: 15.2 Behavior NR CRP Median: 5.4 Min: 2.9 Max: 7.3	CDAI Median: 301 Min: 264 Max: 358	Corticosteroids: 100 Thiopurines: 100	corticosteroids in previous 6-12 mo: 67 no previous corticosteroids: 15 : 15	NR
Candy, 1995[53]	Placebo + Prednisolone, 30 Route: Oral + Oral Dose: NA + 1 mg/kg every day	Male, %: 37 Race NR Smoking, % Smoker, 67 CD NR	Age at diagnosis NR Disease duration Median: 3.7 Min: 0.1 Max: 18.7 Age at enrollment Median: 31.8 Min: 21 Max: 62	Severity, % Severe disease: 43 Location, % Ileal: 20 Ileo-colonic: 63.3 Colonic: 16.7 Behavior NR CRP Median: 3.9 Min: 2.8 Max: 5.3	CDAI Median: 282 Min: 240 Max: 356	Corticosteroids: 100	Corticosteroids corticosteroids in the last 6 months: 63 no previous corticosteroids: 7 : 7	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Cezard, 2009[194]	Placebo, 62	Male, %: 58 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 0.6 Age at enrollment Mean: 11.6	Severity NR Location, % Ileal: 11 Ileo-colonic: 69 Colonic: 19 Perianal: 31 Behavior NR CRP NR	HBI Mean: 0.9	NR	NR	NR
Cezard, 2009[194]	Mesalamine (Pentasa), 60 Dose: 50 mg/kg every day	Male, %: 62 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 1.1 Age at enrollment Mean: 12	Severity NR Location, % Ileal: 13 Ileo-colonic: 68 Colonic: 18 Perianal: 33 Behavior NR CRP NR	HBI Mean: 0.7	NR	NR	NR
Crombe, 2011[226] EPIMAD	Infliximab + immunomodulator, 103 Route: Unknown + Unknown Dose: 5 mg/kg every 8 weeks + NR	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	5ASA Corticosteroids	NR	NR
Crombe, 2011[226] EPIMAD	Infliximab + no IMM, 17 Route: Unknown Dose: NA	Gender NR Race NR Smoking NR CD, %: 100	NR	NR	Disease activity index NR	5ASA Corticosteroids	NR	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
de Vries, 2008[227]	Infliximab + Immunomodulator, 93	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
de Vries, 2008[227]	Infliximab + No corticosteroids, 45	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Immunomodulators	NR	NR
de Vries, 2008[227]	Infliximab + No immunomodulator, 54	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Corticosteroids	NR	NR
de Vries, 2008[227]	Infliximab + Corticosteroid, 102	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	Immunomodulators	NR	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
D'Haens, 2008[48]	Budesonide + (6)-Methylprednisolone, 64 Route: Oral + Oral Dose: 9 mg every days + 32 mg every day	Male, %: 42.2 Race, % W: 95.3 Smoking, % Current smoker, 35.9 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 28.7	Severity NR Location, % Ileo-colonic: 43.8 Colonic: 32.8 Behavior NR CRP Median: 25	CDAI Mean: 306 IBDQ Mean: 136	TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines Budesonide	5ASA: 3.1	NR
D'Haens, 2008[48]	Infliximab + Azathioprine, 65 Route: IV + Oral Dose: 5 mg/kg + 2-2.5 mg/kg	Male, %: 33.8 Race, % W: 98.5 Smoking, % Current smoker, 43.1 CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 30	Severity NR Location, % Ileo-colonic: 47.7 Colonic: 30.8 Behavior NR CRP Median: 19	CDAI Mean: 330 IBDQ Mean: 122	TNF-alpha inhibitors: 100 Methotrexate Azathioprine: 100 Methylprednisolone	5ASA: 4.6	NR
Escher, 2004[190]	Prednisolone, 26 Dose: 1 mg/kg every day	Male, %: 69.2 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 0.8 Age at enrollment Mean: 13	Severity NR Location, % Ileal: 26.9 Ileo-colonic: 65.4 Colonic: 3.8 Behavior NR CRP NR	CDAI Mean: 268 PCDAI Mean: 45	NR	NR	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Escher, 2004[190]	Budesonide, 22 Dose: 9 mg every day	Male, %: 31.8 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 0.6 Age at enrollment Mean: 13	Severity NR Location, % Ileal: 59.1 Ileo-colonic: 31.8 Colonic: 9.1 Behavior NR CRP NR	CDAI Mean: 239 PCDAI Mean: 39	NR	NR	NR
Griffiths, 1993[221]	Mesalamine (Pentasa), 7 Route: Oral Dose: 50 mg/kg every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 188.3 HBI Mean: 3.71	NR	NR	NR
Griffiths, 1993[221]	Placebo, 6 Route: Oral Dose: NA every day	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 182.5 HBI Mean: 3.5	NR	NR	NR
Issenman, 1993[196]	Discontinued corticosteroids, 8	Male, %: 100 Race NR Smoking NR CD, %: 212.5	Age at diagnosis Mean: 13.2 Disease duration NR Age at enrollment Mean: 13.2	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Issenman, 1993[196]	Prednisone, 9 Route: Oral Dose: 2 mg/kg every days	Male, %: 100 Race NR Smoking NR CD NR	Age at diagnosis Mean: 14.5 Disease duration NR Age at enrollment Mean: 14.5	Severity NR Location NR Behavior NR CRP NR	CDAI Mean: 64.1	Corticosteroids: 100	5ASA	NR
Lees, 2009[145]	Adalimumab, 30	Male, %: 36.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Median: 32.3	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lees, 2009[145]	Infliximab + Azathioprine, 51 Route: IV Dose: NR + NR	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lees, 2009[145]	Infliximab + Corticosteroid, 32 Route: IV + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Lees, 2009[145]	Infliximab + Azathioprine/6-MP/methotrexate + corticosteroids, 55 Route: IV + Unknown Dose: NR + NR	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Lees, 2009[145]	Infliximab + Never user concomitant azathioprine/6-MP/methotrexate /corticosteroids, 19 Route: IV Dose: NR	Gender NR Race NR Smoking NR CD, %: 100	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Levine, 2002[198]	Budesonide, 62 Dose: 9 mg every day	Male, %: 59.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 14.1	Severity NR Location NR Behavior NR CRP NR	PCDAI Mean: 25.8	NR	immunomodulators: 29	NR
Levine, 2002[198]	Prednisone, 58 Dose: 40 mg every day	Male, %: 60.3 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13.7	Severity NR Location NR Behavior NR CRP NR	PCDAI Mean: 29.6	NR	immunomodulators: 20.6	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Levine, 2003[191]	Prednisone + Mesalamine, 14 Dose: 40 mg every day + 3-4 g every day	Male, %: 50 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 14.15	Severity NR Location NR Behavior NR CRP NR	PCDAI Mean: 28.9	NR	NR	NR
Levine, 2003[191]	Budesonide + Mesalamine, 19 Dose: 3 mg every 8 hours + 3-4 g every day	Male, %: 68.4 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13.8	Severity NR Location NR Behavior NR CRP NR	PCDAI Mean: 29.3	NR	NR	NR
Malik, 2011[229] Royal Hospital Sick Children	Infliximab + no steroid, 13 Route: IV Dose: 5 mg/kg every 2 weeks	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	Methotrexate	NR	NR
Malik, 2011[229] Royal Hospital Sick Children	Infliximab + Methotrexate, 21	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	Corticosteroids	NR	NR
Malik, 2011[229] Royal Hospital Sick Children	Infliximab + no MTX, 7	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	Corticosteroids	NR	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Malik, 2011[229] Royal Hospital Sick Children	Infliximab + steroid, 15	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	Methotrexate	NR	NR
Markowitz, 2000[192]	6-MP + Prednisone, 27 Dose: 1.5 mg/kg every day + 40 mg every day	Male, %: 55.6 Race, % W: 93 Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13	Severity NR Location, % Ileal: 14.8 Ileo-colonic: 70.4 Colonic: 14.8 Behavior NR CRP NR	PCDAI Mean: 46.7 HBI Mean: 7.7 partial HB Mean: 6.6	NR	NR	NR
Markowitz, 2000[192]	Placebo + Prednisone, 28 Dose: 40 mg every day	Male, %: 64.3 Race, % W: 93 Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment Mean: 13.4	Severity NR Location, % Ileal: 3.6 Ileo-colonic: 78.6 Colonic: 17.9 Behavior NR CRP NR	PCDAI Mean: 44.7 HBI Mean: 7.4 partial HB Mean: 6.5	NR	NR	NR
Mate-Jimenez, 2000[52]	6-MP, 16 Route: Oral Dose: 1.5 mg/kg every day	Gender NR Race NR Smoking, % Smoker, 75 CD NR	Age at diagnosis NR Disease duration Mean: 4.5 Age at enrollment NR	Severity NR Location, % Colonic: 37.5 Perianal: 25 Behavior NR CRP NR	CDAI Mean: 191	Corticosteroids: 100	NR	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Mate-Jimenez, 2000[52]	Methotrexate, 15 Route: Oral Dose: 15 mg every 1 week	Gender NR Race NR Smoking, % Smoker, 66.7 CD NR	Age at diagnosis NR Disease duration Mean: 4.3 Age at enrollment NR	Severity NR Location, % Colonic: 40 Perianal: 20 Behavior NR CRP NR	CDAI Mean: 200	Corticosteroids: 100	NR	NR
Mate-Jimenez, 2000[52]	5-ASA, 7 Route: Oral Dose: 3 g every day	Gender NR Race NR Smoking, % Smoker, 85.7 CD NR	Age at diagnosis NR Disease duration Mean: 3.5 Age at enrollment NR	Severity NR Location, % Colonic: 14.3 Perianal: 14.3 Behavior NR CRP NR	CDAI Mean: 215	Corticosteroids: 100	NR	NR
Present, 1980[60]	6-MP Route: Unknown Dose: 1.5 mg/kg every 24 hours	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Present, 1980[60]	Placebo Route: Oral Dose: NA	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Rhodes, 1971[61]	Azathioprine, 16 Route: Oral Dose: 4 mg/kg every 24 hours	Male, %: 75 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Min: 1 Max: 14 Age at enrollment Min: 14 Max: 69	Severity NR Location, % Ileal: 50 Ileo-colonic: 37.5 Colonic: 12.5 Behavior NR CRP NR	Disease activity index NR	Sulfasalazine: 18.8 Prednisolone: 18.8	NR	NR
Rhodes, 1971[61]	Placebo, 16 Route: Oral Dose: NA	Male, %: 75 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Min: 1 Max: 16 Age at enrollment Min: 14 Max: 69	Severity NR Location, % Ileal: 50 Ileo-colonic: 37.5 Colonic: 12.5 Behavior NR CRP NR	Disease activity index NR	Corticosteroids: 18.8 Sulfasalazine: 18.8	NR	NR
Russell, 2011[236]	Adalimumab + no IMM (Thio or MTX) +/- steroid, 24 Route: Unknown + Unknown Dose: 40 mg every 15 days + NR	Gender NR Race NR Smoking NR CD, %: 283.3	NR	NR	Disease activity index NR	Corticosteroids	TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines Immunomodulators	NR
Russell, 2011[236]	Adalimumab + IMM (Thio or MTX) +/- steroid, 46 Route: Unknown + Unknown Dose: NR	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	Corticosteroids	TNF-alpha inhibitors Corticosteroids Methotrexate Thiopurines Immunomodulators	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Saha, 1998[197]	Placebo	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Saha, 1998[197]	Prednisone	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Thayu, 2010[199]	Infliximab	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR
Thayu, 2010[199]	Placebo	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %	
Thayu, 2010[199]	Corticosteroid	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR	
Thayu, 2010[199]	Methotrexate	Gender NR Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration NR Age at enrollment NR	Severity NR Location NR Behavior NR CRP NR	Disease activity index NR	NR	NR	NR	
Thayu, 2010[237] CHOP	Corticosteroid	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	Corticosteroids: 100	NR	NR	30
Thayu, 2010[237] CHOP	No infliximab	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	NR	NR	NR	30
Thayu, 2010[237] CHOP	No MTX	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	NR	NR	NR	30

