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CADTH HEALTH TECHNOLOGY ASSESSMENT

# Drugs for the Management of Rheumatoid Arthritis: Clinical Evaluation


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CADTH would like to acknowledge the following individuals for their contributions:

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Joan Peterson was involved in the grey literature screening, the tabulation and verification of the data, and the study quality assessment.

Zemin Bai contributed to the study quality assessment.

## Abbreviations

| | |
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| ACR | American College of Rheumatology |
| CAPA | Canadian Arthritis Patient Alliance |
| CI | confidence interval |
| CrI | credible interval |
| CRP | C-reactive protein |
| csDMARD | conventional synthetic disease-modifying antirheumatic drug |
| DAS28 | Disease Activity Score 28-Joint Count |
| DMARD | disease-modifying antirheumatic drug |
| ESR | erythrocyte sedimentation rate |
| EULAR | European League of Associations in Rheumatology |
| HAQ-DI | Health Assessment Questionnaire – Disability Index |
| HCQ | hydroxychloroquine |
| HRQoL | health-related quality of life |
| IL | interleukin |
| IR | inadequate response |
| JAK | Janus kinase |
| LEF | leflunomide |
| MA | meta-analysis |
| MACE | major adverse cardiac event |
| MCS | Mental Component Score |
| MTX | methotrexate |
| NICE | National Institute for Health and Care Excellence |
| NMA | network meta-analysis |
| PCS | Physical Component Score |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RA | rheumatoid arthritis |
| ROB | risk of bias |
| SC | subcutaneous |
| SAE | serious adverse event |
| SEB | subsequent entry biologic |
| SF-36 | Short Form (36) Health Survey |
| SMD | standardized mean difference |
| SSZ | sulfasalazine |
| TB | tuberculosis |
| TNF | tumour necrosis factor |
| tsDMARD | targeted synthetic disease-modifying antirheumatic drug |
| WDAE | withdrawal due to adverse event |

## Definitions

| | |
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| Moderate rheumatoid arthritis | Patients with moderate disease activity as defined by the American College of Rheumatology guidelines 2015.[1] |
| Severe rheumatoid arthritis | Patients with high disease activity as defined by the American College of Rheumatology guidelines 2015.[1] |
| Treatment-experienced | Patients previously treated for rheumatoid arthritis. Example of previous treatments include: conventional synthetic DMARD (csDMARD); combination csDMARDs (double- or triple-csDMARD therapies); biologic drug alone; biologic drug in combination with methotrexate, tofacitinib, or any of the emerging drugs for rheumatoid arthritis. |
| Treatment intolerance | Intolerance to treatment due to an adverse event or contraindication to treatment. |
| Treatment failure | Less than optimal response to treatment due to a lack of efficacy (i.e., patient does not attain low disease activity). |
| Inadequate treatment | Patients with treatment intolerance or treatment failure. |
| csDMARD monotherapy | Methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. |
| Double-csDMARD therapy | Any two of methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. |
| Triple-csDMARD therapy | Methotrexate with sulfasalazine and hydroxychloroquine. |
| csDMARD combination therapy | Double or triple-csDMARD therapy. |

# Executive Summary

## Context and Policy Issues

An important area of research in the field of rheumatoid arthritis (RA) deals with patients who have an inadequate response (IR) to methotrexate (MTX). These patients are often treated with biologics or with double- or triple-conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapies. Newer treatment options include targeted synthetic DMARDs (tsDMARDs), such as tofacitinib and baricitinib, as well as biosimilars.

Comparative efficacy and safety — including, for example, direct comparisons of one biologic with another, as well as comparisons between double- and triple-csDMARD therapy and csDMARD combination therapy with biologics — are lacking. It is important for patients, clinicians, and policy-makers to know of any differences in the benefits and harms of the different treatment options. Assessing the available direct and indirect evidence using a network meta-analysis (NMA) can provide evidence to address this knowledge gap.

## Objective and Research Question

The objective of this review is to assess the benefits and harms of drugs used in adult patients with moderate to severe RA in whom treatment with MTX has failed or who are intolerant to MTX.

The research question was: What is the comparative clinical efficacy and safety of csDMARD therapies (alone or in combination), biologics (including biosimilars), and tsDMARDs in adult patients with moderate to severe RA in whom treatment with MTX has failed or who are intolerant to MTX?

## Methods

A literature search was performed May 3, 2016 in MEDLINE, Embase, the Cochrane Library (Wiley), Cochrane CENTRAL, and PubMed. Regular database search alerts were established to update the search until March 1, 2017. References of three Cochrane reviews were also considered. Two reviewers independently selected included studies; data extraction and Cochrane Risk of Bias assessments were performed by one reviewer and verified by a second reviewer.

The primary outcome is the ACR 50. The ACR, which is based on American College of Rheumatology guidelines, is a score that indicates how much a patient's RA has improved. ACR 50 represents a 50% improvement. ACR response rates are binary composite outcomes consisting of the following outcomes on disease activity: the number of tender and swollen joints, a patient's assessment of pain, the patient's and physician's global assessments of disease activity, and an acute-phase reactant value (either the erythrocyte sedimentation rate [ESR] or a C-reactive protein level [CRP]). Secondary efficacy outcomes are as follows: ACR 20 and ACR 70, disease severity as measured by the Disease Activity Score 28-Joint Count (DAS 28), disability as measured by the Health Assessment Questionnaire – Disability Index (HAQ-DI), remission (DAS28 < 2.6), health-related quality of life (HRQoL) as measured by Short Form (36) Health Survey [SF-36] physical and mental component scores, fatigue, pain, and radiographic progression.

The primary safety outcome is withdrawal due to adverse event (WDAEs). Secondary safety outcomes included serious adverse events (SAEs) and mortality, as well as the notable harms of serious infections, tuberculosis (TB), cancer, leukemia, lymphoma, congestive heart failure, major adverse cardiac events (MACEs), and herpes zoster.

Bayesian NMAs were conducted on the outcomes listed previously when there were more than three studies; odds ratios and 95% credible intervals (CrIs) were calculated. Meta-analyses (MAs) were conducted when only direct pairwise comparisons were possible. Descriptive analyses were performed when there were insufficient data to conduct NMAs or MAs.

## Key Findings

This report included 98 unique studies, of which 91 had usable data for analysis. Risk of bias (ROB) assessments only revealed elevated proportions of high ROB for incomplete efficacy and safety outcome data. Half of the included studies reported vaguely on random sequence generation and allocation concealment. Overall, half of studies were judged to be at high ROB.

### Methotrexate as a Common Comparator

Several treatments were favoured over a csDMARD in combination with MTX in terms of disease response, including combination therapy of MTX and etanercept, abatacept (IV), adalimumab, tofacitinib, 8 mg/kg tocilizumab, subcutaneous (SC) golimumab, certolizumab pegol, rituximab, 4 mg baricitinib, biosimilars etanercept (HD203, SB4, Anbainuo), biosimilar infliximab CT-P13, monotherapy of 8 mg/kg tocilizumab, as well as triple-csDMARD therapy (MTX, sulfasalazine [SSZ], and hydroxychloroquine [HCQ]) and MTX with HCQ. Triple-csDMARD therapy was also found to be comparable to biologics, tsDMARDs, and biosimilars in combination with MTX, and favoured over etanercept monotherapy and 4 mg/kg tocilizumab monotherapy in terms of disease response (ACR 50). In general, of the biologic monotherapies that were analyzed, most had lower odds of benefit based on disease response (ACR 50), remission, and HRQoL (for certain biologics only) than biologics in combination with MTX; however, biologics in combination with MTX had higher odds of SAEs and WDAEs. Treatment with 8 mg/kg tocilizumab monotherapy demonstrated some benefits in terms of ACR 50 and remission, but no data were available to assess its efficacy in terms of HRQoL, pain, and fatigue. Moreover, there was insufficient evidence from the efficacy and safety outcomes to clearly identify any one biologic monotherapy in the analysis as being more beneficial than another. Several of the biologics, tsDMARDs, and biosimilars in combination with MTX were found to be as efficacious as MTX monotherapy, but there were very often no statistically significant differences in efficacy or safety between biologics, tsDMARDs, and biosimilars taken in combination with MTX.

There were insufficient data to detect a difference between treatments for mortality and the following notable harms: serious infections, TB, cancer, leukemia, lymphoma, congestive heart failure, MACEs, and herpes zoster. Abatacept in combination with MTX had lower odds of SAEs compared with several biologic monotherapies and combination therapies with MTX, tofacitinib in combination with MTX, and a few biosimilar etanercept drugs (SB4 and HD203). Etanercept and one of its biosimilars (SB4), both in combination with MTX, had lower odds of WDAEs compared with csDMARD dual therapy and tofacitinib. Double-csDMARD therapy of SSZ and HCQ also had lower odds of WDAEs compared with tofacitinib in combination with MTX. Among biosimilars, MTX combination therapy with SB4 (biosimilar etanercept) or SB5 (biosimilar adalimumab) had lower odds of WDAEs compared

with other treatments; however, this is based on data from one study for each in the network. More long-term safety data on these newer treatments are needed.

### Conventional Synthetic DMARD as a Common Comparator

When a csDMARD other than MTX is administered concomitantly with a biologic, tsDMARD, or biosimilar, there is insufficient evidence to draw conclusions on the comparative benefits of the treatments (based on disease severity, disability, physical and mental HRQoL, pain, and fatigue) and harms of the treatments (mortality, TB, cancer, leukemia, lymphoma, congestive heart failure, MACEs, and herpes zoster).

## Strengths and Limitations

Strengths of this review include the method of accounting for the impact of various study designs (e.g., adaptive design studies, older versus newer studies), differing patient characteristics, differing background therapy (i.e., MTX or another csDMARD), and data quality through sensitivity analyses planned a priori. In addition, the validity of the NMAs was assessed by testing the assumptions of homogeneity, consistency, and similarity. Using NMAs, it was possible to compare treatments that had not been directly compared with one another in any studies through mixed- and indirect-treatment comparisons. The literature search was comprehensive and executed in accordance with the protocol specified a priori; it also included grey literature to reduce the impact of publication bias.

Limitations of the included studies involved differences in study design (e.g., around one-third of trials used an adaptive design), treatment doses, and background therapies. We attempted to reduce the impact of these differences by limiting the analysis to data at the time of adaptation for adaptive design trials. Analysis was restricted to standard doses only, which may not be generalizable to what patients are prescribed (or adhere to) in practice, but allowed for greater homogeneity in the analysis. Patients in randomized controlled trials (RCTs) may not be representative of patients in clinical practice; thus, results from this review are not generalizable to all patients. NMAs were separated based on use of MTX or a different csDMARD as a comparator for insight into the effect of the background therapy. Included studies also did not always report on all of the outcomes of interest, so comparisons of benefits or harms across several outcomes were not possible for all treatments (e.g., double- and triple-csDMARD therapies did not have data for many outcomes). Lastly, data conversions and imputations were required at times to include studies in analysis, which may have introduced bias.

## Conclusions and Implications for Decision- or Policy-Making

To the authors' knowledge, this was the first comprehensive systematic review and NMA that included monotherapies and double- and triple-csDMARD therapies as well as biologics, tsDMARDs, and biosimilars, both as monotherapies and in combination with csDMARDs. Among all the treatment comparisons considered for patients with moderate to severe RA and an IR to MTX, various treatment strategies were found to be effective for different outcomes, but there was inconclusive evidence on the comparative efficacy and safety of the treatments to one another in this analysis. Due to the method of analyzing adaptive design trial data before the time of adaptation, the results of this review are limited to the shorter term; evidence from observational studies should also be considered to provide further context regarding the applicability of these findings to clinical practice. It is also important to recall that the majority of included studies had a high or unclear ROB;

therefore, the results from this report should be interpreted with caution. In selecting a treatment, it is important to balance the benefits and harms of treatments based on patient preference and treatment goals, access to treatment (e.g., infusion clinics), and affordability. A decision on the next treatment option should be made after the patient and physician have discussed these important factors.

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# Table of Contents



## Tables

## Figures

## Rationale

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease characterized by inflammation of the synovial lining of the joints, tendons, and periarticular structures.[1] RA affects 0.5% to 1.0% of the population in Western countries,[2] with a lower prevalence closer to the equator or in more rural areas.[3] Untreated, RA leads to joint destruction, functional limitation, and severe disability,[4,5] and has a significant impact on health-related quality of life (HRQoL).[6,7]

People with RA would like to achieve total disease remission without significant joint damage and impact on their lives, but they recognize that this might not be possible. For those in whom total remission may be unrealistic, their goal is to have the lowest disease activity they can in order to be as productive and pain-free as possible.

Definitive treatments that have disease-modifying potential include glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) — such as methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (LEF), and cyclosporine — as well as biologic DMARDs (referred to henceforth as biologics) and targeted synthetic DMARDs (tsDMARDs), such as tofacitinib and baricitinib. The use of csDMARDs and biologics leads to an improvement in pain and a reduction in functional disability for patients with RA, as well as to additional long-term outcomes, such as reduced radiographic progression[8,9] and disability.[10,11]

Conventional synthetic DMARDs, including MTX, are usually the first drug of choice for people with RA.[12-14] When csDMARDs, including MTX, are ineffective, partially effective,[15] or have associated side effects, treatment options include other csDMARDs, biologics, tsDMARDs, or biosimilars.[12-14]

Patients who have had an inadequate response (IR) to MTX comprise one of the most commonly studied RA patient populations.[16-18] The European League of Associations in Rheumatology (EULAR) clinical practice guideline (CPG) recommends that patients who have had an IR to MTX and have moderate to severe disease activity should receive a biologic or tsDMARD, with current practice being to start a biologic.[19] The American College of Rheumatology (ACR) CPG is more general in its recommendation, in that it suggests these patients receive a combination of csDMARDs, receive a biologic (i.e., a tumour necrosis factor [TNF] inhibitor or non-TNF inhibitor), or receive the tsDMARD tofacitinib as monotherapy or in combination with a csDMARD.[13] In contrast, the National Institute for Health and Care Excellence (NICE) recommends that these patients receive two six-month trials of csDMARDs (either MTX monotherapy or a combination therapy of two csDMARDs) in combination with low-dose glucocorticoids before trying a biologic.

