| 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 |
| 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 |
| 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 ASAMs; aminosalicylates; rval; se Questionnaire; ership skillsield of computer science/engineerig. | Lymphoma | 1 retrospective  15,164 IBD | High | NA | Direct | Imprecise | Neither favored  Observational OR 1.0  Low |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 vsASA | 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 |
| 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 |
| 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.