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %	
Thayu, 2010[237] CHOP	Infliximab	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	infliximab: 100	NR	NR	30
Thayu, 2010[237] CHOP	Methotrexate	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	Methotrexate: 100	NR	NR	30
Thayu, 2010[237] CHOP	No steroids	Gender NR Race NR Smoking NR CD NR	NR	NR	Disease activity index NR	NR	NR	NR	30
Thomson, 1990[224]	Placebo, 105 Route: Oral Dose: NA every 8 hours	Male, %: 45.7 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 5.3 Age at enrollment Mean: 37.4	NR	CDAI Mean: 60.1	NR	sulphasalazine: 16.2	NR	2
Thomson, 1990[224]	5-ASA, 101 Dose: 500 mg every 8 hours	Male, %: 42.6 Race NR Smoking NR CD NR	Age at diagnosis NR Disease duration Mean: 6 Age at enrollment Mean: 34.1	NR	CDAI Mean: 51.8	NR	sulphasalazine: 15.8	NR	2

Evidence Table 23. Population characteristics of randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Intervention, n	Demographics	Age, in years	Disease characteristics	Disease activity index	Medications taken during study, %	Medications taken BEFORE study, %	Medications taken FOR INDUCTION, %
Van Assche, 2008[89]	Infliximab, 40 Route: IV Dose: 5 mg/kg every 8 weeks	Male, %: 47.5 Race NR Smoking, % Smoker, 47.5 CD NR	Age at diagnosis NR Disease duration Median: 9 Min: 2 Max: 25 Age at enrollment Mean: 35.4	Severity NR Location, % Colonic: 12.5 Behavior NR CRP Median: 3.2	CDAI Mean: 138.1	TNF-alpha inhibitors: 100	TNF-alpha inhibitors: 100 Methotrexate Thiopurines	NR
Van Assche, 2008[89]	Infliximab + Immunomodulator, 40 Route: IV + Oral Dose: 5 mg/kg every 8 weeks + see below	Male, %: 42.5 Race NR Smoking, % Smoker, 45 CD NR	Age at diagnosis NR Disease duration Median: 9 Min: 1 Max: 36 Age at enrollment Mean: 35.6	Severity NR Location, % Colonic: 32.5 Behavior NR CRP Median: 3.4	CDAI Mean: 137.6	TNF-alpha inhibitors: 100 Methotrexate Thiopurines	TNF-alpha inhibitors: 100 Methotrexate Thiopurines	NR

Abbreviations: 5ASA = 5-aminosalicylic acid; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; g = gram; HBI = Harvey-Bradshaw Index; Max. = maximum; Min. = minimum; NA = not applicable; NR = not reported; TNF = tumor necrosis factor

Evidence Table 24. Outcomes from randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Thayu, 2010[199]	Infliximab	Placebo	Weight (Fat mass - height z score)	NA NA	Beta-coefficient, 0.29 (95% CI, 0.06 to 0.52)	P: <0.05
Thayu, 2010[199]	Infliximab	Placebo	Weight (lean mass - height z score)	Active Yes NA	Beta-coefficient, 0.30 (95% CI, 0.02 to 0.58)	P: <0.05
Thayu, 2010[199]	Corticosteroid	Placebo	Weight (Fat mass - height z score)	Active Yes NA	Beta-coefficient, 0.69 (95% CI, 0.12 to 1.26)	P: <0.05
Thayu, 2010[199]	Methotrexate	Placebo	Weight (Fat mass - height z score)	Active Yes NA	Beta-coefficient, 0.30 (95% CI, 0.04 to 0.56)	P: <0.05
Cezard, 2009[194]	Mesalamine (Pentasa) Dose: 50 mg/kg every 1 day	Placebo	HBI (Relapse rate: HBI >5)	Active No NR	Incidence 29 / 60 (57%)	Incidence 35 / 62 (63%)
Escher, 2004[190]	Prednisolone Dose: 1 mg/kg every 1 day	Budesonide Dose: 9 mg every 1 day	CDAI (Absolute CDAI) @ 8 weeks	NA Yes	G1-G2: Mean, 97	G1-G2: Mean, 149; P: 0.047
Escher, 2004[190]	Prednisolone Dose: 1 mg/kg every 1 day	Budesonide Dose: 9 mg every 1 day	CDAI (Absolute CDAI) @ 4 weeks	NA Yes		P: 0.034
Escher, 2004[190]	Prednisolone Dose: 1 mg/kg every 1 day	Budesonide Dose: 9 mg every 1 day	CDAI (Remission: CDAI < 150) @ 8 weeks	NA Yes	Incidence 17 / 24 (71%)	Incidence 12 / 22 (55%); P: 0.25
Escher, 2004[190]	Prednisolone Dose: 1 mg/kg every 1 day	Budesonide Dose: 9 mg every 1 day	Other infections (pharyngitis)	Active Yes Yes	Incidence 1 / 26 (4%)	Incidence 2 / 22 (9%)
Levine, 2003[191]	Prednisone + mesalamine Dose: 40 mg every 1 day + 3-4 g every 1 day	Budesonide + mesalamine Dose: 3 mg every 8 hours + 3-4 g every 1 day	Other infections (herpetic skin infection)	Active Yes Yes	Incidence 1 / 14 (7%)	Incidence 0 / 19 (0%)
Levine, 2003[191]	Prednisone + mesalamine Dose: 40 mg every 1 day + 3-4 g every 1 day	Budesonide + mesalamine Dose: 3 mg every 8 hours + 3-4 g every 1 day	PCDAI (Remission definition: PCDAI <10) @ 4 weeks	NA Yes	Incidence 8 / 14 (57%)	Incidence 9 / 19 (47%)
Levine, 2003[191]	Prednisone + mesalamine Dose: 40 mg every 1 day + 3-4 g every 1 day	Budesonide + mesalamine Dose: 3 mg every 8 hours + 3-4 g every 1 day	PCDAI (Remission definition: PCDAI <10) @ 8 weeks	NA Yes	Incidence 6 / 14 (43%)	Incidence 8 / 19 (42%)
Levine, 2003[191]	Prednisone + Mesalamine Dose: 40 mg every 1 days + 3-4 g every 1 day	Budesonide + Mesalamine Dose: 3 mg every 8 hours + 3-4 g every 1 day	PCDAI (Remission definition: PCDAI <10) @ 12 weeks	NA Yes	Incidence 7 / 14 (50%)	Incidence 9 / 19 (47%)