Provincial drug plans in Canada differ in their coverage for this patient group. Some permit patients who have had an IR to MTX to receive a biologic as a second-line therapy after a trial of triple-csDMARD therapy, while others require non-response in patients on as many as three different csDMARDs (monotherapy and/or combination therapy).[20-31] Given the uncertainty about which treatment has the most benefits — and a good safety profile among patients with moderate to severe RA in whom treatment with MTX has failed or who are intolerant to MTX — it is an important area of research. Thus, this patient population is the focus of this review; it will be referred to as “IR MTX,” indicating that the patients in question had an IR to MTX, whether due to a lack of efficacy, the occurrence of adverse events, or other reasons.

The Arthritis Society asked its members about their lived experience with MTX and received 133 responses. For some, it is well tolerated: “Ten years on methotrexate, and still taking it. No serious side effects to date,” one said; similarly, another responded, “No side effects from methotrexate except weight gain.”

For those who did report side effects, severe nausea was commonly mentioned: “I vomited for days after taking the medicine (bi-weekly).” Some individuals found subcutaneous (SC) methotrexate easier to tolerate than the oral formulation: “Pill form methotrexate made me extremely ill. Injectable was fine.” Not so for others: “The nausea was extreme, taking both pills and injections.” Other side effects described included “brain fog,” a “hangover feeling,” and fatigue and headaches after weekly or monthly injections. Several individuals described spending “at least one day” or “24 to 48 hours” in bed after injection. For others, feeling unwell was constant: “horrible the entire time” or “mood changed constantly.”

Loss of hair and teeth was reported — “loss of hair all over the body;” “lost all hair, lost 10 teeth” — resulting in a “loss of identity.” Also noted were mouth sores, food sensitivities, loss of appetite, a metallic taste in the mouth, racing heart, rise in blood pressure, profuse sweating, and bruising on the stomach and legs. Others described additional health complications following MTX treatment: fatty liver hepatitis, lymphoma, pneumonia requiring hospitalization, chronic ulcerative colitis, and bladder problems.

The introduction of biologics has revolutionized the management of RA. Biologics provide clinically important and statistically significant improvements in pain and function in patients who do not respond to csDMARDs such as MTX. While biologics appear to cause fewer side effects and have much greater success in slowing structural joint destruction than MTX, they are much costlier than csDMARDs.[32,33]

Affordability of treatment was a concern for many Arthritis Society respondents. “The drugs are so expensive. It is crazy to think there are drugs out there that can help control, not cure, the rheumatoid arthritis and yet a lot of us can't afford them.” Some respondents had private health insurance through family members or their own employment. “Even with health insurance and annual renewal of government coverage, it's still hundreds of dollars each month until I reach my deductible.” “I've had challenges every time I've changed jobs. The time it takes to get my insurance coverage in place is never fast enough, and I end up having to pay for at least a month’s worth of medication without any coverage. If I didn't have insurance coverage through work, there is no question that I could not afford this medication.”

The Canadian Arthritis Patients Alliance (CAPA) reported that receiving a diagnosis of RA and then finding an appropriate therapy was a multi-year process for some patients. CAPA explained that for patients relying on publicly funded drug plans, treatment with two disease-modifying drugs must fail before they receive coverage for a biologic. This can result in a substantial delay in getting their disease under control, which could result in permanent joint damage. A respondent to the Arthritis Society explained: “I have encountered irreversible damage to my joints because I was not diagnosed early enough. Once I became sick, it took me over a year to get someone to refer me to a rheumatologist. Then I had to fail on all the first-line treatments before I could qualify for a biologic. Once I finally could access biologics, my life improved immensely.”

Biologics are commonly used for patients with a suboptimal response or intolerance to csDMARDs such as MTX. In these patients (who are IR csDMARD or who are IR MTX), biologics or other csDMARDs (including the use of two csDMARDs) are used in combination with MTX.

In addition, in 2012, the tsDMARD tofacitinib (Xeljanz)[34] was approved to treat RA patients in the US. Most biologics and tofacitinib are approved internationally for the treatment of RA, although the indications for use differ slightly between countries. Table 1 provides an overview of the standard doses of biologics, tsDMARDs, and biosimilars approved by Health Canada for the treatment of RA.

## Table 1: Approved Doses of Biologics, Small Molecules, and Biosimilars Included in the Clinical Review

| Drug Class | Drug (Generic Name) | Trade Name | Year First Approved | Health Canada–Approved Dose |
|---|---|---|---|---|
| **TNF Inhibitors** | | | | |
| TNF Inhibitors | Etanercept | Enbrel | 1998 (FDA);[35] (Health Canada in 2000)[36] | 25 mg SC twice weekly or 50 mg every week |
| | Infliximab | Remicade | 1998 (FDA);[37] (Health Canada in 2001)[38] | 3 mg/kg IV; initial dose at 0 weeks, 2 weeks, and 6 weeks, then every 8 weeks |
| | Adalimumab | Humira | 2002 (FDA);[39] (Health Canada in 2004)[40] | 40 mg SC every 2 weeks |
| | Certolizumab pegol | Cimzia | 2008 (FDA);[41] (Health Canada in 2009)[42] | 400 mg SC (divided into two injections) initially and at week 2 and week4, then 200 mg every 2 weeks[a] |
| | Golimumab | Simponi | 2009 (FDA);[43] (Health Canada in 2011)[44] | 50 mg SC every 4 weeks (monthly) |
| | | | | 2 mg/kg IV; initial dose at 0 weeks and 4 weeks, then every 8 weeks |
| **Non-TNF Inhibitors** | | | | |
| IL-1 inhibitor | Anakinra[b] | Kineret | 2001 (FDA);[45] (Health Canada in 2002)[46] | 100 mg SC, every day |
| B-lymphocyte–depleting drug (anti-CD20 therapy) | Rituximab | Rituxan | 1997 for lymphoma;[47] 2006 for RA (Health Canada, FDA)[48,49] | 2 doses of 1,000 mg IV every 2 weeks |
| T-cell co-stimulatory inhibitor | Abatacept | Orencia | IV: 2005[50] (Health Canada in 2006)[51]<br>SC: 2011[52] (Health Canada in 2013)[53] | 10 mg/kg IV; initial dose at 0 weeks, 2 weeks, and 4 weeks, then every 4 weeks (< 60 kg: 500 mg; 60 kg to 100 kg: 750 mg; > 100 kg: 1,000 mg) |
| | | | | 125 mg SC initial loading dose; second dose within 1 day, then once weekly |
| IL-6 inhibitor | Tocilizumab | Actemra (RoActemra in Europe) | 2010 (FDA)[54]; (Health Canada in 2010)[55] | 4 mg/kg IV every 4 weeks; increase to 8 mg/kg based on clinical response |
| | | | | 162 mg SC every 2 weeks; increase to every week based on clinical response |
| | Sarilumab | Kevzara | 2017 (Health Canada)[56] | 200 mg every 2 weeks SC; reduction to 150 mg every 2 weeks SC to manage neutropenia, thrombocytopenia, and elevated liver enzymes |

| Drug Class | Drug (Generic Name) | Trade Name | Year First Approved | Health Canada–Approved Dose |
|---|---|---|---|---|
| | Sirukumab[c] | Plivensia (CNTO-136) | All applications for approval have been withdrawn.[57] | NA |
| **Targeted Synthetic DMARDs** | | | | |
| Janus-associated kinase inhibitor | Tofacitinib | Xeljanz | 2012;[34] (Health Canada in 2014)[58] | 5 mg p.o. twice daily |
| | Baricitinib[b] | Olumiant | 2017 (EMA, Japan);[59,60] under review by Health Canada[61] | EMA-approved dose: 4 mg once daily p.o.; can be reduced to 2 mg once daily if disease under control[59] |
| **Subsequent Entry Biologics (Biosimilars)** | | | | |
| Biosimilar of infliximab | CT-P13 | Remsima[d]/ Inflectra | 2013 (EMA);[62] (Health Canada in 2014)[63,64] | 3 mg/kg IV; initial dose at 0 weeks, 2 weeks, and 6 weeks, then every 8 weeks |
| | SB2 | Flixabi | 2016 (EMA)[65] | EMA-approved dose: 3 mg/kg at 9 weeks, 2 weeks, and 6 weeks, then every 8 weeks (IV);[66] has not received Health Canada Notice of Compliance |
| Biosimilar of etanercept | HD203 | Davictrel | 2014 (South Korea)[67] | 25 mg twice weekly SC |
| | SB4 | Benepali<br>Brenzys | 2015 (EMA);[68]<br>2015 (South Korea);[69]<br>2016 (Health Canada)[70] | 50 mg/week SC;<br>25 mg twice weekly SC |
| | Unknown | Anbainuo | Unknown | Has not received Health Canada Notice of Compliance |
| Biosimilar of adalimumab | ABP501 | Amjevita | 2016 (FDA)[71]; no submission under review with Health Canada | 40 mg every two weeks SC |
| | ZRC-3197 | Exemptia | Unknown | Has not received Health Canada Notice of Compliance |
| | SB5 | Unknown | Under review by EMA | Has not received Health Canada Notice of Compliance |

DMARD = disease-modifying antirheumatic drug; EMA = European Medicines Agency; FDA = US Federal Drug Administration; IL = interleukin; IV = intravenous; NA = not applicable; p.o. = orally; SC = subcutaneously; TNF = tumour necrosis factor.

[a] 400 mg every 4 weeks can be used for a maintenance dose.

[b] Almost never used to treat adult RA, according to the clinical expert.

[c] Applications for approval have been withdrawn globally after sirukumab was not approved by the FDA.

[d] Manufacturer has suspended sale.[72]

The systemic symptoms and joint inflammation of RA are mediated by the activation of T-cells,[73] B-cells, macrophages,[74] and other immune cells.[75] These interactions lead to the expression of chemokines, metalloproteinases, and inflammatory cytokines, such as TNF-alpha and various interleukins (IL).[76,77] The interaction of lymphocytes and inflammatory cytokines with host cells such as fibroblasts, osteoclasts, and chondrocytes leads to bone and cartilage destruction, a hallmark of RA.[76,78] As briefly mentioned in Table 1, the mechanism of action differs between the biologics (i.e., inhibition of TNF-alpha versus interleukin-1 versus interleukin-6 versus B-cells versus T-cell co-stimulatory molecule

CD28). It is possible that, due to different contributions of these cytokines and processes to the disease expression, the use of therapy targeting one cytokine may be more efficacious or safer than therapy targeting another cytokine or mechanism.

As shown in Cochrane systematic reviews of the biologics and tofacitinib published in the Cochrane Library, these medications provide clinically important improvements in pain and disability in RA patients compared with placebo, MTX or csDMARD.[79-88] However, the existing Cochrane systematic reviews reviewed each drug only individually — that is, they were systematic reviews of each of the biologics.[33,89] Treatment guidelines published recently[12-14,90] as well as consensus statements[91-93] are also based on systematic reviews of these interventions; but most are outdated and none, to our knowledge, included indirect comparisons. This was primarily due to the relative lack of head-to-head comparative effectiveness trials, which has been a barrier in comparing the effectiveness of one biologic with that of another. Therefore, a review summarizing all evidence to date is needed.

Patients, clinicians, and policy-makers need to know if there are any important differences between the various biologics in terms of benefits and harms. Ideally, this requires head-to-head comparison studies. Few studies to date have compared two biologics[94-102] other than those comparing a biosimilar to its reference product, as required for regulatory approval.[103] In the absence of head-to-head studies, indirect comparisons provide the best evidence for demonstrating any differences between the available biologics.[104,105] When randomized controlled trials (RCTs) fail to make head-to-head comparisons, a common comparator can be used to make an indirect comparison.[106] For ethical reasons, it is not possible to conduct a trial with a placebo arm for more than 12 weeks to 16 weeks as, after that time, the efficacy of the biologic compared with the placebo is established.[107,108] Thus, the common comparator across many trials is MTX monotherapy, because the study personnel provide participants in the control arm with a placebo version of the experimental drug as well as MTX in order to extend the trial length.[108] A major limitation of previous systematic reviews was the lack of the use of indirect comparisons, which precluded the possibility of assessing the comparative benefits and harms of treatments to help identify the most appropriate treatment for patients with RA.

Using both direct and indirect comparisons is the essence of a network meta-analysis (NMA); the resulting review differs from the usual review, such that it is not intended to examine only one intervention for RA, but aims to systematically review and simultaneously compare the existing RCTs of biologics (including biosimilars), tsDMARDs, and csDMARD combination therapies for RA.[109,110]

# Policy Question

The policy question for this project, which was developed by CADTH's jurisdictional clients, is: In patients with moderate to severe RA who have failed or are intolerant to MTX, what is the optimal drug therapy?

## Objective

The objective of this review is to assess the benefits and harms of drugs used in adult patients with moderate to severe RA in whom treatment with MTX has failed or who are intolerant to MTX.

## Research Question

There is one research question for this review. This was developed to address the aforementioned policy issues:

- What is the comparative clinical efficacy and safety of csDMARD therapies (alone or in combination), biologics (including biosimilars), and tsDMARDs in adult patients with moderate to severe RA in whom treatment with MTX has failed who are intolerant to MTX?