Evidence Table 24. Outcomes from randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Alemzadeh, 2002[200]	Corticosteroid	Placebo	Height (not specified)	Active Yes NA		P: 0.007
Alemzadeh, 2002[200]	Corticosteroid	Placebo	Height (not specified)	Active Yes NA		P: 0.005
Levine, 2002[198]	Prednisone Dose: 40 mg every 1 day	Budesonide Dose: 9 mg every 1 day	Height (post-remission linear growth in percentiles) @ 24 weeks	NR No NA	G1-G2: -2.35	G1-G2: 0.25; P: 0.1
Levine, 2002[198]	Prednisone Dose: 40 mg every 1 day	Budesonide Dose: 9 mg every 1 day	Other infections (herpetic infections)	NR No NA	Incidence 2 / 58 (3%)	Incidence 0 / 62 (0%)
Levine, 2002[198]	Prednisone Dose: 40 mg every 1 day	Budesonide Dose: 9 mg every 1 day	Weight (weight gain in kg) @ 8 weeks	NR No NA	G1-G2: Mean, 4.6	G1-G2: Mean, 2.54; P: <0.01
Markowitz, 2000[192]	6-MP + prednisone Dose: 1.5 mg/kg every 1 days+ 40 mg every 1 day	Placebo + prednisone Dose: 40 mg every 1 day	HBI (Remission definition: <3) @ 4 weeks	NA Yes	Incidence 25 / 27 (93%)	Incidence 22 / 28 (79%)
Markowitz, 2000[192]	6-MP + prednisone Dose: 1.5 mg/kg every 1 day + 40 mg every 1 day	Placebo + prednisone Dose: 40 mg every 1 day	HBI (Remission definition: HBI< 3)	NA Yes	Incidence 24 / 27 (89%)	Incidence 25 / 28 (89%)
Markowitz, 2000[192]	6-MP + prednisone Dose: 1.5 mg/kg every 1 day + 40 mg every 1 day	Placebo + prednisone Dose: 40 mg every 1 day	HBI (Relapse rate definition: HBI ≥ 4) @ 24 weeks	NA Yes	Incidence (4%)	Incidence (28%)
Markowitz, 2000[192]	6-MP + prednisone Dose: 1.5 mg/kg every 1 day + 40 mg every 1 day	Placebo + prednisone Dose: 40 mg every 1 day	HBI (Relapse rate definition: HBI ≥ 4)	NA Yes	Incidence (9%)	Incidence (47%) P: 0.007
Markowitz, 2000[192]	6-MP + prednisone Dose: 1.5 mg/kg every 1 day + 40 mg every 1 day	Placebo + prednisone Dose: 40 mg every 1 day	Height (linear growth (cm)) @ 24 weeks	Active Yes Yes	G1-G2: 3.4 (2.9)	G1-G2: 1.9 (2.4); P: 0.06
Markowitz, 2000[192]	6-MP + prednisone Dose: 1.5 mg/kg every 1 day + 40 mg every 1 day	Placebo + prednisone Dose: 40 mg every 1 day	Height (linear growth (cm)) @ 78 weeks	Active Yes Yes	G1-G2: 6.8 (4.1)	G1-G2: 5.3 (4); P: 0.3
Markowitz, 2000[192]	6-MP + prednisone Dose: 1.5 mg/kg every 1 day + 40 mg every 1 day	Placebo + prednisone Dose: 40 mg every 1 day	Need for surgery (not specified) @ 78 weeks	NA Yes	Incidence 1 / 27 (4%)	Incidence 3 / 28 (11%); P: 0.63

Evidence Table 24. Outcomes from randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Saha, 1998[197]	Prednisone	Placebo	Height (height standard deviation score) @ 208 weeks	Active Yes NA	F-B: Mean, 0	F-B: Mean, 0.13
Saha, 1998[197]	Prednisone	Placebo	Height (height standard deviation score) @ 156 weeks	Active Yes NA	F-B: Mean, -0.1	F-B: Mean, -0.09
Saha, 1998[197]	Prednisone	Placebo	Height (height standard deviation score)	Active Yes NA	F-B: Mean, -0.47	F-B: Mean, -0.31
Saha, 1998[197]	Prednisone	Placebo	Height (height standard deviation score) @ 104 weeks	Active Yes NA	F-B: Mean, -0.24	F-B: Mean, -0.13
Issenman, 1993[196]	Discontinued corticosteroids	Prednisone Route: Oral Dose: 2 mg/kg every 1 day	Height (cm) @ 104 weeks	Active No NA	B: Mean, 155.8 (SD, 19.1) F-B: Mean, 10.3 (SD, 6) G1-G2: -1.2	B: Mean, 159.5 (SD, 13.4) F-B: Mean, 9.1 (SD, 4.6)
Issenman, 1993[196]	Discontinued corticosteroids	Prednisone Route: Oral Dose: 2 mg/kg every 1 day	Height (height velocity >10% (cm/ 2 years)) @ 104 weeks	Active No NA	Incidence 6 / 8 (75%)	Incidence 9 / 9 (100%)
Griffiths, 1993[221]	Mesalamine (Pentasa) Route: Oral Dose: 50 mg/kg every 1 day	Placebo Route: Oral Dose: NA every 1 day	CDAI (Absolute CDAI) @ 8 weeks	NA Yes	B: Mean, 188.3 (SE, 20.9) F: Mean, 152.3 (SE, 31.4) F-B: Mean, -36 (SE, 38.1) G1-G2: 112	B: Mean, 182.5 (SE, 21.6) F: Mean, 258.4 (SE, 49.4) F-B: Mean, 76 (SE, 38)
Griffiths, 1993[221]	Mesalamine (Pentasa) Route: Oral Dose: 50 mg/kg every 1 day	Placebo Route: Oral Dose: NA every 1 day	CDAI (Response: 50-pt drop in CDAI) @ 8 weeks	NA Yes	Incidence 3 / 7 (43%)	Incidence 0 / 6 (0%)
Griffiths, 1993[221]	Mesalamine (Pentasa) Route: Oral Dose: 50 mg/kg every 1 day	Placebo Route: Oral Dose: NA every 1 day	HBI (Absolute HBI) @ 8 weeks	NA Yes	B: Mean, 3.71 (SE, 0.61) F: Mean, 3.43 (SE, 1.21) F-B: Mean, -0.29 (SE, 1.36) G1-G2: 3.5	B: Mean, 3.5 (SE, 0.99) F: Mean, 6.67 (SE, 1.82) F-B: Mean, 3.17 (SE, 1.62)
Griffiths, 1993[221]	Mesalamine (Pentasa) Route: Oral Dose: 50 mg/kg every 1 day	Placebo Route: Oral Dose: NA every 1 day	HBI (Response: significant decrease in HBI) @ 8 weeks	NA Yes	Incidence 3 / 7 (43%)	Incidence 0 / 6 (0%)

Evidence Table 24. Outcomes from randomized controlled trials and observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Group1	Group2	Outcome (definition)	AE collection / ITT	Results, Group 1	Results, Group 2
Griffiths, 1993[221]	Mesalamine (Pentasa) Route: Oral Dose: 50 mg/kg every 1 day	Placebo Route: Oral Dose: NA every 1 day	Lloyd-Still index (Response: Lloyd-Still improvement) @ 8 weeks	NA NA	Incidence 4 / 7 (57%)	Incidence 2 / 6 (33%)
Griffiths, 1993[221]	Mesalamine (Pentasa) Route: Oral Dose: 50 mg/kg every 1 day	Placebo Route: Oral Dose: NA every 1 day	Lloyd-Still index (absolute score) @ 8 weeks	NA Yes	B: Mean, 71.1 (SE, 4.72) F: Mean, 75 (SE, 4.45) F-B: Mean, 3.86 (SE, 3.69) G1-G2: -8.7	B: Mean, 75.2 (SE, 4.93) F: Mean, 70.4 (SE, 2.36) F-B: Mean, -4.8 (SE, 4.47) G1-G2: -8.7 P: 0.171
Griffiths, 1993[221]	Mesalamine (Pentasa) Route: Oral Dose: 50 mg/kg every 1 day	Placebo Route: Oral Dose: NA every 1 day	van Hees index (absolute score) @ 8 weeks	NA Yes	B: Mean, 175.1 (SE, 6.8) F: Mean, 175.7 (SE, 12.3) F-B: Mean, 0.6 (SE, 17.4) G1-G2: 5.3	B: Mean, 171.4 (SE, 13.1) F: Mean, 177.3 (SE, 10.1) F-B: Mean, 5.86 (SE, 10.4) G1-G2: 5.3 P: 0.475
Griffiths, 1993[221]	Mesalamine (Pentasa) Route: Oral Dose: 50 mg/kg every 1 day	Placebo Route: Oral Dose: NA every 1 days	van Hees index (Response: significant decrease in van Hees index) @ 8 weeks	NA Yes	Incidence 4 / 7 (57%)	Incidence 1 / 6 (17%)

AE = adverse events; B = baseline value; CDAI = Crohn's Disease Activity Index; CI = confidence interval; cm = centimeter; F = final values; F-B = change score; g = grams; G1-G2 = change score in group 1 minus the change score in group 2; HBI = Harvey-Bradshaw Index; ITT = intention-to-treat analysis; mg = milligrams; mg/kg = milligrams per kilogram; NA = not applicable; NR = not reported; PCDAI = Pediatric Crohn's Disease Activity Index; pt = point; SD = standard deviation; SE = standard error

Evidence Table 25. Quality of randomized controlled trials reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

Author, year	Allocation sequence adequate	Allocation concealment adequate	Blinding	Incomplete outcome data	Other potential threats	Pharmaceutical support	Company involvement in design, conduct or reporting	Overall study quality*
Cezard, 2009[194]	Yes	Yes	Yes	Unclear	Yes	No	NA	Fair
Escher, 2004[190]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Griffiths, 1993[221]	Yes	Unclear	Yes	No	Yes	Yes	UTD	Fair
Levine, 2003[191]	Unclear	Unclear	Unclear	Unclear	Unclear	UTD	NA	Poor
Markowitz, 2000[192]	Yes	Yes	Yes	Yes	Yes	No	NA	Good

Abbreviations: NA = not applicable; UTD = unable to determine

*Study Quality Criteria: Criteria for a judgment of "GOOD" (i.e. low risk of bias): These studies have the least bias and results are considered valid- A study that adheres mostly to the commonly held concepts of high quality including the following: a) A formal randomized controlled study; b)Clear description of the population, setting, interventions, and comparison groups; c) Appropriate measurements of outcomes; d) Appropriate statistical and analytic methods and reporting; e) No reporting errors; f) Low dropout rate; and g) Clear reporting of dropouts. Criteria for a judgment of "FAIR": a) These studies are susceptible to some bias, but it is not sufficient to invalidate the results; b) do not meet all the criteria required for a rating of good qualities because they have some deficiencies, but no flaw is likely to cause major bias; and c) The study may be missing information, making it difficult to assess limitations and potential problems. Criteria for a judgment of "POOR" (i.e. high risk of bias): a) These studies have significant flaws that imply biases of various types that may invalidate the results; b) Have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Evidence Table 26. Quality of observational studies reporting on the effectiveness of pharmacologic therapies for the management of moderate to severe Crohn's disease in children

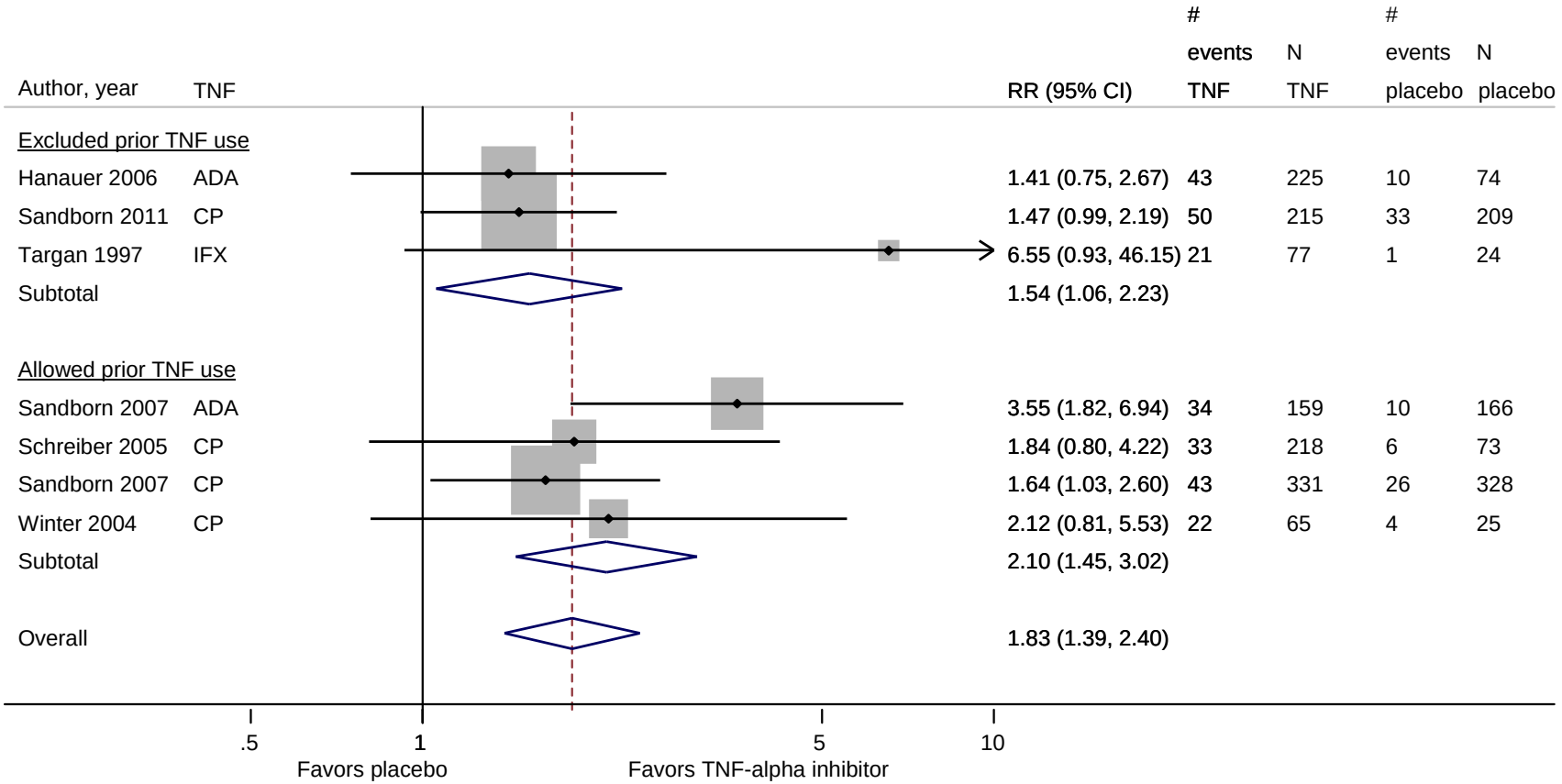
Author, year	Main outcomes / Patient characteristics / Interventions described	Distribution of confounders described	Study groups from same population	Losses to followup accounted for	Adequate adjustment for confounding	Overall study quality*	Pharmaceutical support / Company involvement in design, conduct or reporting
Alemzadeh, 2002[200]	Yes / Yes / Yes	No	UTD	UTD	No	Poor	No / NA
Levine, 2002[198]	Yes / Yes / Yes	Yes	Yes	UTD	Yes	Fair	No / NA
Saha, 1998[197]	Yes / Yes / Yes	No	Yes	UTD	UTD	Poor	No / NA
Thayu, 2010[199]	Yes / Yes / UTD	Yes	UTD	Yes	Yes	Fair	No / NA

Abbreviations: NA = not applicable; UTD = unable to determine

**Overall study quality: Good indicates all "YES" responses in reporting, selection bias, and confounding domains of questionnaire. Fair indicates mostly "YES" for Reporting and all "YES" for Selection Bias and Confounding bias. Poor indicates at least 1 "NO" or "Unable to determine" for selection or confounding bias.*

Appendix E. Additional Meta-Analyses

Figure 1. Pooled relative risk of remission* at week 2 comparing a TNF-alpha inhibitor with placebo by trials that allowed and did not allow prior TNF-alpha inhibitor use



Pooled Relative Risk and 95% Confidence Intervals of Remission at Week 2

ADA = adalimumab; CI = confidence interval; CP = certolizumab pegol; IFX = infliximab; RR = relative risk; TNF = tumor necrosis factor-alpha inhibitor

* In all trials, remission was defined as a Crohn's Disease Activity Index less than 150.

Boxes indicate individual trial point estimates. The box size denotes the weight of the trial, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each trial. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q = 2.22 with 2 degrees of freedom (p = 0.33); Q = 3.54 with 3 degrees of freedom (p = 0.32); Q = 7.41 with 6 degrees of freedom (p = 0.29)

I-squared statistic = 10%; 15%; 19%

Appendix F. Summary of Studies Comparing the Safety of Pharmacologic Therapies Among Patients With Inflammatory Bowel Disease

(reference list located in full report)

Mortality

Infliximab Versus No Infliximab

One retrospective study of inflammatory bowel disease patients (80 percent Crohn's disease) compared 743 users of infliximab followed a median of 5 years to 666 never users of a biologic followed a median of 12 years.[153] Safety was assessed using chart review and physician and patient contact. Two percent mortality was observed in both groups and an OR was provided (OR, 0.8; 95% CI, 0.3 to 1.8), although concomitant medications, disease severity, or other demographic or disease characteristics may not have been accounted for in the analysis. One of these deaths was from progressive multifocal leukoencephalopathy (PML), which is described in further detail in the PML section of the main report.[33 167] This study[153] may have underestimated the relative risk of cancer and death among patients treated with infliximab because of a flaw known as immortal time bias resulting from differential exclusion of followup time in the study groups.[238]

Combination of Infliximab and Immunomodulators Versus Infliximab

Two single center studies of 221 patients (92 percent[173] and 81 percent[129] Crohn's disease) reported mortality in inflammatory bowel disease patients for the combination of infliximab and thiopurines versus infliximab.[129 173] Concomitant medications were reported at the time of the first infliximab infusion. No deaths were reported in either study.

Combination of Infliximab and Corticosteroids Versus Infliximab

The same center reported no deaths among 42 users of infliximab and corticosteroids users or among 58 users of infliximab without corticosteroids.[173]

Thiopurines Versus No Thiopurines

A prospective study included 19,846 inflammatory bowel disease patients (60 percent Crohn's disease) seen by 817 adult and pediatric gastroenterologists in France.[130] One percent mortality was observed in thiopurine users and never users followed for up to three years (Peto OR, 1.2; 95% CI, 0.9 to 1.6). The study also reported mortality among those receiving a thiopurine at study entry (46 deaths, <1 percent), discontinuing a thiopurine prior to study entry (45 deaths, 2 percent), or never receiving thiopurines (95 deaths, <1 percent). The study reported a *p-value* less than 0.0006 for a difference in the comparison between these three groups.

Corticosteroids Versus No Corticosteroids

One retrospective cohort of 554 inflammatory bowel disease patients evaluated mortality in users and non-users of corticosteroids or corticotrophin using a chart review of patients seen at the study center between 1946 and 1965.[142] Suicide was recorded in four of 430 corticosteroid users compared with zero of 124 non-users.