## Methods

### Scope and Protocol

The CADTH clinical evaluation will bring together and build upon existing systematic reviews and NMAs conducted by Cochrane.[88,89,111] To inform the final scope of the therapeutic review, a proposed scope was developed with the assistance of clinical experts and CADTH's federal, provincial, and territorial customers. In addition, targeted stakeholder feedback from patient groups and industry was solicited.

The protocol was written a priori and registered with the International Prospective Register of Systematic Reviews (PROSPERO) prior to the completion of screening and study selection: CRD42016041498. An update to the protocol was made in July 2017 to indicate that this review is focused on a subset of the population identified in the protocol in order to address the specific policy questions of interest in a timely manner.

### Literature Search Strategy

The de novo literature searches were performed by information specialists using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; the Cochrane Library through Wiley; EBM Reviews – Cochrane CENTRAL Register of Controlled Trials through Ovid; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were traditional DMARDs (i.e., csDMARDs: methotrexate, hydroxychloroquine, sulfasalazine, leflunomide); biologic DMARDs (i.e., biologics: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, anakinra, tocilizumab, abatacept, rituximab); small molecules (i.e., tsDMARD: tofacitinib); subsequent entry biologics (i.e., biosimilar: infliximab subsequent entry biologic [SEB]); products under development (biosimilar adalimumab, etanercept, baricitinib, sarilumab, sirukumab) and rheumatoid arthritis.

Methodological filters were applied to limit retrieval to RCTs and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was limited to English language and by publication year (for certain drugs only). Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

Due to the use of existing systematic reviews as a baseline,[88,89,111] the de novo searches were limited by various publication years (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, anakinra, tocilizumab, abatacept, rituximab: published from January 1, 2015 to present; MTX published from January 1, 2014 to present; HCQ, SSZ, LEF,

infliximab SEB, adalimumab SEB, etanercept SEB, tofacitinib, baricitinib, sarilumab, sirukumab: no publication date limit).

The searches were completed on May 3, 2016. Regular alerts were established to update the search until March 1, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the CADTH *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of regulatory agencies, Health Technology Assessment agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. See Appendix 1 for more information on the grey literature search strategy.

## Patient Group Input

CADTH received patient input specific to this project in August 2016 from the Arthritis Society and CAPA. To collect information for the purpose of this project, the Arthritis Society surveyed its membership and promoted the survey through its social media channels. It received 149 responses. CAPA's board prepared its group's submission drawing on the knowledge and experience of five board members with RA and its network of members.

The input was used to help inform the protocol. The groups' comments are integrated into the report where applicable.

## Selection Criteria

Studies were eligible for inclusion in the review if they met the study design, population, intervention, and comparator criteria; studies were eligible for inclusion in the analysis if, in addition to the previous criteria, they met the outcomes of interest (Table 2). RCTs were considered for inclusion for efficacy outcomes. RCTs, controlled clinical trials, clinical trial registries, and FDA, Health Canada, European Medicines Agency (EMA) reports, labels, and warnings were considered for inclusion for safety outcomes. Further details on the biologics and biosimilars are available in Table 1. A list of the interventions of interest — including TNF blockers, IL-1 and IL-6 inhibitors, T-cell co-stimulatory inhibitor, B-lymphocyte–depleting drug, tsDMARDs, SEBs (now termed biosimilars), and combinations of csDMARDs — is also available in Table 2.

Only standard doses approved by Health Canada were eligible for analysis. In the event that a drug had two different dosing strategies where the total dose remained the same (e.g., etanercept 25 mg twice weekly or 50 mg every week) both dosing strategies were included as part of the same treatment node. Drugs that involved different routes of administration (e.g., abatacept IV and SC routes are both approved by Health Canada) were considered as separate treatment nodes. In the event that more than one biosimilar for the same reference product was marketed, each biosimilar was considered a separate node because it may not have the same modification in molecular structure as the reference product (e.g., Inflectra, Remsima and Flixabi as biosimilar infliximab drug). Patient groups of interest were those who had intolerance to or failure of MTX (i.e., IR MTX).

The primary efficacy outcome for this report is the ACR 50. The ACR is a score that indicates how much a patient's RA has improved. ACR 50 represents a 50% improvement. While the ACR 20 is often used in clinical trials, the ACR 50 provides a more stable comparison between the placebo and treatment arms because the placebo arm response

does not fluctuate as much as in the ACR 20. Moreover, results of the ACR 50 are also in line with the ACR20, as they use the same scale.[112]

## Table 2: Population, Intervention, Comparator, Outcome, and Study Designs of Interest

| Inclusion Criteria | |
|---|---|
| **Population** | **Inclusion:**<br>• Treatment-experienced adults with moderate to severe, active RA who have failed or are intolerant to MTX (inadequate responders)[a]<br><br>**Exclusion:**<br>• Patients who are MTX-naive<br>• Patients who are treatment-experienced, but only inadequate responders to sulfasalazine<br>• Patients who are treatment-experienced, but only inadequate responders to leflunomide<br>• Patients who are treatment-experienced, but only inadequate responders to hydroxychloroquine<br>• Patients who are inadequate responders to a biologic DMARD (biologic)<br>• Patients who are in clinical remission, have low disease activity, or have early RA |
| **Interventions** | **Inclusion**:<br>• Mono-, double, or triple-csDMARD therapies (eligible csDMARDs: methotrexate, hydroxychloroquine, sulfasalazine, leflunomide)<br>• Any of the biologics alone or in combination with csDMARDs (i.e., adalimumab, certolizumab pegol, etanercept, anakinra, golimumab, infliximab, tocilizumab, abatacept, rituximab, sirukumab, and sarilumab)<br>• tsDMARDs (i.e., tofacitinib, baricitinib) alone or in combination with csDMARDs<br>• Biosimilars (i.e., biosimilars of etanercept, infliximab, and adalimumab) alone or in combination with csDMARDs<br><br>**Exclusion**:<br>• Doses of any of the eligible drugs that are above or below the standard dose approved by Health Canada[c]<br>• MTX compared with itself, placebo, or a drug that is not of interest<br>• Older csDMARDs (i.e., auranofin, intramuscular gold, azathioprine, cyclosporine, and chloroquine)<br>• Combination biologics (i.e., two or more biologics given concurrently) |
| **Comparators** | **Inclusion**:<br>• Any of the drugs of interest or placebo<br><br>**Exclusion**:<br>• Studies with only one arm that is eligible<br>• Studies comparing multiple doses of the same drug without a comparator<br>• Studies comparing different routes of administration of the same drug without a comparator |

| Inclusion Criteria | |
|---|---|
| **Outcomes** | **Efficacy**<br>• ACR 20, 50, 70[d]<br>• Disease Activity Score (DAS/DAS 28)<br>• Disability (Health Assessment Questionnaire – Disability Index [HAQ-DI])<br>• Remission (DAS 28 remission < 2.6)<br>• Radiographic progression<br>• Health-related quality of life (SF-36 Physical and Mental Component Scores)<br>• Fatigue<br>• Pain<br><br>**Harms**<br>• Serious adverse events<br>• Withdrawal due to adverse events<br>• Mortality<br><br>**Notable harms**<br>• Serious infections<br>• Tuberculosis<br>• Cancer<br>• Leukemia<br>• Lymphoma<br>• Congestive heart failure<br>• Major adverse cardiac events<br>• Herpes zoster |
| **Study Design** | **Inclusion**:<br>*Efficacy*<br>• Randomized controlled trials<br><br>*Safety*[e]<br>• Randomized controlled trials<br>• Controlled clinical trials<br><br>**Exclusion**:<br>• Non-controlled studies (i.e., observational designs)<br>• Single-arm studies<br>• Trials with a randomization phase of < 12 weeks' duration |
| **Additional Exclusion Criteria** | |
| **Exclusions** | • Non-English publications<br>• Conference abstracts |

ACR = American College of Rheumatology; csDMARD = conventional synthetic disease-modifying antirheumatic drug; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; RA = rheumatoid arthritis; SF-36 = Short Form (36) Health Survey; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

[a] Studies where it is unclear whether patients were inadequate responders to MTX or a different csDMARD will be included in the reference case and removed in a sensitivity analysis.

[b] Applications for approval were withdrawn globally in October 2017 after sirukumab was not approved by the FDA.

[c] Drugs not approved by Health Canada at the time of review had the doses approved by other countries or doses submitted for approval.

[d] ACR 50 will be the primary ACR response outcome reported in the main text of the results.

[e] Safety data as found in grey literature sources (i.e., clinical trial registries, FDA, Health Canada, and European Medicines Agency reports, labels, and warnings) were also included.

Duplicates of studies identified across databases and from within the existing Cochrane systematic reviews were removed. Two reviewers then independently screened titles and abstracts for relevance to the clinical research questions. Full texts of potentially relevant articles were retrieved and independently assessed for possible inclusion based on the predetermined selection criteria (Table 2). The two reviewers compared their chosen included and excluded studies and discussed any disagreements until a consensus was reached. The selection process was standardized using DistillerSR, an online systematic review software tool (https://distillercer.com/products/distillersr-systematic-review-software/). This was done to maintain consistency across reporting from reviewers for the process of selecting studies and extracting data. Similarly, the grey literature sources (see Section 5.2) were searched independently by two reviewers. Records that met the selection criteria were cross-referenced against published articles included from the literature search to identify any articles that were associated with a particular grey literature source. If the grey literature record was not associated with any of the published studies, it was included in the review as a grey literature reference.

The study selection process is presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Figure 1).

## Data Extraction

Any published studies, as well as grey literature sources (e.g., studies registered that had data reported in clinical trial registries) were eligible to have data extracted. One reviewer performed data extraction; this was checked for accuracy by a second independent reviewer. A standardized data extraction form designed a priori in DistillerSR was used. Data extraction included: characteristics of included studies, including trial design, eligibility criteria, location, funding source, and trial registry number; characteristics of trial participants, including type of intervention, dose, duration, and concomitant medication; risk of bias (ROB) assessment; and results of the clinical efficacy and safety outcomes. Any disagreements were resolved by consensus when possible; otherwise, the judgment of a third reviewer was considered final.

The original, primary publication for each unique study was used for data extraction. However, in the event of multiple publications for a single primary study, the original article published was identified as the parent article and any subsequent publications (reporting specific outcomes or sub-populations from the original study) were identified as companions for the study. Supplemental online appendices contributing additional information for the parent and/or companion articles were also compiled. Data extraction (in the presence of multiple publications for a single primary study, as described earlier) was handled by extracting the most recently adjudicated data for each outcome specified a priori in the protocol. Data were extracted from figures using WebPlotDigitizer (www.arohatgi.info/WebPlotDigitizer) if not reported in tables or the text of the publication. When data on an outcome of interest were missing from the published article(s), data from clinical trial registry records were extracted. For grey literature records that were not associated with an included study, data were extracted using the same process.

Studies included from the previous Cochrane reviews went through the same *de novo* data extraction process for outcomes and baseline characteristics as for newly identified studies in the literature search.

In the event that a study reported multiple time points for an outcome of interest, the end-of-treatment time point was extracted for analysis except in the case of trials involving an adaptive design. Adaptive design trials have become more common in research for RA as they allow a study to plan for modifications to trial design and/or dose modifications with the use of a predefined interim analysis.[113,114] In this report, we distinguish between four major types of adaptive designs: 1) early escape trials, 2) rescue therapy trials, 3) treatment switching trials based on non-response criteria, and 4) planned treatment switching trials (Table 3). For studies involving an adaptive design, we extracted the data up until the time of adaptation to ensure that treatment effects could be attributed to a specific treatment. This was done to ensure that data included for analysis represented results with patients receiving the originally randomized treatment in order to address the policy and research questions.

Event data were extracted and analyzed as the number of participants with an event rather than the number of events. While it is possible for participants to experience an event more than once, this was not often reported in the studies; it would not be appropriate to combine this data with the number of patients with an event in an analysis. When a study reported the DAS or DAS 28 erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), the scale using the ESR was selected.

## Table 3: Definition of Adaptive Design Trials

| Adaptive Design | Description |
|---|---|
| Early Escape Trial | After a predetermined period (e.g., 12 weeks or 16 weeks) receiving treatment, patients who do not attain a predefined level of disease response are withdrawn from the trial and may enter an open-label extension phase. |
| Rescue Therapy Trial | After a predetermined period of receiving treatment, patients who do not attain a predefined level of disease response are permitted to receive rescue therapy (e.g., dose adjustment or addition of a DMARD or corticosteroid, receipt of one or more doses of active treatment for those in the comparator arm, increased dose of active drug). |
| Treatment Switching Trial (Based on Non-Response) | After a predetermined period (e.g., 12 weeks or 16 weeks) receiving treatment, patients who do not attain a predefined level of disease response are switched to another treatment arm for the remainder of the study. |
| Treatment Switching Trial (Planned) | Investigators plan a priori to either switch patients (e.g., in a control group) to another arm or re-randomize them to switch to one of a few possible treatment arms. The planned treatment switch could occur either:<br>a) as the only adaptation in the study duration, or<br>b) as the second adaptation after an initial adaptation (typically involving patients who had an IR). |

### Quality of Evidence

We assessed all unique studies included in this review using the Cochrane Risk of Bias tool. The ROB assessment comprised the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, and “other risks of bias.” The assessment for each domain is made in a “risk of bias” table that first describes what was reported to have occurred in the study and then involves a judgment by the ROB reviewer as to whether the study adequately met the requirements of the domain (“LOW” ROB) or not (“HIGH” ROB), or if there was insufficient information to make a decision (“UNCLEAR” or unknown ROB). The domain “blinding of outcome assessors” was assessed separately for subjective and objective outcomes

because subjective outcomes would be strongly influenced by a lack of proper blinding.[115] In addition, a separate consideration was made for the domain “incomplete outcome reporting” for efficacy and safety data. When all domains for a study were at low, unclear, or high ROB, the study was considered overall to be at low ROB, unclear ROB, or high ROB, respectively. In addition, if both selective outcome reporting and allocation concealment had high ROB, a study was considered to have high ROB overall, as this would have an impact on the conduct of the study.