Lymphoma

Infliximab Versus Never User of Biologics

One retrospective study including 1,409 inflammatory bowel disease patients aimed to evaluate the long term safety of infliximab at their center.[153] The study compared 743 infliximab users followed for 5 years with 666 never users of a biologic followed for 12 years. Two lymphoma cases were reported among infliximab users and three lymphoma cases in never users of biologics corresponding to less than 1 percent lymphoma in each group.[153] The corresponding Peto OR was 0.6 (95% CI, 0.1 to 3.5).[153] This study[153] may have underestimated the relative risk of cancer and death among patients treated with infliximab because of a flaw known as immortal time bias resulting from differential exclusion of followup time in the study groups.[238]

Combination of Infliximab and Immunomodulators Versus Infliximab

One retrospective study of 100 inflammatory bowel disease patients reported no cases of lymphoma over 26 months median followup.[173]

Combination of Infliximab and Corticosteroids Versus Infliximab

One retrospective study of 100 inflammatory bowel disease patients reported no cases of lymphoma over 26 months median followup.[173]

Immunomodulators Versus No Immunomodulators

Four observational studies including 37,943 inflammatory bowel disease patients compared immunomodulators with no immunomodulators and reported on lymphoma.[130 133 231 232] One prospective study aimed to assess the risk of lymphoproliferative disorders in inflammatory bowel disease patients with thiopurine use over 3 years of followup.[130] Sixty percent of the 11,759 patients had Crohn's disease. One non-Hodgkin's lymphoma and 22 non-Hodgkin's lymphoproliferative disorder cases were reported. The study reported an adjusted HR of 5.3 (95% CI, 2.2 to 12.6) for incident lymphoproliferative disorder between thiopurine users and thiopurine non-users.

One case-control study[133] and one retrospective study[232] including 17,675 patients reported the association between azathioprine and lymphoma. The case-control study compared azathioprine users versus non-users.[133] Fifteen of 15,471 inflammatory bowel disease cases had codes indicating lymphoma. The age and smoking adjusted OR comparing azathioprine users with non-users was 3.2 (95% CI, 1.0 to 10.2). For each tertile increase in azathioprine exposure, the odds of lymphoma increased by 37 percent (age and smoking adjusted OR, 1.4; 95% CI, 0.8 to 2.4). This database may include cases that have been reported in other studies included in this review.[136 239] A retrospective study reported three cases of lymphoma among 626 (< 1 percent)

patients with azathioprine use recorded in their charts compared with five lymphoma cases among 1,578 inflammatory bowel disease patients with no history of azathioprine use.[232] Thirty-nine percent of patients had Crohn's disease. One Crohn's disease patient who had not been treated with azathioprine had lymphoma.

A retrospective study of inflammatory bowel disease patients (34 percent Crohn's disease) reported four non-Hodgkin's lymphoma cases among 238 patients with a record of azathioprine, methotrexate, or cyclosporine in their medical records compared with zero cases among 544 patients with no reported history of azathioprine, methotrexate or cyclosporine.[231] One of the lymphoma cases had Crohn's disease.

Corticosteroids Versus No Corticosteroids

The retrospective study including 15,164 inflammatory bowel disease patients that could include overlapping lymphoma patients as another study also reported lymphoma by corticosteroid use.[136] Less than 1 percent of the corticosteroid and no corticosteroid groups had lymphoma. The corresponding Peto OR is 1.0 (95% CI, 0.3 to 3.1).

Mesalamine Versus No Mesalamine

The same study reported lymphoma by mesalamine use in inflammatory bowel disease patients.[136] The Peto OR for mesalamine versus no mesalamine is 1.0 (95% CI, 0.3 to 2.6).

Cervical Cancer

Infliximab Versus No Infliximab

Two retrospective studies including 1,205 female inflammatory bowel disease patients reported cervical cancer by infliximab use.[141 152] A retrospective study within a case-control study of women with inflammatory bowel disease who had received at least one Papanicolaou (Pap) test reported that none of the 10 cervical cancer cases (defined as cervical intraepithelial neoplasia grade III or greater) used infliximab within three years of their cancer compared with 11 of 1,155 (1 percent) inflammatory bowel disease women who had normal Pap tests.[152] Another retrospective study within a case-control study included 40 inflammatory bowel disease patients with at least one normal Pap test prior to inflammatory bowel disease diagnosis and two Pap tests after inflammatory bowel disease diagnosis. No case of cervical cancer was observed.[141] None of the seven women with a record of infliximab use in their charts and none of the 33 women with no recorded infliximab use was diagnosed with cervical cancer.[141]

TNF-Alpha Inhibitor Versus No TNF-Alpha Inhibitor

One retrospective study within a case-control study including 362 patients compared infliximab or adalimumab use with no use with risk of cervical dysplasia as recorded in pathology records.[144] The study included women diagnosed with inflammatory bowel disease prior to age 60 who had no history of abnormal cervical smears prior to inflammatory bowel disease diagnosis and at least one cervical smear after inflammatory bowel disease diagnosis. One cervical adenocarcinoma was reported among the 362 women with inflammatory bowel disease. None of 33 women with adalimumab or infliximab use were diagnosed with cervical cancer compared with one of 329 (<1 percent) women with no record of use.[144]

Immunomodulators Versus No Immunomodulators

Four retrospective studies including 1,942 patients reported cervical cancer by immunomodulators use.[141 144 152 231] One study reported immunomodulators use within 3 years among three of 10 (30 percent) cervical cancer cases compared with 123 of 1,155 (11 percent) non-cases (age, ethnicity, and smoking adjusted OR, 3.5; 95% CI, 0.8 to 14.5).[152] Other medications were not accounted for in the analyses. Another study reported that cervical cancer was diagnosed in 0 of 107 women with a record of thiopurine use for at least three months compared with one of 233 women with no thiopurine use or less than three months of thiopurine use.[144] This study also reported no cervical cancer cases among 13 users of methotrexate for at least three months compared with the same single cervical cancer case among the 349 (<1 percent) women with no use or less than three months of methotrexate use.[144] A study reported that none of the 22 women with a record of thiopurine use in their charts and none of the 18 women with no recorded thiopurine use was diagnosed with cervical cancer.[141] Methotrexate use was not recorded in any of the 40 charts.

One study did not aim to study cervical cancer but specifically reported that cervical cancer was not an observed cancer among those reported. The retrospective study of inflammatory bowel disease patients reported no cervical cancer cases among 238 patients with a record of azathioprine, methotrexate, or cyclosporine in their medical records as well as no cervical cancer cases among 544 with no reported history of azathioprine, methotrexate, or cyclosporine. Of the included patients, 375 were women.[231]

Corticosteroids Versus No Corticosteroids

Two retrospective studies including 1,205 patients reported cervical cancer by corticosteroid use.[141 152] One study reported corticosteroid use within 3 years among seven of 10 (70 percent) cervical cancer cases compared with 508 of 1,155 (44 percent) non-cases (age, ethnicity, and smoking adjusted OR, 2.8; 95% CI, 0.7 to 11.0).[152] One invasive cervical cancer was reported. The invasive cervical cancer case had ulcerative colitis. Another study reported that none of the 12 women with a record of greater than 15 mg of prednisone use in their charts and none of the 28 women having less than 15 mg prednisone use was diagnosed with cervical cancer.[141]

Aminosalicylates Versus No Aminosalicylates

A study reported aminosalicylate use within 3 years among 8 of 10 (80 percent) cervical cancer cases compared with 769 of 1,155 (67 percent) non-cases (age, ethnicity, and smoking adjusted OR, 1.7; 95% CI, 0.3 to 8.0).[152]

Colorectal Cancer

Immunomodulators Versus No Immunomodulators

A pooled registry study of 1,149 inflammatory bowel disease patients reported colorectal neoplasia in two patients receiving thiopurines without aminosalicylates compared to 14 cases among patients who had never received thiopurines nor aminosalicylates (adjusted HR 0.1; 95% CI 0.0 – 0.8).[234]

Combination of Immunomodulators With Aminosalicylates Versus Never User of These Medications

A pooled registry study of 1,149 inflammatory bowel disease patients reported colorectal neoplasia in one patient who received thiopurines with aminosalicylates (0.3 cases per 1,000 person-years compared to 14 cases among patients who had never received thiopurines nor aminosalicylates (2.9 cases per 1,000 person-years).[234]

Aminosalicylates Versus No Aminosalicylates

Two retrospective studies including 10,552 inflammatory bowel disease patients compared aminsalicylate use to never use with risk of colorectal cancer.[234 235] Neither study found a statistically significance association with colorectal cancer risk. The effect estimates suggested modest effects of aminosalicylates in opposite directions. The Dutch pooled registry study reported that aminosalicylates were associated with a decreased risk of cancer (adjusted HR 0.6; 95% CI 0.2 – 1.4)[234] compared to a slightly elevated effect in the Canadian study (adjusted HR 1.2; 95% CI 0.8 – 1.7).[235] The inconsistent effects may be partly explained by the adjustments in the analyses. Both studies adjusted for demographics, but the Dutch study also adjusted for disease location, dysplasia hx, surgery hx, folic acid use, calcium use, other medication use and type of inflammatory bowel disease.[234]

Other Cancers

Infliximab Versus No Infliximab

One retrospective study of 1,409 inflammatory bowel disease patients (80 percent Crohn's disease) compared infliximab with never user of a biologic and reported on cancer risk.[153] Three percent of the infliximab group (21 cancers among 743 patients contributing 3,775 person-years) and 5 percent of the never users of biologics (30 of 666 patients contributing 6,704 person-years) had cancer. The study reported an adjusted OR of 1.0 (95% CI, 0.6 to 1.7). An unadjusted rate ratio corresponding to the events and person-time provided was 3.6 (95% CI, 1.9 to 6.4). This study[153] may have underestimated the relative risk of cancer and death among patients treated with infliximab because of a flaw known as immortal time bias resulting from differential exclusion of followup time in the study groups.[238]

Combination of Infliximab and Immunomodulators Versus Infliximab

Two single center studies of 221 patients (92 percent[173] and 81 percent[129] Crohn's disease) reported on cancer in inflammatory bowel disease patients for the combination of infliximab and thiopurines versus infliximab.[129 173] Concomitant medications were reported at the time of the first infliximab infusion. No cancers were reported in either study.

Combination of Infliximab and Corticosteroids Versus Infliximab

The same retrospective study of 100 inflammatory bowel disease patients reported no cancers during the 26-month median study period comparing 42 patients taking infliximab and a corticosteroid with 58 patients taking infliximab without a corticosteroid.[173]

Other Combinations With Infliximab

One retrospective study of 147 inflammatory bowel disease patients met the inclusion criteria but the cancer cases' concomitant medications may be misclassified as described above.[227] Nine cancers were reported. The cancers occurred in seven of 93 patients taking infliximab and an immunomodulator (with or without corticosteroids) and two of 54 (4 percent) patients taking infliximab without an immunomodulator. When examining concomitant corticosteroids (with or without immunomodulators), the cancers occurred in four of 102 (4 percent) patients taking infliximab and a corticosteroid compared with five of 45 (11 percent) patients taking infliximab without a corticosteroid.

Immunomodulators Versus No Immunomodulators

Four observational studies including 37,943 inflammatory bowel disease patients compared immunomodulators with no immunomodulators and reported on cancer risk.[130 133 231 232] A prospective study of 19,486 patients followed a median of 35 months reported cancers in 2 percent of current or previous thiopurine users and 1 percent of never users of thiopurine.[130] The study reported $P < 0.0006$ for a difference in the comparison between these three groups. The corresponding Peto OR comparing ever with never users was 1.4 (95% CI, 1.1 to 1.8).

A retrospective study (39 percent Crohn's disease) with 13.7 mean years of followup reported cancers in 5 percent of the 626 azathioprine patients and 4 percent of the 1,578 no azathioprine group. The corresponding Peto OR was 1.1 (95% CI, 0.7 to 1.7).[232] Another retrospective study with 8 years median followup reported 14 (6 percent) cancers in 238 ever users of thiopurines, methotrexate, or cyclosporine and 16 (3 percent) cancers in 544 who had not used these medications according to chart review. The corresponding Peto OR was 2.1 (95% CI, 0.9 to 4.6).[231]

A case-control study comparing inflammatory bowel disease cancer cases with inflammatory bowel disease patients without cancer reported that 11 percent of cancer patients had been prescribed azathioprine compared with 13 percent of controls.[133] After excluding 43 non-melanoma skin cancers (azathioprine versus no azathioprine OR, 1.0), there were 392 incident cases of cancer among 15,471 inflammatory bowel disease patients with at least one year of relevant data between 1987 and 2001. After adjusting for age and smoking, the OR was 1.1 (95% CI, 0.8 to 1.5). Although the number of Crohn's disease patients and their azathioprine use was not reported, the azathioprine versus no azathioprine OR in Crohn's disease was reported as 1.1 (95% CI, 0.7 to 1.8), although it is unclear if this relationship was adjusted.

Infections

Infliximab Versus No Infliximab

A retrospective study of 1,409 inflammatory bowel disease patients (80 percent Crohn's disease) reported serious infections that required hospitalization, prolonged hospitalization, led to significant disability, or were life-threatening or fatal.[153] Serious infections within 12 weeks of the last infliximab infusion were reported in 48 (6 percent) of 743 infliximab users (5 years of followup) compared with 62 (9 percent) of 666 never users of a biologic (12 years of followup). The corresponding Peto OR was 0.7 (95% CI, 0.5 to 1.0).

Combination of Infliximab With Immunomodulators Versus Infliximab

The retrospective study of 1,409 inflammatory bowel disease patients (80 percent Crohn's disease) reported that non-serious infections were not affected by methotrexate or thiopurine use, although the magnitude of the association was not reported.[153] No infections requiring hospitalization were observed in a hospital-based registry of 121 patients (81 percent Crohn's disease).[129]

Combination of Infliximab With Corticosteroids Versus Infliximab

The retrospective study of 1,409 inflammatory bowel disease patients (80 percent Crohn's disease) reported non-serious infections were more likely to occur during periods when corticosteroids were used (OR 2.7, 95% CI 1.2 to 6.1).[153]

Other Combinations With Infliximab

Two retrospective studies including 247 inflammatory bowel disease patients met the inclusion criteria but the concomitant medications of the patients with infections may be misclassified as described in the mortality section.[173 227] One retrospective study of 100 inflammatory bowel disease patients (92 Crohn's disease) reported infections in four of 82 patients receiving infliximab and a thiopurine compared with no infections in 18 patients receiving infliximab without a thiopurine.[173] Examining the combination of infliximab and corticosteroids in these same 100 patients, infections occurred in zero of 42 patients on infliximab and corticosteroids and four of 58 patients on infliximab without a corticosteroid. The observed infections were varicella-zoster, pneumonia, E. coli, and sepsis. The study also reported that no opportunistic infections were observed. Another retrospective study of 147 patients (138 Crohn's disease) followed a median of 9 years reported serious infection requiring hospitalization in 19 percent of 93 patients taking infliximab and an immunomodulator and 33 percent of 54 patients taking infliximab without an immunomodulator.[227] In the same 147 patients, serious infections were reported in 18 percent of 102 patients taking infliximab and corticosteroids and 40 percent of 45 patients taking infliximab without corticosteroids. Among these 36 patients, there were 57 unique hospitalizations with infection as the main reason for the hospitalization.[227]

Immunomodulators Versus No Immunomodulators

Two studies including 302 inflammatory bowel disease patients compared immunomodulators with no immunomodulators and reported on infections.[155 176] A prospective study reported specific benign infections (benign upper respiratory infections and human papillomavirus and herpes simplex virus cutaneous infections) among 230 inflammatory bowel disease patients (162 Crohn's disease) with well-controlled disease.[155] Azathioprine use was assessed by chart review over an average of one year of followup. Active ascertainment of infections was performed by physical exams at each visit, with use of standardized forms for benign infections. Inflammatory bowel disease patients with and without use of azathioprine averaged two upper respiratory tract infections per year. Azathioprine users were more likely to have a flare-up of human papillomavirus or herpes simplex virus than patients not on

azathioprine (1 flare per year among azathioprine users versus 0.2 flares per year among non-users).

One retrospective study including 72 patients (23 Crohn's disease) tested for cytomegalovirus infections in intestinal biopsies taken from inpatients with active inflammatory bowel disease.[176] They reported that 17 percent (2 out of 12) of patients with azathioprine use had cytomegalovirus infection compared with 12 percent (7 out of 60) of patients without azathioprine use.[176] Two of the eight cytomegalovirus infection positive patients had Crohn's disease.

Immunomodulators Versus Corticosteroids

One study including 10,141 inflammatory bowel disease patients compared immunomodulators with corticosteroids and reported on infections.[230] Because the study reported rate ratios comparing corticosteroids with immunomodulators, the comparisons reported here also compared corticosteroids with immunomodulators. The number of serious infections requiring hospitalization (as identified by ICD-9-CM codes) was 32 in corticosteroid users (4,066 person-years) compared with 27 in immunomodulator users (3,964 person-years). They adjusted for age, gender, inflammatory bowel disease type, year of diagnosis, mean comorbidity index, number of doctor visits, and number of medications, and reported a serious infection rate ratio of 1.1 (95% CI, 0.6 to 1.9) comparing corticosteroids (with or without infliximab) with immunomodulators. The rate ratio comparing corticosteroids only with immunomodulators only for serious infections was 1.2 (95% CI, 0.7 to 2.1). *Clostridium difficile* (*C. difficile*) was a non-serious infection of interest. The number of *C. difficile* infections was 57 in corticosteroid users (4,063 patient-years) compared with 14 in immunomodulator users (3,972 patient-years). The adjusted rate ratio comparing corticosteroids (with or without infliximab) with immunomodulators was 3.4 (95% CI, 1.9 to 6.1). The adjusted rate ratio comparing corticosteroids alone with immunomodulators alone was 2.7 (95% CI, 1.5 to 4.6).

A retrospective study of 27 users of thiopurines with or without corticosteroids (41 percent Crohn's disease) reported that almost 20 percent of both groups had infections including two cases of shingles and one case each of EBV viremia, PCP pneumonia, and viral meningitis.[157]

Combination of Azathioprine and Aminosalicylates Versus Azathioprine

One retrospective study including 199 inflammatory bowel disease patients (122 Crohn's disease) reported that 2 percent (2 out of 104) of inflammatory bowel disease patients who filled prescriptions for both azathioprine and aminosalicylates at the hospital pharmacy had an infection reported in their charts compared with 2 percent (2 out of 95) of patients who filled prescriptions for azathioprine alone.[156] The severity and type of infection were not defined.

Corticosteroids Versus No Corticosteroids

One retrospective cohort including 554 inflammatory bowel disease patients reported infections in corticosteroid or corticotrophin users and non-users according to a chart review of patients seen at the hospital clinic between 1946 and 1965.[142] Infections of unspecified severity or type were recorded in 17 of 124 (14 percent) corticosteroid or corticotrophin non-users compared with 95 of 430 (22 percent) corticosteroid or corticotrophin users. The corresponding Peto OR was 1.7 (95% CI, 1.0 to 2.8).