Where multiple publications were present for a single primary study (i.e., parent and companion study publications, design and rationale documents, protocols, clinical trial registry records, and supplementary appendices), the original primary publication was assessed and the other available sources were considered to inform the ROB assessment.

Assessments were performed by a reviewer and verified by a second reviewer. Disagreements were resolved through consensus or by a third reviewer if consensus could not be reached.

Grey literature sources (regulatory agencies, websites of regulatory agencies, clinical trial registries) were searched and any eligible sources were included in the review to reduce the risk of publication bias. Publication bias was also assessed using funnel plots and Egger’s test on outcomes with at least 10 studies to aid in interpreting the review findings.

### Data Conversion and Imputation

For continuous outcomes, the selected measure for analysis was the mean difference from baseline to end of treatment. When mean change from baseline results were not available, other available data were extracted with an aim to calculate a mean change. In the event that a measure of dispersion (e.g., standard deviation, standard error) was not reported for the mean change from baseline, all efforts were made to find a measure of dispersion reported at baseline and/or end of treatment in the published study or within the clinical trial registry. When the measure of dispersion (e.g., standard deviation, standard error) was not available for the change from baseline data, we assumed that the measure of dispersion was the same between baseline and the end of treatment in order to calculate the measure of dispersion for the mean change from baseline. If no measure of dispersion was found for a primary study among any of its published and unpublished materials, the standard error was imputed by taking the median standard error across other studies of similar patient populations. Since it is difficult to ensure that the populations are the same across studies, any studies requiring such imputation were excluded from the reference case analysis and included only in a sensitivity analysis.

Calculations were required to obtain standard deviations and 95% confidence intervals (CIs) into standard errors for the mean change from baseline. In the event that a study reported the median and range, the mean and standard error were calculated using the methods outlined by Hozo et al.[116] If the median and interquartile range was presented, the median was assumed to be equivalent to the mean and the interquartile range was divided by 1.35 based on guidance in the Cochrane Handbook (Version 5.1.0).[117]

### Data Analysis

The study and patient characteristics for the included studies are presented narratively and summarized to accompany synthesized data.

An NMA was conducted when there were more than three studies contributing data to an outcome. When the NMA model did not properly converge (i.e., due to a large proportion of studies with all-arm zero events for binary data), a proportional continuity correction was applied. When model convergence was not robust following a continuity correction,[118] pairwise meta-analysis (MA) was used to analyze the outcome when there were at least two treatments being compared. A pairwise MA could not be conducted when all but one of the eligible studies had all-arm zero events. A descriptive analysis was performed when both MA and NMA were not feasible or appropriate (i.e., due to studies with all-arm zero events for binary outcomes, for which the effect cannot be estimated, or when there were fewer than two studies eligible for a pairwise comparison).

Data from studies with adaptive designs could only be included up to the time of adaptation, and any study in which the adaptation occurred before 12 weeks was excluded from analysis based on the review selection criteria. Additionally, studies without the standard dose of a treatment or that had only one arm with eligible data were excluded from analysis.

Additional details on the statistical analysis plan are available in Appendix 2.

### *Network Meta-Analysis*

Bayesian NMAs were conducted for outcomes pre-specified in the protocol, following assessment of heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols.[119] The minimum required length of treatment for analysis was three months. The effect estimate depended on the outcome of interest and availability of data. Only the standard doses approved by Health Canada were included for analysis; if Health Canada had not yet approved a treatment, the approved dose of another regulatory agency (i.e., FDA, EMA) was selected; if not approved anywhere, the phase III trial doses being investigated for approval were analyzed. Both fixed- and random-effects models were conducted; model selection was based on the deviance information criterion and residual deviance. R (R Foundation for Statistical Computing, Vienna, Austria) and WinBUGS (MRC Biostatistics Unit, Cambridge, UK) were used for Bayesian NMA according to the routing that accommodates evidence structures, which may consist of multi-arm trials as developed at the University of Bristol and University of Leicester (http://www.bristol.ac.uk/population-health-sciences/centres/cresyda/mpes/). A generalized linear model was used with a logit link function for binary outcomes; a generalized linear model with an identity link function was used for continuous outcomes.

Given that it is unethical to conduct an RCT with a placebo arm for more than 12 weeks to 16 weeks in RA (due to a lack of clinical equipoise and sufficient time to demonstrate clinical efficacy during that period),[107,108] trials often provide those receiving placebo of the experimental drug with concomitant MTX (or other csDMARD) monotherapy in order to extend the trial length for longer-term outcomes (e.g., radiographic progression, quality of life, safety).[108] MTX monotherapy with a placebo of another drug (placebo + MTX) was identified as the common comparator (i.e., index node about which all other treatments are anchored) for the Bayesian NMAs. In most studies, concomitant MTX was permitted for participants, but all other csDMARDs were not. However, certain studies did not specifically indicate if participants were receiving MTX due to either 1) unclear reporting (e.g., only indicating a csDMARD was permitted for concomitant use); or 2) permitting participants to receive their choice of one of several csDMARDs that may have included MTX. To ensure greater homogeneity of the evidence network, analyses were conducted by subgroups. Studies permitting concomitant treatment with only MTX (common comparator: placebo + MTX) were included in one evidence network. In the other evidence network (common

comparator: placebo + csDMARD), studies either: 1) restricted concomitant therapy to a csDMARD that was not MTX; 2) permitted the use of one or more csDMARDs; or 3) did not provide information on the type of concomitant csDMARD(s) permitted.

Posterior densities for unknown parameters were estimated using Markov chain Monte Carlo methods. Basic parameters were assigned informative prior distributions for the between-study variance, following Turner et al.[120]; non-informative or vague priors were considered when there were issues of model convergence. Findings are summarized as the point estimates and 95% credible intervals (CrIs). Point estimates were reported as the odds ratio for binary outcomes; for continuous outcomes, the mean difference was reported, or the standardized mean difference was reported when more than one scale was used across included studies. Consistency between direct and indirect evidence was formally assessed using back-calculation and node-splitting techniques. Model diagnostics also included trace plots and the Gelman–Rubin–Brooks statistic to assess and ensure model convergence. Three chains were fit in WinBUGS for each analysis, each employing approximately 20,000 iterations, with a burn-in of approximately 20,000 iterations.

Graphical methods of displaying the geometry for each evidence network were used to investigate the shape, symmetry, and complexity of the evidence networks being analyzed.[121,122] The nodes represent specific treatments and the lines connecting nodes represent a direct comparison between two treatments within included studies. Nodes are proportional to the total number of participants who had received a particular treatment and contributed data; line thickness is proportional to the number of studies involving a particular direct comparison. For each evidence network, we presented the total number of participants, treatments, and direct comparisons.

For sensitivity analyses, the 81 studies that were of poor methodological quality (i.e., unclear or high ROB overall) were removed from the network. Inclusion of treatment doses above and below the standard dose was another sensitivity analysis. The following sensitivity analyses were also conducted: 1) imputed standard errors for studies with no measure of dispersion (e.g., standard deviation, standard error) available (done taking the median standard error from other studies included in the evidence network); 2) publication date before 2007; 3) publication date from 2007 onwards; 4) end-of-treatment data from adaptive design trials; 5) including only studies that explicitly mentioned patients who had an IR to MTX rather than an IR to any csDMARD before study entry; and 6) including only studies with overall low ROB.

Sensitivity analyses planned post hoc included: 1) an analysis that included patients who were IR MTX and biologic-naive; 2) an analysis excluding studies that were conducted in Asian patients only; 3) an analysis of studies that were conducted in Asian patients only; 4) a restricted time point analysis of end of treatment (or adaptive time point) data from week 12 to week 16; and 5) an analysis excluding triple-csDMARD therapy studies published before 2000. Results of the sensitivity analyses are reported as the odds ratio with 95% CrIs for binary outcomes and the mean difference (or standardized mean difference) with 95% CrIs. Direct comparisons that were present in both the reference case and sensitivity analyses were examined to determine the direction of the change (if there was a change in statistical significance) or whether no change occurred.

*Meta-Analysis*

When an NMA was not possible, use of pairwise MAs was explored. When no pairwise comparisons were present in two or more trials, the results were analyzed descriptively. MAs were undertaken using fixed- or random-effects models when data were available, sufficiently similar, and of sufficient quality. The effect sizes for the identified binary outcomes were expressed in terms of the odds ratio. In cases when events were rare, the Peto odds ratio was used.[123]

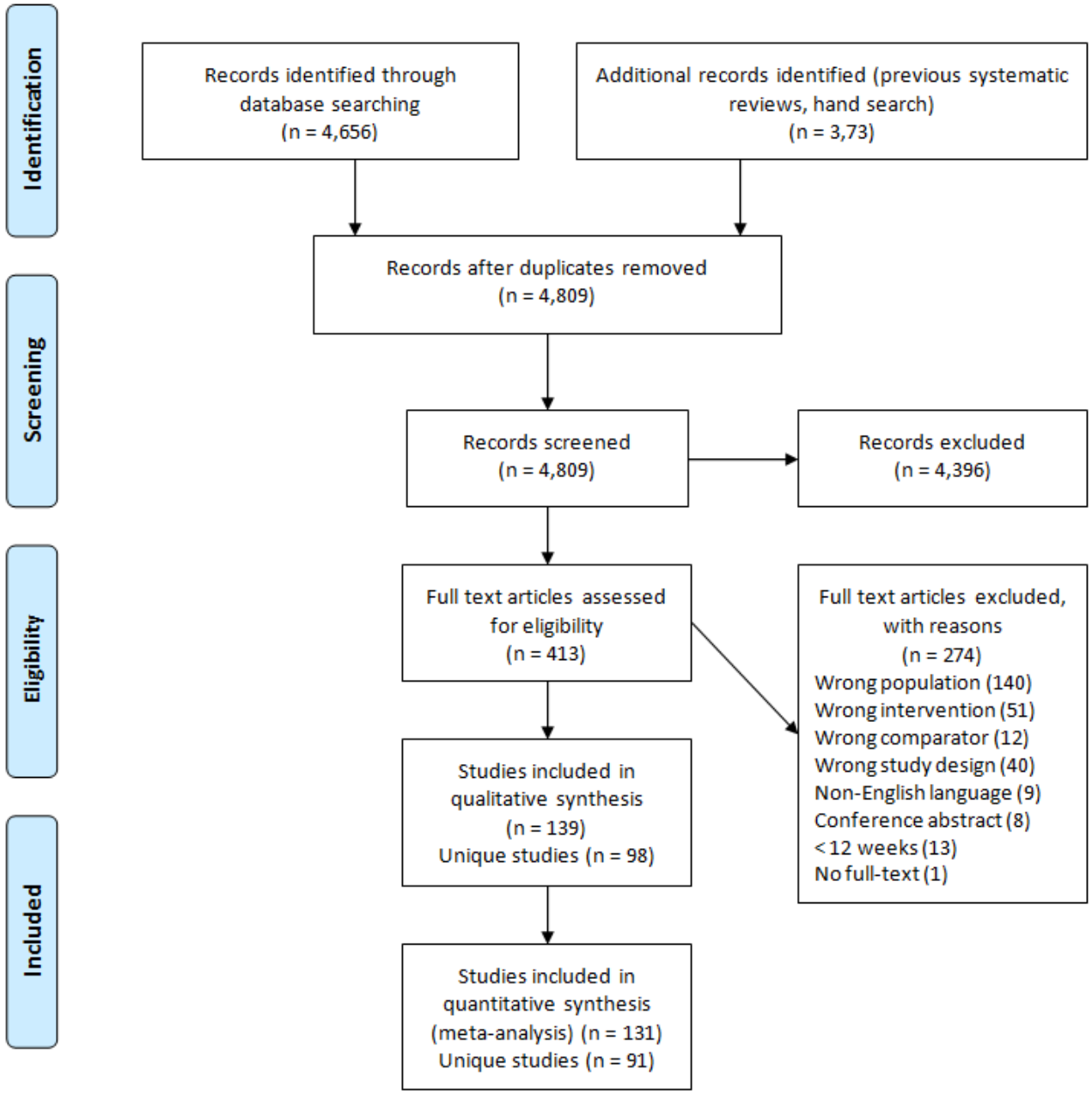
Results were assessed for both clinical heterogeneity and methodological heterogeneity. Clinical heterogeneity was assessed by checking that the populations, interventions, and comparators were not so different from each other that combining them would be inappropriate. Methodological diversity was assessed by checking that the studies were similar in terms of study design and ROB. Once satisfied that the studies were minimally diverse and that it was appropriate to pool them in a meta-analysis, an assessment of the statistical heterogeneity was undertaken by examining the forest plot and result of the $I^2$ statistic; the forest plots provided a visual sense of heterogeneity while the $I^2$ statistic indicated the presence of statistical heterogeneity. If the effects observed across trials were inconsistent and varied to a large extent (e.g., $I^2 > 50\%$), the results were explored again to assess whether the differences could be explained by some clinical or methodological feature.

# Results

## Selection of Primary Studies

The literature search yielded 4,656 citations; 373 records were additionally retrieved from existing systematic reviews (n = 364), grey literature (n = 4), and through a hand search (n = 5). Altogether, 4,809 citations were identified after removing 220 duplicate records. Screening of titles or abstracts led to the exclusion of 4,396 of these records. The full texts of the 413 remaining records were assessed and 98 unique studies and 41 companion publications were included in the systematic review.[94-102,124-253] There were 91 unique RCTs and 40 companion publications eligible for analysis.[94-102,124-128,130-158,160-165,167-176,178-200,202-209,211-224,226-230,232-253] One clinical controlled trial was included in the systematic review, but it did not report any safety outcomes; thus, it was not eligible for the analysis.[129] Three ClinicalTrials.gov records were included as unique studies, as they were not associated with any published studies.[130,211,213] Three studies were not included in the analysis because they involved an adaptive design at eight weeks,[201,225,231] which meant the data eligible for analysis in our review (i.e., data before the adaptive design) were less than the pre-specified 12-week duration. A minimum of 12 weeks was determined based on this being the shortest time frame for demonstrating efficacy of a drug versus placebo in RA.[107] Three studies and one companion publication were not analyzed with the other studies because all participants received the experimental drug (a biologic in these cases) in an open-label, lead-in phase, and those who responded to a biologic were randomized to one of the study arms; this represents a different population than the other studies because participants had already been shown to respond to the biologic prior to the randomization phase.[159,166,177,210] The PRISMA flowchart for the study selection process is found in Figure 1. A full list of included studies is available in Appendix 3 and excluded studies (with reasons) in Appendix 4.

## Figure 1: PRISMA Flow Diagram[254]




PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

## Study Characteristics

Detailed trial characteristics of the included studies that reported on the outcomes of interest are available in Table 3. Forty-one RCTs[94,95,97,100,102,135,143,151,153,158,160,162,163,171,174-176,178,180,184-188,193,207,208,211,214-217,223,229,234,240,243,245,247-249] and 18 companion publications used an adaptive design that involved one of the following adaptations when participants did not reach a predefined level of disease response:

1) Early escape from the trial
2) Rescue therapy
3) Treatment switch based on non-response criteria defined a priori
4) Planned treatment switch.

Data available up to the time of first trial adaptation were analyzed for these RCTs, which occurred most often between 12 weeks and 16 weeks after initiation of treatment (see Appendix 5 for details on each adaptive design trial).

The 91 RCTs included for analysis had their data extracted and analyzed at the end of the treatment period, except for the 41 adaptive design trials that were analyzed at the time of adaptation. Treatment duration varied greatly across studies from three months to 36 months. Due to the presence of adaptive design trials, the treatment duration eligible for analysis ranged from three months to 24 months, with the most common treatment durations being four, three, and six months, respectively.

In the included studies, women comprised an average of 80.6% of the total number of participants (range: 43.3% to 100%). Patients enrolled in the RCTs were adults diagnosed with RA in whom treatment with a csDMARD had failed or who were intolerant to at least one csDMARD. The majority of included studies enrolled participants who had an IR to MTX, while 14 studies permitted the concomitant use of an unspecified csDMARD (i.e., either the report did not specify which csDMARD participants could take or investigators permitted participants a choice between MTX or another csDMARD). Sample sizes of RCTs ranged from 28 to 1,220 participants, with a median of 313 participants. More specifically, 10 studies had a sample size < 100, six studies had a sample size > 1,000, and the rest had a sample size between 100 participants and 1,000 participants. A summary of the patient characteristics of the included studies is available in Table 4. Appendix 6 provides further details on the study characteristics (Table 43) and patient characteristics (Table 44) of included studies.

## Table 4: Summary of Trial Characteristics

| Trial Characteristics | Categories | Number of Unique Included Studies |
|---|---|---|
| Publication Status | Unique studies | 98 |
| | Unique studies reporting outcomes of interest | 91 |
| Study Design (Unique studies) | Parallel RCT | 52 |
| | Adaptive design RCT | 41 |
| | Open-label, lead-in phase[a] RCT | 4 |
| | Controlled clinical trial | 1 |
| Intervention Comparison (Unique studies reporting outcomes of interest) | Placebo control | 6 |
| | Active control (MTX monotherapy) | 49 |
| | Active control (csDMARD monotherapy) | 13 |
| | Active control (csDMARD combination therapy) | 4 |
| | Active control (biologic) | 19 |
| Publication Year (Unique Studies) | | Range: 1995 to 2017 |
| Randomized[b] Sample Size (Unique Studies) | Small (< 100 participants) | 11 |
| | Medium (100 to 500 participants) | 55 |
| | Large (> 500 participants) | 32 |
| Duration of Study (Unique Studies) | < 3 months[c] | 2 |
| | 3 months to 6 months | 79 |
| | > 6 months to one year | 12 |
| | > 1 year | 5 |
| Treatment Duration Eligible for Analysis (Unique Studies) | 3 months to 6 months | 65 |
| | > 6 months to one year | 22 |
| | > 1 year | 11 |

csDMARD = conventional synthetic disease-modifying antirheumatic drug; MTX = methotrexate; RCT = randomized controlled trial.
[a] Patients who respond during the open-label, lead-in phase are eligible to enter the randomization phase.
[b] Sample size at baseline in the case of the one included clinical controlled trial.
[c] Studies with an adaptive design before 3 months.

## Table 5: Summary of Patient Characteristics

| Baseline Characteristics | Pooled Baseline Estimates, Mean (Range) |
|---|---|
| Mean age (years) | 52.5 (43.2 to 58.1) |
| Gender (% female) | 80.7 (43.3 to 100) |
| Mean duration of RA (years) | 7.84 (0.94 to 13.0) |
| Caucasian (%) | 35.3 (0 to 99.4) |
| Total mean of Tender Joint Count | 23.34 (7.1 to 37.2) |
| Total mean of Swollen Joint Count | 16.46 (6.3 to 31.0) |

RA = rheumatoid arthritis.

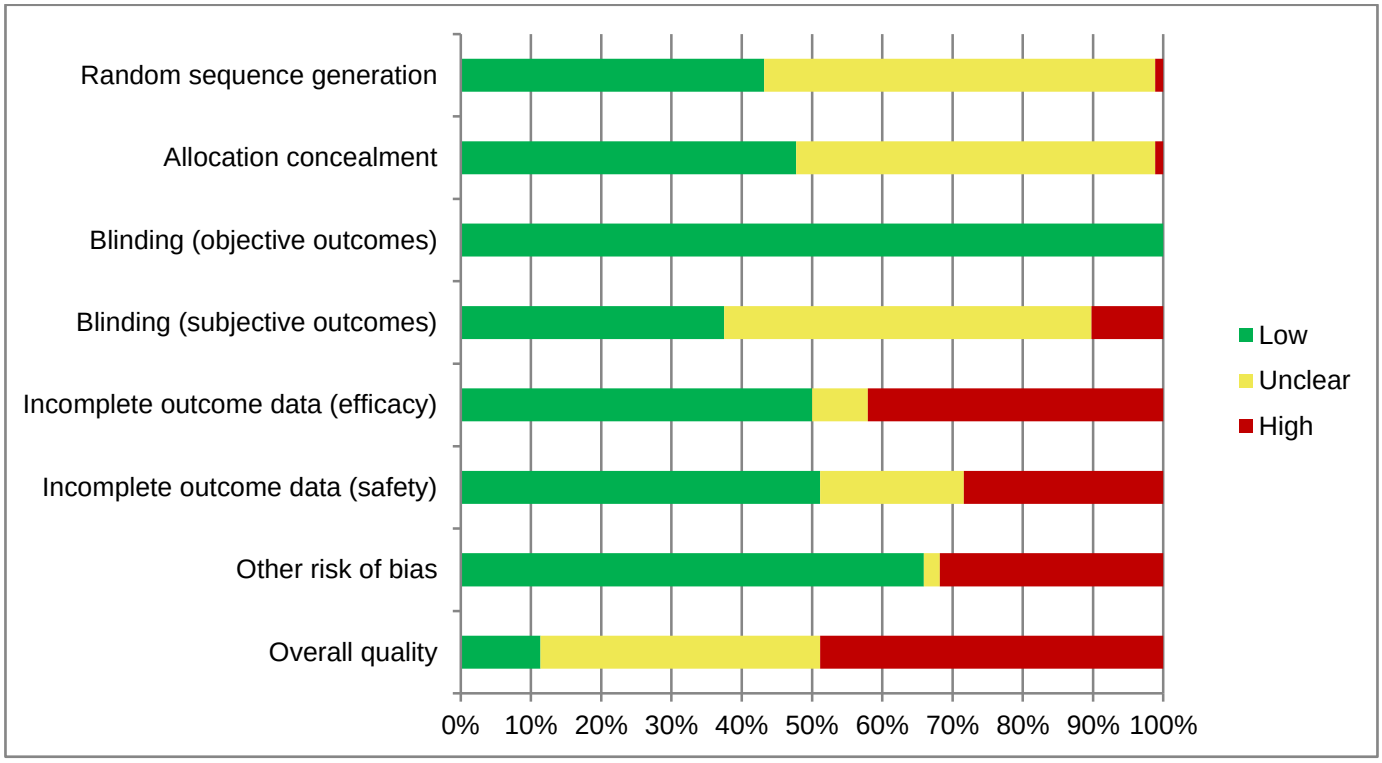
## Risk of Bias

A ROB assessment was performed for all unique studies using the Cochrane Collaboration's ROB tool. Figure 2 provides an overall summary of the results for all the included RCTs. More detailed results at the study level are reported in Appendix 7.

Three of the studies included in analysis did not have their ROB assessed because they were grey literature sources.[130,211,213] Of the 88 assessed, just over half of the included studies inadequately reported on random sequence generation and allocation concealment, resulting in an unclear ROB. The remaining studies all had a low ROB in these domains, except for one.[192] All studies reporting objective outcomes had a low ROB for blinding. For studies reporting subjective outcomes, about half (52%) were considered to have an unclear ROB because there were no details on how blinding was maintained for participants. About one-third of studies (38%) had low ROB because they provided sufficient details on how blinding was maintained for participants, personnel, and outcome assessors. While a majority of studies had a low ROB for incomplete outcome data for efficacy and safety, 42% and 28% of studies had a high ROB for incomplete outcome data for efficacy outcomes and safety outcomes, respectively. For this review, the domain "Other Bias" was predominantly used to assess whether outcome data were reported at the time of adaptation in adaptive design trials (see Table 3 for definitions). Thirteen adaptive design trials had a low ROB because they reported on outcome data at the time of adaptation; 26 adaptive design trials had a high ROB because they did not adequately report on outcome data at the time of adaptation (two adaptive design trials did not have ROB assessed because they were from grey literature sources). There were two conventional design trials that had an unclear ROB because of small sample sizes that affected the ability to demonstrate non-inferiority[169] or resulted in baseline imbalances, but the impact on the results was unclear.[170] One other conventional design trial had a high ROB due to imbalanced randomization.[227] Among all studies assessed for ROB, half were judged to have a high ROB and only 10 were considered to have a low ROB overall; the rest (39%) had an unclear ROB overall.

Studies also poorly reported the definitions of study outcomes (e.g., DAS28 using ESR or CRP, Health Assessment Questionnaire [HAQ] or Health Assessment Questionnaire – Disability Index [HAQ-DI]) and did not conduct true intention-to-treat analyses (i.e., all randomized patients are analyzed according to their original assignment) for reported outcomes. The use of adaptive designs also limited the ability to incorporate data from later time points from studies in this review because the true treatment effect was unclear, with changes to therapy or high attrition after the point of adaptation. Eleven studies, reporting outcomes of interest, failed to report measures of dispersion along with mean change from baseline values in at least one outcome of interest.[131,156,171,172,178,186,191,233,236,241,244] This required either imputation using baseline or end-of-study standard deviations or standard errors if available, or exclusion of studies from the reference case analysis. (Missing standard errors for these were imputed in a sensitivity analysis.)

## Figure 2: Summary of Risk of Bias Assessment




## Data Synthesis

A total of 13 NMAs were conducted for 12 outcomes for the reference case where the common comparator was MTX monotherapy. (The Short Form [36] Health Survey [SF-36] Physical and Mental Component Scales were assessed separately for HRQoL.) A total of seven NMAs were conducted on seven outcomes for the reference case where the common comparator was a csDMARD (i.e., not necessarily MTX). These outcomes had sufficient data for network models (Table 6).

For each outcome, the mean differences or odds ratios from the NMA of the reference case are provided comparing the standard approved dose of each drug with either MTX monotherapy (placebo + MTX) or csDMARD monotherapy (placebo + csDMARD). For tocilizumab, both the 4 mg/kg and 8 mg/kg standard doses were included. Both approved doses of sarilumab (150 mg and 200 mg) were included. Baricitinib has not yet been approved in Canada, but the dose of 4 mg daily (orally) was selected given its approval in the European Union.[255] Sirukumab was under review with Health Canada at the time of analysis; thus, the phase III trial doses (50 mg every four weeks and 100 mg every two weeks, SC) were used in this review.[256] Johnson & Johnson withdrew all applications for regulatory approval in October 2017, which was after the analysis was completed for this review.[57]

For continuous outcome measures that used a standardized mean difference (SMD) (i.e., DAS28, pain, and fatigue), the results were interpreted using the rule of thumb as defined by Cohen[257] that identifies a small effect size (SMD = 0.2 to < 0.5), medium effect size (SMD = 0.5 to < 0.8), and large effect size (SMD ≥ 0.8).

Fifty-seven studies did not clearly report on the route of administration of MTX (i.e., oral or SC); 14 studies permitted participants to take concomitant MTX orally or SC. Thirteen studies permitted only oral MTX use, and 11 studies included in the analysis did not permit the participants to receive MTX. In most cases, it was not clear whether participants of the included studies were receiving oral or SC MTX, and since this was often the background therapy, the route of administration may have differed.