Infusion and Injection-Site Reactions

Combination of Infliximab and Immunomodulators Versus Infliximab

Five observational studies including 1,189 inflammatory bowel disease patients compared a combination of infliximab and immunomodulators with infliximab alone and reported infusion reactions.[173 181 225 228] A retrospective study of 144 inflammatory bowel disease patients (139 Crohn's disease) who received 30 minutes to 1 hour of infusion instead of the standard 2 hours did not report the number of patients who experienced infusion reaction but did report an OR of 1.4 comparing a combination of infliximab and immunomodulators (thiopurines or methotrexate) with infliximab without immunomodulators (95% CI, 0.3 to 7.7) after adjustment for unspecified factors.[181] The unadjusted OR comparing a combination of infliximab and thiopurines with infliximab was 1.1 (95% CI, 0.3 to 3.7).

Another retrospective study of 1 hour compared to 2 hour infusions reported 3 percent of patients who received immunosuppressants had an infusion reaction compared to 9 percent of patients who received infliximab alone.[184]

A retrospective study that followed inflammatory bowel disease patients for 8 months to 17 years reported a p-value only comparing a combination of infliximab and immunomodulators with infliximab. Patients who received the combination of infliximab and immunomodulators were less likely to have any adverse event within 24 hours of infusion than patients receiving infliximab without immunomodulators (univariate $P = 0.002$).[228]

A retrospective study of 651 inflammatory bowel disease patients reported 63 infusion reactions in 2,079 (3 percent) infliximab and immunomodulator infusions and 83 infusion reactions in 1,272 (7 percent) infliximab without immunomodulator infusions (during or within 2 hours after infusion).[225] A retrospective study of 100 inflammatory bowel disease patients (92 with Crohn's disease) reported infusion reactions in two of 82 patients using infliximab and a thiopurine compared with zero of 18 patients using infliximab without a thiopurine.[173] Both patients who experienced an infusion reaction had Crohn's disease.

Combination of Infliximab and Thiopurines Versus Combination of Infliximab and Methotrexate

The retrospective study of 144 inflammatory bowel disease patients receiving 30 minute to 1-hour infusions instead of 2-hour infusions reported an unadjusted OR for infusion reaction comparing a combination of infliximab and methotrexate or prednisolone with a combination of infliximab and thiopurines of 1.2 (95% CI, 0.5 to 3.0).[181]

Combination of Infliximab and Corticosteroids Versus Infliximab

Three retrospective studies including 989 inflammatory bowel disease patients compared infusion reactions in patients who received a combination of infliximab and corticosteroids versus infliximab without corticosteroids.[173 225] A study of 100 inflammatory bowel disease patients (92 Crohn's disease) reported two Crohn's disease patients experiencing an infusion reaction in 58 patients receiving infliximab and corticosteroids versus zero in 42 patients receiving infliximab without corticosteroids.[173] A retrospective study of 651 inflammatory bowel disease patients reported 33 infusion reactions in 611 infusions of infliximab with corticosteroids

compared with 113 infusion reactions in 2,750 infusions of infliximab without corticosteroids.[225] A retrospective study of 1 hour compared to 2 hour infusions reported 6 percent of patients who received corticosteroid premedication had an infusion reaction compared to 4 percent of patients who received infliximab alone.[184]

Bone Fractures

Corticosteroids Versus No Corticosteroids

One retrospective cohort (n = 554) evaluated bone fractures in inflammatory bowel disease patients using a corticosteroid or corticotrophin compared with non-users according to a chart review of patients seen at the hospital clinic between 1946 and 1965.[142] A pathologic fracture was recorded in zero of 124 corticosteroid non-users compared with six of 430 corticosteroid users (1 percent).

Appendix G. Subgroup Analysis Tables

(reference list located in full report)

Table 1. Comparative effectiveness of pharmacologic therapies to induce remission in sub-populations of patients with Crohn's disease

Subgroup	Remission	Steroid-free remission	Other outcomes
Baseline CRP	**Remission = CDAI < 150 at week 4**[38] ***Baseline CRP < 10 mg/L*** **Placebo (7%)** **Adalimumab (18%)** ***Baseline CRP > 10 mg/L*** **Placebo (7%)** **Adalimumab (25%)** **(*P* = 0.67)** Remission = CDAI < 150 at week 4[37] *Baseline CRP < 1mg/dL* Placebo (16%) Adalimumab 40mg/20mg (14%) Adalimumab 80mg/40mg (21%) Adalimumab 160mg/80mg (31%) *Baseline CRP ≥1mg/dL* Placebo (7%) Adalimumab 40mg/20mg (23%) Adalimumab 80mg/40mg (27%) Adalimumab 160mg/80mg (43%)	Corticosteroid-free remission (CDAI < 150) at week 26[45] *Baseline CRP <0.8 mg/dL* Infliximab + azathioprine (51%; OR = 2.0; *P* = 0.05) Infliximab (40%; OR = 1.3; *P* = 0.43) Azathioprine (34%; ref) *Baseline CRP ≥ 0.8 mg/dL* Infliximab + azathioprine (64%; OR = 4.6; *P* < 0.001) Infliximab (48%; OR = 2.4; *P* = 0.004) Azathioprine (28%; ref)	
Corticosteroid use	**Remission = CDAI < 150 at week 4**[38] ***Baseline corticosteroid use*** **Placebo (4%)** **Adalimumab (33%)** ***No baseline corticosteroid use*** **Placebo (10%)** **Adalimumab (15%)** **(*P* = 0.01)**	Corticosteroid-free remission (CDAI < 150) at week 26[45] *Baseline steroid use <20 mg* Infliximab + azathioprine (56%; OR = 2.7; *P* < 0.001) Infliximab (43%; OR = 1.6; *P* = 0.08) Azathioprine (33%; ref) *Baseline steroid use ≥20 mg* Infliximab + azathioprine (61%; OR = 6.9; *P* < 0.001) Infliximab (49%; OR = 4.3; *P* = 0.01) Azathioprine (18%; ref)	Reduction of ≥ 50% in number of draining fistulas[44] *Concomitant oral corticosteroid use of 20 mg/day* Placebo (20%) Infliximab (67%; OR = 8.0; *P* = 0.14) *Concomitant oral corticosteroid use of <20 mg/day* Placebo (17%) Infliximab (53%; OR = 5.7; *P* = 0.15) *No concomitant oral corticosteroid use* Placebo (30%) Infliximab (64%; OR = 4.2; *P* = 0.01)

Subgroup	Remission	Steroid-free remission	Other outcomes
Immunomodulator use	**Remission = CDAI < 150 at week 4[38]** ***Baseline immunomodulator (AZA, MP, MTX) use*** **Placebo (7%)** **Adalimumab (22%)** ***No baseline immunomodulator (AZA, MP, MTX) use*** **Placebo (7%)** **Adalimumab (21%)** **(*P* = 0.88)** Remission = CDAI < 150 at week 4[37] *Concomitant immunomodulator (AZA, MP, MTX) use* Placebo (9%) Adalimumab 40mg/20mg (22%) Adalimumab 80mg/40mg (10%) Adalimumab 160mg/80mg (36%) *No concomitant immunomodulator (AZA, MP, MTX) use* Placebo (13%) Adalimumab 40mg/20mg (16%) Adalimumab 80mg/40mg (30%) Adalimumab 160mg/80mg (35%) **Remission = CDAI < 150 at week 10[33]** ***Concomitant immunomodulator use*** **Placebo (25%)** **Natalizumab (40%)** ***No concomitant immunomodulator use*** **Placebo (33%)** **Natalizumab (35%)** **(*P* < 0.05)**	**Corticosteroid-free remission (CDAI < 150) at week 12[46]** ***Prior AZA/MP use*** **AZA/MP + placebo (34%)** **AZA/MP + infliximab (64%)** ***No prior AZA/MP use*** **AZA/MP + placebo (41%)** **AZA/MP + infliximab (83%)** **(*P* = 0.10)** **Corticosteroid-free remission (CDAI < 150) at week 52[46]** ***Prior AZA/MP use*** **AZA/MP + placebo (12%)** **AZA/MP + infliximab (27%)** ***No prior AZA/MP use*** **AZA/MP + placebo (32%)** **AZA/MP + infliximab (52%)** **(*P* = 0.82)**	Reduction of ≥ 50% in number of draining fistulas[44] *Concomitant thiopurine use* Placebo (44%) Infliximab (59%; OR = 1.8; *P* = 0.46) *No concomitant thiopurine use* Placebo (18%) Infliximab (65%; OR = 8.3; *P* = 0.001)
TNF-alpha inhibitor use	**Remission = CDAI < 150 at week 10[33]** ***Prior treatment with TNF-alpha inhibitor*** **Placebo (22%)** **Natalizumab (33%)** ***No prior treatment with TNF-alpha inhibitor*** **Placebo (35%)** **Natalizumab (39%)** **(*P* > 0.05)**		