Table 6 provides an overview of each analysis by outcome and patient group. Tables for each outcome described in the following sections report all treatment comparisons that were made. If a treatment does not appear in a particular outcome's results table, it is an indication that the treatment was not included in the analysis. Results for sensitivity analyses are available in Appendix 8.

## Table 6: Overview of Evidence and Analyses Performed

| Method of Analysis | Methotrexate as a Common Comparator | Conventional Synthetic DMARD as a Common Comparator |
|---|---|---|
| **Efficacy Outcomes** | | |
| Network Meta-Analysis | • ACR 20, ACR 50, ACR 70<br>• DAS 28<br>• Disability (HAQ-DI)<br>• Remission<br>• Radiographic progression<br>• Pain<br>• Fatigue<br>• Health-related quality of life (Physical and Mental Component Scores) | • ACR 20, ACR 50, ACR 70<br>• DAS 28<br>• Disability (HAQ-DI) |
| Meta-Analysis | NA | NA |
| Descriptive Analysis | NA | • Health-related quality of life (SF-36 Physical and Mental Component Scores)<br>• Remission<br>• Pain<br>• Fatigue |
| **Safety Outcomes** | | |
| Network Meta-Analysis | • Withdrawal due to adverse events<br>• Serious adverse events | • Withdrawal due to adverse events<br>• Serious adverse events |
| Meta-Analysis | • Serious infections<br>• Mortality<br>• Tuberculosis<br>• Cancer<br>• Herpes zoster | NA |

| Method of Analysis | Methotrexate as a Common Comparator | Conventional Synthetic DMARD as a Common Comparator |
|---|---|---|
| Descriptive Analysis | • Mortality<br>• Serious infections<br>• Tuberculosis<br>• Cancer<br>• Leukemia<br>• Lymphoma<br>• Congestive heart failure<br>• Herpes zoster | • Mortality<br>• Serious infections<br>• Tuberculosis<br>• Cancer<br>• Leukemia<br>• Major adverse cardiac event<br>• Herpes zoster |

ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; DAS 28 = Disease Activity Score 28; HAQ-DI = Health Assessment Questionnaire – Disability Index; NA = not applicable; SF-36 = Short Form (36) Health Survey.
Note: Certain outcomes are listed in both the meta-analysis and descriptive analysis. This is the case when there were one or more pairwise meta-analyses that could be performed. The remaining treatment comparisons that did not appear in more than one study were reported in a descriptive analysis.

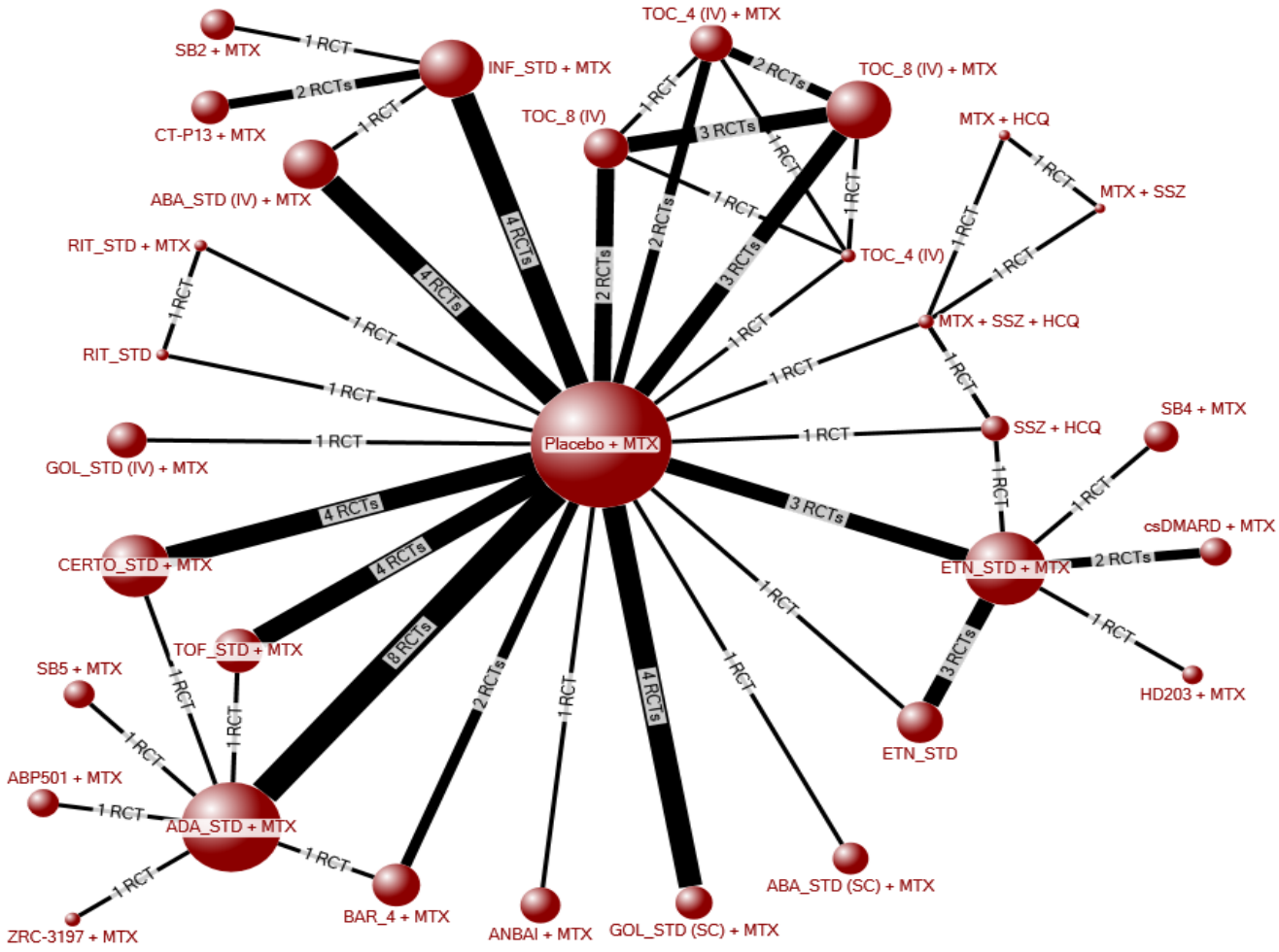
## Disease Severity

The results for disease severity based on the ACR 50 are presented in this section. Full results for the ACR 20 and ACR 70 are presented in Appendix 9 (tables 84 to 87).

### *Methotrexate as a Common Comparator*

Fifty-seven RCTs reporting ACR 50 were included in the reference case NMA: 48 two-arm studies, eight three-arm studies, and one five-arm study.[95,99,100,102,128,130,132,136-139,150,155,165,167,169,171,174-176,178-180,185,186,188,190,191,193-195,199,204-207,213-216,218,224,226,227,229,230,232,234,236,237,240,243-245,248,251,253] The evidence network involved 18,995 participants and 31 treatments, forming 82 direct comparisons. Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in Figure 3. The odds ratios for all treatment comparisons with MTX monotherapy as the common comparator are available in Table 7.

## Figure 3: Evidence Network: ACR 50 (Placebo + Methotrexate)




ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; ANBAI = Anbainuo (biosimilar adalimumab); BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar of infliximab; ETN = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; HD203 = etanercept biosimilar; INF = infliximab; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; RIT = rituximab; SB2 = biosimilar infliximab 3 mg/kg; SB4 = biosimilar etanercept 50 mg; SB5 = biosimilar adalimumab; SC = subcutaneous; SSZ = sulfasalazine; STD = standard dose; RCT = randomized controlled trial; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; ZRC-3197 = biosimilar of adalimumab.

Compared with MTX monotherapy, participants receiving the following treatments had statistically significantly higher odds of achieving ACR 50 disease response, by treatment category: 1) double-csDMARD therapy with MTX and HCQ and triple-csDMARD therapy with MTX, HCQ, and SSZ; 2) the TNF inhibitors: etanercept in combination with MTX; infliximab in combination with MTX; adalimumab in combination with MTX; golimumab in combination with MTX (IV and SC routes); and certolizumab pegol in combination with MTX; 3) the non-TNF inhibitors: abatacept (IV and SC) in combination with MTX; 8 mg/kg tocilizumab monotherapy; 8 mg/kg tocilizumab combination therapy with MTX; 4 mg/kg tocilizumab in combination with MTX; and rituximab in combination with MTX; 4) the

tsDMARDs tofacitinib in combination with MTX and 4 mg baricitinib in combination with MTX; and 5) the biosimilars HD203 (biosimilar etanercept) in combination with MTX; SB4 (biosimilar etanercept) in combination with MTX; Anbainuo (biosimilar etanercept) in combination with MTX; CT-P13 (biosimilar infliximab) in combination with MTX; SB5 (biosimilar adalimumab) in combination with MTX; ZRC-3197 (biosimilar adalimumab) in combination with MTX; and ABP501 (biosimilar adalimumab) in combination with MTX (Table 7). All of the biologic and tsDMARD monotherapy treatment arms did not have a statistically significant ACR 50 response compared with MTX monotherapy (Table 7).

Several treatments were found to have statistically significantly higher odds of achieving ACR 50 disease response compared with double-csDMARD therapy with MTX and any other csDMARD. The csDMARD combinations that were found to have higher odds compared with csDMARD + MTX were: MTX in combination with HCQ (odds ratio = 7.41; 95% CrI, 1.03 to 50.72) and triple-csDMARD therapy with MTX, SSZ, and HCQ (odds ratio = 8.33; 95% CrI, 1.92 to 36.61), though the CrIs were wide. The other treatments with statistically significantly greater odds of achieving ACR 50 compared with a csDMARD in combination with MTX include: 1) the TNF inhibitors: etanercept in combination with MTX; adalimumab in combination with MTX; golimumab (SC) in combination with MTX; and certolizumab pegol in combination with MTX; 2) the non-TNF inhibitors: abatacept (IV) in combination with MTX; 8 mg/kg tocilizumab (monotherapy); 8 mg/kg tocilizumab in combination with MTX; and rituximab in combination with MTX; 3) the tsDMARDs tofacitinib in combination with MTX and 4 mg baricitinib in combination with MTX; 4) the biosimilars HD203 (biosimilar etanercept) in combination with MTX; SB4 (biosimilar etanercept) in combination with MTX; Anbainuo (biosimilar etanercept) in combination with MTX; and CT-P13 (biosimilar infliximab) in combination with MTX. Interestingly, only participants receiving triple-csDMARD therapy with MTX, SSZ, and HCQ had statistically significantly higher odds of achieving ACR 50 response compared with double-csDMARD therapy with MTX and SSZ (odds ratio = 4.87 [95% CrI, 1.11 to 24.93]). When the double-csDMARD combination therapy of SSZ and HCQ was the comparator, it was found that triple-csDMARD therapy (MTX + SSZ + HCQ), tofacitinib in combination with MTX, golimumab (SC) in combination with MTX, certolizumab pegol in combination with MTX, and two biosimilar etanercept drugs (HD203 and Anbainuo) in combination with MTX had greater odds of achieving ACR 50.

Both etanercept monotherapy and 4 mg/kg tocilizumab monotherapy had lower odds of achieving an ACR 50 response compared with triple-csDMARD therapy with MTX, SSZ, and HCQ (odds ratio = 0.20 [95% CrI, 0.05 to 0.77] and odds ratio = 0.17 [95% CrI, 0.03 to 0.80], respectively). Aside from triple-csDMARD therapy, 11 treatments in combination with MTX had higher odds of meeting the ACR 50 response criteria compared with etanercept monotherapy, including all three biosimilar etanercept drugs (HD203, SB4, and Anbainuo) in combination with MTX. The other treatments were etanercept, abatacept (IV), adalimumab, tofacitinib, 8 mg/kg tocilizumab, golimumab (SC), certolizumab pegol, and 4 mg baricitinib, all in combination with MTX (Table 7). However, when these three biosimilar etanercept drugs in combination with MTX were compared against etanercept in combination with MTX, there was no statistically significant difference in ACR 50 disease response. In addition, no other treatments demonstrated any statistically significant higher odds of ACR 50 compared with etanercept in combination with MTX.

Compared with 4 mg/kg tocilizumab (IV) monotherapy, patients receiving MTX combination therapy with tofacitinib, 8 mg/kg tocilizumab (IV), golimumab (SC), certolizumab pegol, 4 mg

baricitinib, HD203 (biosimilar etanercept), and Anbainuo (biosimilar etanercept) had higher odds of achieving the ACR 50 response criteria (Table 7).

There were no other statistically significant comparisons between treatments for the outcome of ACR 50 response (Table 7).

## Table 7: ACR 50 (Placebo + MTX): Odds Ratios, Relative Risks, and Risk Differences for All Treatment Comparisons — Random-Effects Model

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| csDMARD + MTX | Placebo + MTX | 1.06 (0.47 to 2.70) | 1.05 (0.50 to 2.26) | 0.01 (–0.06 to 0.14) |
| MTX + SSZ | | 1.81 (0.24 to 13.41) | 1.65 (0.26 to 5.51) | 0.08 (–0.09 to 0.52) |
| MTX + HCQ | | 7.88 (1.33 to 48.99) | 4.39 (1.28 to 7.57) | 0.39 (0.03 to 0.75) |
| SSZ + HCQ | | 2.02 (0.91 to 4.66) | 1.81 (0.92 to 3.29) | 0.09 (–0.01 to 0.26) |
| MTX + SSZ + HCQ | | 8.84 (2.60 to 33.24) | 4.63 (2.19 to 7.15) | 0.42 (0.14 to 0.70) |
| ETN_STD | | 1.76 (0.93 to 3.54) | 1.62 (0.94 to 2.75) | 0.07 (–0.01 to 0.20) |
| ETN_STD + MTX | | 3.95 (2.29 to 7.51) | 2.94 (1.98 to 4.34) | 0.22 (0.12 to 0.38) |
| ABA_STD (IV) + MTX | | 4.12 (2.59 to 6.75) | 3.03 (2.18 to 4.10) | 0.23 (0.14 to 0.35) |
| ABA_STD (SC) + MTX | | 3.68 (1.51 to 8.88) | 2.81 (1.43 to 4.69) | 0.21 (0.05 to 0.42) |
| ADA_STD + MTX | | 3.99 (2.84 to 5.62) | 2.96 (2.33 to 3.72) | 0.23 (0.16 to 0.30) |
| TOF_STD + MTX | | 5.83 (3.45 to 9.79) | 3.73 (2.68 to 4.93) | 0.32 (0.20 to 0.44) |
| TOC_4 (IV) | | 1.53 (0.58 to 3.97) | 1.44 (0.61 to 2.96) | 0.05 (–0.05 to 0.23) |
| TOC_8 (IV) | | 3.80 (2.11 to 6.92) | 2.87 (1.87 to 4.14) | 0.22 (0.10 to 0.36) |
| TOC_4 (IV) + MTX | | 2.71 (1.43 to 5.09) | 2.26 (1.37 to 3.47) | 0.15 (0.04 to 0.28) |
| TOC_8 (IV) + MTX | | 4.31 (2.62 to 7.20) | 3.11 (2.21 to 4.23) | 0.25 (0.14 to 0.37) |
| GOL_STD (SC) + MTX | | 6.00 (3.27 to 11.35) | 3.80 (2.58 to 5.27) | 0.32 (0.19 to 0.48) |
| GOL_STD (IV) + MTX | | 2.90 (1.21 to 7.12) | 2.38 (1.19 to 4.19) | 0.16 (0.02 to 0.37) |
| INF_STD + MTX | | 3.00 (1.78 to 5.08) | 2.44 (1.63 to 3.48) | 0.17 (0.07 to 0.28) |
| CERTO_STD + MTX | | 5.35 (3.42 to 8.67) | 3.56 (2.66 to 4.67) | 0.30 (0.20 to 0.41) |
| RIT_STD | | 3.56 (0.92 to 15.08) | 2.74 (0.92 to 5.82) | 0.20 (–0.01 to 0.55) |
| RIT_STD + MTX | | 5.54 (1.47 to 23.02) | 3.63 (1.39 to 6.60) | 0.30 (0.05 to 0.63) |
| BAR_4 + MTX | | 5.44 (3.16 to 9.69) | 3.59 (2.52 to 4.91) | 0.30 (0.18 to 0.44) |
| HD203 + MTX | | 7.11 (2.46 to 23.00) | 4.16 (2.10 to 6.59) | 0.37 (0.13 to 0.63) |
| SB4 + MTX | | 4.65 (1.78 to 13.60) | 3.27 (1.64 to 5.61) | 0.26 (0.07 to 0.52) |
| ANBAI + MTX | | 8.76 (3.02 to 26.39) | 4.61 (2.44 to 6.82) | 0.42 (0.17 to 0.66) |
| CT-P13 + MTX | | 4.13 (1.82 to 9.95) | 3.03 (1.66 to 4.93) | 0.24 (0.08 to 0.45) |
| SB2 + MTX | | 2.62 (0.98 to 7.02) | 2.20 (0.99 to 4.18) | 0.14 (–0.002 to 0.36) |
| SB5 + MTX | | 3.73 (1.49 to 9.34) | 2.84 (1.41 to 4.79) | 0.21 (0.05 to 0.43) |
| ZRC-3197 + MTX | | 3.87 (1.29 to 11.77) | 2.90 (1.25 to 5.28) | 0.22 (0.03 to 0.49) |
| ABP501 + MTX | | 3.59 (1.45 to 8.79) | 2.76 (1.38 to 4.67) | 0.20 (0.04 to 0.42) |
| MTX + SSZ | csDMARD + MTX | 1.70 (0.19 to 13.51) | 1.56 (0.22 to 6.20) | 0.07 (–0.14 to 0.50) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| MTX + HCQ | | 7.41 (1.03 to 50.72) | 4.01 (1.02 to 10.34) | 0.38 (0.004 to 0.74) |
| SSZ + HCQ | | 1.91 (0.69 to 4.93) | 1.71 (0.73 to 3.79) | 0.08 (–0.05 to 0.24) |
| MTX + SSZ + HCQ | | 8.33 (1.92 to 36.61) | 4.29 (1.62 to 10.10) | 0.41 (0.11 to 0.69) |
| ETN_STD | | 1.66 (0.72 to 3.73) | 1.53 (0.76 to 3.10) | 0.06 (–0.05 to 0.17) |
| ETN_STD + MTX | | 3.73 (1.98 to 7.04) | 2.78 (1.61 to 4.98) | 0.21 (0.12 to 0.32) |
| ABA_STD (IV) + MTX | | 3.90 (1.38 to 10.08) | 2.87 (1.26 to 6.42) | 0.23 (0.06 to 0.36) |
| ABA_STD (SC) + MTX | | 3.48 (0.94 to 11.41) | 2.64 (0.96 to 6.56) | 0.20 (–0.01 to 0.42) |
| ADA_STD + MTX | | 3.78 (1.39 to 9.21) | 2.82 (1.27 to 6.16) | 0.22 (0.06 to 0.32) |
| TOF_STD + MTX | | 5.49 (1.87 to 14.52) | 3.53 (1.55 to 7.90) | 0.31 (0.13 to 0.45) |
| TOC_4 (IV) | | 1.44 (0.37 to 5.10) | 1.36 (0.43 to 3.88) | 0.04 (–0.12 to 0.23) |
| TOC_8 (IV) | | 3.58 (1.19 to 9.91) | 2.71 (1.14 to 6.26) | 0.21 (0.03 to 0.36) |
| TOC_4 (IV) + MTX | | 2.56 (0.82 to 7.15) | 2.14 (0.85 to 5.08) | 0.14 (–0.03 to 0.29) |
| TOC_8 (IV) + MTX | | 4.07 (1.42 to 10.70) | 2.95 (1.29 to 6.63) | 0.24 (0.07 to 0.38) |
| GOL_STD (SC) + MTX | | 5.67 (1.88 to 15.77) | 3.59 (1.55 to 8.13) | 0.31 (0.12 to 0.48) |
| GOL_STD (IV) + MTX | | 2.75 (0.74 to 9.17) | 2.25 (0.79 to 5.78) | 0.15 (–0.04 to 0.37) |
| INF_STD + MTX | | 2.83 (0.97 to 7.44) | 2.30 (0.98 to 5.28) | 0.16 (–0.01 to 0.29) |
| CERTO_STD + MTX | | 5.05 (1.82 to 12.98) | 3.37 (1.51 to 7.46) | 0.29 (0.12 to 0.42) |
| RIT_STD | | 3.36 (0.63 to 17.71) | 2.57 (0.68 to 7.64) | 0.19 (–0.06 to 0.55) |
| RIT_STD + MTX | | 5.23 (1.01 to 26.54) | 3.38 (1.01 to 9.05) | 0.29 (0.002 to 0.63) |
| BAR_4 + MTX | | 5.14 (1.77 to 13.79) | 3.39 (1.49 to 7.61) | 0.29 (0.11 to 0.45) |
| HD203 + MTX | | 6.70 (2.15 to 20.61) | 3.85 (1.75 to 8.14) | 0.35 (0.12 to 0.60) |
| SB4 + MTX | | 4.40 (1.55 to 12.45) | 3.05 (1.40 to 6.43) | 0.25 (0.07 to 0.48) |
| ANBAI + MTX | | 8.25 (1.95 to 32.91) | 4.30 (1.61 to 10.22) | 0.40 (0.12 to 0.66) |
| CT-P13 + MTX | | 3.90 (1.13 to 12.64) | 2.86 (1.10 to 6.97) | 0.22 (0.02 to 0.44) |
| SB2 + MTX | | 2.46 (0.63 to 8.62) | 2.07 (0.69 to 5.51) | 0.13 (–0.06 to 0.36) |
| SB5 + MTX | | 3.54 (0.93 to 11.94) | 2.67 (0.94 to 6.76) | 0.20 (–0.01 to 0.43) |
| ZRC-3197 + MTX | | 3.65 (0.85 to 14.54) | 2.73 (0.88 to 7.29) | 0.21 (–0.02 to 0.49) |
| ABP501 + MTX | | 3.39 (0.90 to 11.16) | 2.60 (0.92 to 6.51) | 0.19 (–0.02 to 0.41) |
| MTX + HCQ | MTX + SSZ | 4.33 (1.00 to 21.90) | 2.46 (1.00 to 10.24) | 0.27 (–0.0004 to 0.58) |
| SSZ + HCQ | | 1.11 (0.16 to 8.44) | 1.09 (0.31 to 6.67) | 0.02 (–0.40 to 0.23) |
| MTX + SSZ + HCQ | | 4.87 (1.11 to 24.93) | 2.70 (1.05 to 12.68) | 0.31 (0.02 to 0.56) |
| ETN_STD | | 0.97 (0.13 to 8.16) | 0.98 (0.27 to 6.57) | –0.004 (–0.44 to 0.20) |
| ETN_STD + MTX | | 2.18 (0.30 to 17.62) | 1.77 (0.53 to 11.43) | 0.14 (–0.29 to 0.37) |
| ABA_STD (IV) + MTX | | 2.29 (0.29 to 18.45) | 1.83 (0.52 to 11.95) | 0.16 (–0.29 to 0.37) |
| ABA_STD (SC) + MTX | | 2.04 (0.23 to 18.92) | 1.69 (0.42 to 11.52) | 0.13 (–0.34 to 0.41) |
| ADA_STD + MTX | | 2.21 (0.29 to 17.39) | 1.79 (0.53 to 11.64) | 0.15 (–0.30 to 0.34) |
| TOF_STD + MTX | | 3.23 (0.40 to 26.35) | 2.25 (0.64 to 14.73) | 0.24 (–0.22 to 0.46) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| TOC_4 (IV) | | 0.84 (0.09 to 8.04) | 0.87 (0.19 to 6.35) | –0.02 (–0.47 to 0.22) |
| TOC_8 (IV) | | 2.11 (0.26 to 17.38) | 1.73 (0.48 to 11.46) | 0.14 (–0.31 to 0.36) |
| TOC_4 (IV) + MTX | | 1.50 (0.19 to 12.41) | 1.37 (0.37 to 9.03) | 0.07 (–0.38 to 0.29) |
| TOC_8 (IV) + MTX | | 2.39 (0.30 to 19.48) | 1.88 (0.54 to 12.33) | 0.17 (–0.29 to 0.38) |
| GOL_STD (SC) + MTX | | 3.35 (0.41 to 27.94) | 2.29 (0.65 to 14.97) | 0.24 (–0.21 to 0.48) |
| GOL_STD (IV) + MTX | | 1.61 (0.19 to 15.15) | 1.44 (0.35 to 10.09) | 0.08 (–0.37 to 0.36) |
| INF_STD + MTX | | 1.66 (0.21 to 13.53) | 1.47 (0.42 to 9.68) | 0.09 (–0.36 to 0.30) |
| CERTO_STD + MTX | | 2.96 (0.38 to 24.28) | 2.15 (0.62 to 13.98) | 0.22 (–0.23 to 0.43) |
| RIT_STD | | 2.00 (0.18 to 23.23) | 1.64 (0.32 to 12.11) | 0.12 (–0.36 to 0.51) |
| RIT_STD + MTX | | 3.12 (0.28 to 35.20) | 2.15 (0.47 to 15.18) | 0.21 (–0.28 to 0.60) |
| BAR_4 + MTX | | 3.04 (0.37 to 24.63) | 2.18 (0.61 to 14.03) | 0.22 (–0.24 to 0.45) |
| HD203 + MTX | | 3.98 (0.44 to 38.03) | 2.48 (0.65 to 16.39) | 0.27 (–0.19 to 0.61) |
| SB4 + MTX | | 2.59 (0.30 to 24.66) | 1.95 (0.51 to 13.20) | 0.17 (–0.27 to 0.50) |
| ANBAI + MTX | | 4.84 (0.50 to 51.64) | 2.73 (0.71 to 18.87) | 0.32 (–0.17 to 0.66) |
| CT-P13 + MTX | | 2.31 (0.27 to 20.72) | 1.83 (0.48 to 12.30) | 0.15 (–0.30 to 0.44) |
| SB2 + MTX | | 1.44 (0.16 to 13.73) | 1.32 (0.31 to 9.34) | 0.06 (–0.39 to 0.34) |
| SB5 + MTX | | 2.06 (0.23 to 18.99) | 1.70 (0.42 to 11.68) | 0.13 (–0.33 to 0.42) |