Subgroup	Remission	Steroid-free remission	Other outcomes
ASA use		Corticosteroid-free remission (CDAI < 150) at week 26[45] *Baseline 5-ASA use* Infliximab + azathioprine (58%; OR = 2.5; *P* = 0.002) Infliximab (49%; OR = 1.9; *P* = 0.04) Azathioprine (35%) *No baseline 5-ASA use* Infliximab + azathioprine (57%; OR = 4.6; *P* < 0.001) Infliximab (39%; OR = 2.4; *P* = 0.03) Azathioprine (23%)	
Antibiotic use			Reduction of ≥ 50% in number of draining fistulas[44] *Concomitant antibiotic use* Placebo (27%) Infliximab (65%; OR = 4.9; *P* = 0.06) *No concomitant antibiotic use* Placebo (25%) Infliximab (61%; OR = 4.7; *P* = 0.01)
Disease location	Remission = CDAI < 175 at month 15[53] *Disease location-ileum* Placebo (17%) Azathioprine (50%; OR = 5.0; *P* > 0.05) *Disease location- colon* Placebo (0%) Azathioprine (20%; OR = 3.7; *P* > 0.05) *Disease location- ileum/colon* Placebo (5%) Azathioprine (45%; OR = 14.7; *P* < 0.05)		Reduction of ≥ 50% in number of draining fistulas[44] *Disease location-ileum* Placebo (0%) Infliximab (73%) *Disease location-colon* Placebo (33%) Infliximab (53%; OR = 2.3; *P* = 0.35) *Disease location-ileum/colon* Placebo (26%) Infliximab (65%%; OR = 5.1; *P* = 0.01) 2-point drop in HBI after week 6[240] *Disease location-ileum* Placebo (38%) Mesalamine (33%) *Disease location- colon* Placebo (33%) Mesalamine (67%) *Disease location- ileum/colon* Placebo (0%) Mesalamine (40%)

Subgroup	Remission	Steroid-free remission	Other outcomes
Other disease characteristics		Corticosteroid-free remission (CDAI < 150) at week 26[45] *Duration of CD < 3 years* Infliximab + azathioprine (51%; OR = 2.9; *P* < 0.001) Infliximab (42%; OR = 2.1; *P* = 0.02) Azathioprine (26%; ref) *Duration of CD ≥ 3 years* Infliximab + azathioprine (64%; OR = 3.4; *P* < 0.001) Infliximab (47%; OR = 1.7; *P* = 0.11) Azathioprine (35%; ref) Corticosteroid-free remission (CDAI < 150) at week 26[45] *Previous CD-related surgery* Infliximab + azathioprine (48%; OR = 2.2; *P* = 0.07) Infliximab (45%; OR = 1.8; *P* = 0.16) Azathioprine (30%; ref) *No previous CD-related surgery* Infliximab + azathioprine (60%; OR = 3.6; *P* < 0.001) Infliximab (44%; OR = 1.8; *P* = 0.03) Azathioprine (30%) Corticosteroid-free remission (CDAI < 150) at week 26[45] *Baseline mucosal lesions* Infliximab + azathioprine (61%; *P* < 0.001 comp to AZA, P=0.12 comp to IFX) Infliximab (51%; *P* = 0.002 comp to AZA) Azathioprine (30%) *No baseline mucosal lesions* Infliximab + azathioprine (40%; *P* = 0.93 comp to AZA, P=0.69 comp to IFX) Infliximab (33%; *P* = 0.37 comp to AZA) Azathioprine (41%) *Unable to determine if baseline mucosal lesions* Infliximab + azathioprine (57%; *P* = 0.003) Infliximab (38%; *P* = 0.14) Azathioprine (21%)	Reduction of ≥ 50% in number of draining fistulas[44] *One enterocutaneous fistula* Placebo (8%) Infliximab (52%; OR = 12.9; *P* = 0.02) *>1 enterocutaneous fistula* Placebo (39%) Infliximab (71%; OR = 3.8; *P* = 0.03)

Results in **BOLD CAPS** reported a p-value for the interaction term.
Sub-populations reported without all strata are not reported with percentages.

Table 2. Comparative effectiveness of pharmacologic therapies to induce remission in sub-populations of patients with Crohn's disease

Subgroup	Remission	Other outcomes
Baseline CRP	Remission = CDAI < 150 at week 26[82] *Baseline CRP <1 mg/dL* Placebo (18%) Adalimumab 40mg every other week (39%) Adalimumab 40mg weekly (38%) *Baseline CRP ≥1 mg/dL* Placebo (17%) Adalimumab 40mg every other week (41%) Adalimumab 40mg weekly (56%) Remission= CDAI < 150 at week 56[82] *Baseline CRP <1 mg/dL* Placebo (13%) Adalimumab 40mg every other week (36%) Adalimumab 40mg weekly (33%) *Baseline CRP ≥1 mg/dL* Placebo (11%) Adalimumab 40mg every other week (37%) Adalimumab 40mg weekly (51%) Remission = CDAI < 150 at week 26[84] *Baseline CRP < 10 mg/L* Placebo (31%) Certolizumab pegol (54%; *P* < 0.001) *Baseline CRP >10 mg/L* Placebo (26%) Certolizumab pegol (42%; *P* = 0.01)	

Subgroup	Remission	Other outcomes
Immunomodulator use	Remission = CDAI < 150 at week 26[82] *Baseline immunomodulator (AZA, MP, MTX) use* Placebo (16%) Adalimumab 40mg every other week (39%) Adalimumab 40mg weekly (44%) *No baseline immunomodulator (AZA, MP, MTX)use* Placebo (21%) Adalimumab 40mg every other week (42%) Adalimumab 40mg weekly (56%) Remission= CDAI < 150 at week 56[82] *Baseline immunomodulator (AZA, MP, MTX) use* Placebo (12%) Adalimumab 40mg every other week (37%) Adalimumab 40mg weekly (39%) *No baseline immunomodulator (AZA, MP, MTX)use* Placebo (13%) Adalimumab 40mg every other week (33%) Adalimumab 40mg weekly (50%) Remission= CDAI <150 at week 56[83] *Concomitant immunomodulator use* Placebo (33%) Adalimumab 40mg every other week (100%) Adalimumab 40mg weekly (83%) *No concomitant immunomodulator use* Placebo (47%) Adalimumab 40mg every other week (73%) Adalimumab 40mg weekly (85%) Remission = avoidance of relapse (75-point increase in CDAI, CDAI > 150, or disease activity requiring intervention) after 1 year[101] *Prior azathioprine dose ≤1.60 kg/mg/day* Placebo (100%) Azathioprine (75%) *Prior azathioprine dose >1.60 kg/mg/day* Placebo (33%) Azathioprine (89%; *P* = 0.017)	No draining fistulas at week 26[241] *Baseline immunomodulator (AZA, MP, MTX) use* Placebo (8%) Adalimumab (26%; *P* = 0.09) *No baseline immunomodulator (AZA, MP, MTX) use* Placebo (19%) Adalimumab (33%; *P* = 0.37) No draining fistulas at week 56[241] *Baseline immunomodulator (AZA, MP, MTX) use* Placebo (8%) Adalimumab (29%; *P* = 0.05) *No baseline immunomodulator (AZA, MP, MTX) use* Placebo (19%) Adalimumab (36%; *P* = 0.24)

Subgroup	Remission	Other outcomes
TNF-alpha inhibitor use	Remission = CDAI < 150 at week 26[82] *TNF-alpha inhibitor experienced at baseline* Placebo (16%) Adalimumab 40mg every other week (32%) Adalimumab 40mg weekly (42%) *TNF-alpha inhibitor naive at baseline* Placebo (18%) Adalimumab 40mg every other week (47%) Adalimumab 40mg weekly (50%) Remission= CDAI < 150 at week 56[82] *TNF-alpha inhibitor experienced at baseline* Placebo (10%) Adalimumab 40mg every other week (31%) Adalimumab 40mg weekly (34%) *TNF-alpha inhibitor naive at baseline* Placebo (14%) Adalimumab 40mg every other week (42%) Adalimumab 40mg weekly (48%) Remission=CDAI < 150 at week 26[242] *Infliximab naïve* Placebo (33%) Certolizumab pegol (53%; *P* < 0.001) *Infliximab experienced* Placebo (14%) Certolizumab pegol (33%; *P* = 0.008)	Serious infection[242] Infliximab naïve Placebo (1%) Certolizumab pegol (2%) Infliximab experienced Placebo (0%) Certolizumab pegol (4%)
Antibiotic use		No draining fistulas at week 26[241] *Baseline antibiotic use* Placebo (11%) Adalimumab (27%; *P* = 0.26) *No baseline antibiotic use* Placebo (14%) Adalimumab (32%; *P* = 0.16) No draining fistulas at week 56[241] *Baseline antibiotic use* Placebo (11%) Adalimumab (27%; *P* = 0.26) *No baseline antibiotic use* Placebo (14%) Adalimumab (36%; *P* = 0.06)

Subgroup	Remission	Other outcomes
Disease location		Relapse = CDAI >150 and 100-point increase in CDAI at month 12[123] *Disease location-ileum* Placebo (57%) 5-ASA (26%; *P* < 0.05) *Disease location-colon* Placebo (55%) 5-ASA (40%; *P* > 0.05) *Disease location- ileum/colon* Placebo (50%) 5-ASA (52%; *P* > 0.05) Relapse = CDAI > 150 after one year[126] *Disease location-ileum* Placebo (27%) Mesalamine (27%; *P* > 0.05) *Disease location-colon* Placebo (43%) Mesalamine (55%; *P* > 0.05) *Disease location- ileum/colon* Placebo (50%) Mesalamine (11%; *P* < 0.05)
Other disease characteristics		Relapse = CDAI >150 and 100-point increase in CDAI at month 12[123] *Baseline inflammation (CRP, ESR)* Placebo (83%) 5-ASA (62%; *P* > 0.05) *No baseline inflammation (CRP, ESR)* Placebo (45%) 5-ASA (22%; *P* > 0.05) Relapse = CDAI >150 and 100-point increase in CDAI at month 12[123] *Previous resection* Placebo (58%) 5-ASA (9%; *P* < 0.05) *No previous resection* Placebo (54%) 5-ASA (41%; *P* > 0.05)

Results in **BOLD CAPS** reported a p-value for the interaction term.
Sub-populations reported without all strata are not reported with percentages.