| ZRC-3197 + MTX | | 2.17 (0.22 to 21.57) | 1.75 (0.40 to 12.27) | 0.13 (–0.33 to 0.47) |
| ABP501 + MTX | | 1.98 (0.22 to 18.46) | 1.65 (0.42 to 11.43) | 0.12 (–0.34 to 0.41) |
| SSZ + HCQ | MTX + HCQ | 0.26 (0.04 to 1.52) | 0.42 (0.19 to 1.38) | –0.29 (–0.64 to 0.07) |
| MTX + SSZ + HCQ | | 1.13 (0.32 to 3.97) | 1.05 (0.64 to 2.44) | 0.03 (–0.24 to 0.30) |
| ETN_STD | | 0.22 (0.03 to 1.45) | 0.38 (0.17 to 1.34) | –0.32 (–0.68 to 0.06) |
| ETN_STD + MTX | | 0.50 (0.08 to 3.18) | 0.68 (0.35 to 2.35) | –0.16 (–0.53 to 0.22) |
| ABA_STD (IV) + MTX | | 0.52 (0.08 to 3.32) | 0.69 (0.36 to 2.43) | –0.16 (–0.53 to 0.22) |
| ABA_STD (SC) + MTX | | 0.47 (0.06 to 3.42) | 0.65 (0.26 to 2.41) | –0.18 (–0.58 to 0.24) |
| ADA_STD + MTX | | 0.51 (0.08 to 3.12) | 0.68 (0.37 to 2.35) | –0.16 (–0.53 to 0.21) |
| TOF_STD + MTX | | 0.74 (0.11 to 4.74) | 0.86 (0.44 to 2.99) | –0.07 (–0.46 to 0.31) |
| TOC_4 (IV) | | 0.19 (0.02 to 1.46) | 0.34 (0.12 to 1.35) | –0.33 (–0.71 to 0.06) |
| TOC_8 (IV) | | 0.48 (0.07 to 3.13) | 0.66 (0.32 to 2.33) | –0.17 (–0.55 to 0.21) |
| TOC_4 (IV) + MTX | | 0.34 (0.05 to 2.26) | 0.52 (0.24 to 1.87) | –0.24 (–0.62 to 0.14) |
| TOC_8 (IV) + MTX | | 0.55 (0.08 to 3.46) | 0.71 (0.37 to 2.50) | –0.15 (–0.52 to 0.23) |
| GOL_STD (SC) + MTX | | 0.76 (0.11 to 5.04) | 0.87 (0.44 to 3.08) | –0.07 (–0.45 to 0.33) |
| GOL_STD (IV) + MTX | | 0.37 (0.05 to 2.70) | 0.55 (0.22 to 2.08) | –0.22 (–0.62 to 0.18) |
| INF_STD + MTX | | 0.38 (0.06 to 2.40) | 0.56 (0.28 to 1.96) | –0.22 (–0.59 to 0.15) |
| CERTO_STD + MTX | | 0.68 (0.10 to 4.31) | 0.81 (0.43 to 2.86) | –0.09 (–0.47 to 0.29) |
| RIT_STD | | 0.46 (0.05 to 4.52) | 0.65 (0.18 to 2.65) | –0.17 (–0.62 to 0.32) |
| RIT_STD + MTX | | 0.71 (0.08 to 6.84) | 0.84 (0.27 to 3.27) | –0.08 (–0.54 to 0.41) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| BAR_4 + MTX | | 0.70 (0.10 to 4.50) | 0.82 (0.42 to 2.88) | –0.09 (–0.47 to 0.30) |
| HD203 + MTX | | 0.90 (0.12 to 7.14) | 0.95 (0.41 to 3.40) | –0.02 (–0.45 to 0.42) |
| SB4 + MTX | | 0.59 (0.08 to 4.48) | 0.76 (0.32 to 2.76) | –0.12 (–0.53 to 0.31) |
| ANBAI + MTX | | 1.11 (0.13 to 9.38) | 1.05 (0.45 to 3.82) | 0.02 (–0.43 to 0.48) |
| CT-P13 + MTX | | 0.52 (0.07 to 3.73) | 0.70 (0.30 to 2.53) | –0.15 (–0.55 to 0.26) |
| SB2 + MTX | | 0.33 (0.04 to 2.52) | 0.51 (0.19 to 1.95) | –0.24 (–0.64 to 0.17) |
| SB5 + MTX | | 0.48 (0.06 to 3.49) | 0.66 (0.26 to 2.43) | –0.17 (–0.59 to 0.25) |
| ZRC-3197 + MTX | | 0.49 (0.06 to 3.99) | 0.68 (0.23 to 2.57) | –0.16 (–0.59 to 0.29) |
| ABP501 + MTX | | 0.45 (0.06 to 3.36) | 0.64 (0.25 to 2.37) | –0.18 (–0.59 to 0.24) |
| MTX + SSZ + HCQ | SSZ + HCQ | 4.36 (1.27 to 15.97) | 2.50 (1.18 to 4.96) | 0.32 (0.05 to 0.59) |
| ETN_STD | | 0.87 (0.36 to 2.12) | 0.89 (0.46 to 1.84) | –0.02 (–0.18 to 0.11) |
| ETN_STD + MTX | | 1.95 (0.94 to 4.27) | 1.62 (0.96 to 3.03) | 0.13 (–0.01 to 0.27) |
| ABA_STD (IV) + MTX | | 2.04 (0.78 to 5.21) | 1.67 (0.85 to 3.51) | 0.14 (–0.05 to 0.30) |
| ABA_STD (SC) + MTX | | 1.82 (0.52 to 5.97) | 1.55 (0.62 to 3.61) | 0.11 (–0.12 to 0.35) |
| ADA_STD + MTX | | 1.98 (0.79 to 4.68) | 1.64 (0.85 to 3.32) | 0.13 (–0.05 to 0.26) |
| TOF_STD + MTX | | 2.88 (1.07 to 7.51) | 2.06 (1.04 to 4.27) | 0.22 (0.01 to 0.39) |
| TOC_4 (IV) | | 0.76 (0.21 to 2.60) | 0.80 (0.28 to 2.14) | –0.04 (–0.24 to 0.16) |
| TOC_8 (IV) | | 1.88 (0.68 to 5.04) | 1.58 (0.76 to 3.37) | 0.12 (–0.08 to 0.30) |
| TOC_4 (IV) + MTX | | 1.34 (0.46 to 3.64) | 1.25 (0.57 to 2.75) | 0.05 (–0.15 to 0.22) |
| TOC_8 (IV) + MTX | | 2.14 (0.81 to 5.44) | 1.72 (0.86 to 3.57) | 0.15 (–0.05 to 0.31) |
| GOL_STD (SC) + MTX | | 2.97 (1.07 to 8.18) | 2.09 (1.04 to 4.41) | 0.23 (0.01 to 0.42) |
| GOL_STD (IV) + MTX | | 1.44 (0.43 to 4.71) | 1.32 (0.52 to 3.15) | 0.06 (–0.15 to 0.30) |
| INF_STD + MTX | | 1.48 (0.56 to 3.84) | 1.35 (0.66 to 2.86) | 0.07 (–0.12 to 0.23) |
| CERTO_STD + MTX | | 2.64 (1.04 to 6.72) | 1.96 (1.03 to 4.07) | 0.20 (0.01 to 0.36) |
| RIT_STD | | 1.76 (0.35 to 9.13) | 1.51 (0.44 to 4.19) | 0.11 (–0.17 to 0.47) |
| RIT_STD + MTX | | 2.74 (0.57 to 13.80) | 1.98 (0.65 to 4.94) | 0.21 (–0.10 to 0.55) |
| BAR_4 + MTX | | 2.69 (1.00 to 7.25) | 1.98 (1.00 to 4.19) | 0.20 (–0.001 to 0.38) |
| HD203 + MTX | | 3.50 (1.10 to 12.29) | 2.26 (1.07 to 4.74) | 0.27 (0.02 to 0.53) |
| SB4 + MTX | | 2.31 (0.77 to 7.31) | 1.79 (0.83 to 3.82) | 0.16 (–0.05 to 0.42) |
| ANBAI + MTX | | 4.31 (1.09 to 17.01) | 2.51 (1.06 to 5.57) | 0.32 (0.02 to 0.59) |
| CT-P13 + MTX | | 2.04 (0.63 to 6.53) | 1.67 (0.72 to 3.81) | 0.14 (–0.09 to 0.37) |
| SB2 + MTX | | 1.29 (0.36 to 4.55) | 1.21 (0.45 to 3.07) | 0.04 (–0.17 to 0.29) |
| SB5 + MTX | | 1.85 (0.52 to 6.22) | 1.56 (0.62 to 3.69) | 0.12 (–0.12 to 0.36) |
| ZRC-3197 + MTX | | 1.91 (0.47 to 7.57) | 1.60 (0.57 to 4.00) | 0.12 (–0.13 to 0.41) |
| ABP501 + MTX | | 1.77 (0.50 to 5.87) | 1.52 (0.59 to 3.58) | 0.11 (–0.13 to 0.35) |
| ETN_STD | MTX + SSZ + HCQ | 0.20 (0.05 to 0.77) | 0.36 (0.18 to 0.83) | –0.34 (–0.63 to –0.05) |
| ETN_STD + MTX | | 0.45 (0.12 to 1.66) | 0.64 (0.37 to 1.39) | –0.19 (–0.48 to 0.11) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ABA_STD (IV) + MTX | | 0.47 (0.11 to 1.74) | 0.66 (0.38 to 1.45) | –0.18 (–0.48 to 0.12) |
| ABA_STD (SC) + MTX | | 0.41 (0.08 to 1.88) | 0.61 (0.27 to 1.49) | –0.21 (–0.54 to 0.14) |
| ADA_STD + MTX | | 0.45 (0.11 to 1.61) | 0.64 (0.39 to 1.39) | –0.19 (–0.48 to 0.10) |
| TOF_STD + MTX | | 0.66 (0.16 to 2.45) | 0.81 (0.47 to 1.77) | –0.10 (–0.41 to 0.21) |
| TOC_4 (IV) | | 0.17 (0.03 to 0.80) | 0.32 (0.12 to 0.86) | –0.36 (–0.66 to –0.04) |
| TOC_8 (IV) | | 0.43 (0.10 to 1.68) | 0.62 (0.34 to 1.40) | –0.20 (–0.50 to 0.11) |
| TOC_4 (IV) + MTX | | 0.31 (0.07 to 1.21) | 0.49 (0.25 to 1.14) | –0.27 (–0.57 to 0.04) |
| TOC_8 (IV) + MTX | | 0.49 (0.12 to 1.83) | 0.68 (0.39 to 1.49) | –0.17 (–0.47 to 0.13) |
| GOL_STD (SC) + MTX | | 0.68 (0.16 to 2.69) | 0.82 (0.46 to 1.83) | –0.09 (–0.41 to 0.23) |
| GOL_STD (IV) + MTX | | 0.33 (0.07 to 1.49) | 0.52 (0.23 to 1.29) | –0.25 (–0.57 to 0.09) |
| INF_STD + MTX | | 0.34 (0.08 to 1.29) | 0.53 (0.29 to 1.19) | –0.25 (–0.54 to 0.05) |
| CERTO_STD + MTX | | 0.61 (0.15 to 2.26) | 0.77 (0.46 to 1.69) | –0.12 (–0.42 to 0.18) |
| RIT_STD | | 0.40 (0.06 to 2.67) | 0.60 (0.18 to 1.70) | –0.21 (–0.58 to 0.23) |
| RIT_STD + MTX | | 0.62 (0.10 to 3.98) | 0.79 (0.28 to 2.04) | –0.11 (–0.51 to 0.32) |
| BAR_4 + MTX | | 0.62 (0.15 to 2.38) | 0.78 (0.45 to 1.72) | –0.12 (–0.43 to 0.20) |
| HD203 + MTX | | 0.80 (0.16 to 4.03) | 0.90 (0.42 to 2.07) | –0.05 (–0.41 to 0.32) |
| SB4 + MTX | | 0.53 (0.11 to 2.51) | 0.72 (0.32 to 1.70) | –0.15 (–0.49 to 0.21) |
| ANBAI + MTX | | 0.99 (0.18 to 5.31) | 0.99 (0.46 to 2.33) | –0.003 (–0.39 to 0.38) |
| CT-P13 + MTX | | 0.47 (0.10 to 2.09) | 0.66 (0.31 to 1.57) | –0.18 (–0.51 to 0.17) |
| SB2 + MTX | | 0.29 (0.06 to 1.43) | 0.48 (0.19 to 1.26) | –0.27 (–0.59 to 0.08) |
| SB5 + MTX | | 0.42 (0.08 to 1.94) | 0.62 (0.27 to 1.51) | –0.20 (–0.54 to 0.15) |
| ZRC-3197 + MTX | | 0.44 (0.08 to 2.30) | 0.64 (0.24 to 1.62) | –0.19 (–0.55 to 0.19) |
| ABP501 + MTX | | 0.40 (0.08 to 1.84) | 0.60 (0.26 to 1.47) | –0.21 (–0.54 to 0.14) |
| ETN_STD + MTX | ETN_STD | 2.24 (1.37 to 3.82) | 1.81 (1.25 to 2.77) | 0.15 (0.06 to 0.26) |
| ABA_STD (IV) + MTX | | 2.34 (1.01 to 5.26) | 1.87 (1.01 to 3.49) | 0.16 (0.003 to 0.31) |
| ABA_STD (SC) + MTX | | 2.10 (0.66 to 6.15) | 1.73 (0.73 to 3.65) | 0.14 (–0.07 to 0.36) |
| ADA_STD + MTX | | 2.27 (1.04 to 4.68) | 1.83 (1.03 to 3.29) | 0.16 (0.01 to 0.27) |
| TOF_STD + MTX | | 3.31 (1.37 to 7.42) | 2.30 (1.24 to 4.22) | 0.24 (0.07 to 0.39) |
| TOC_4 (IV) | | 0.87 (0.26 to 2.72) | 0.89 (0.32 to 2.19) | –0.02 (–0.18 to 0.17) |
| TOC_8 (IV) | | 2.17 (0.86 to 5.11) | 1.77 (0.90 to 3.40) | 0.14 (–0.03 to 0.31) |
| TOC_4 (IV) + MTX | | 1.54 (0.59 to 3.76) | 1.40 (0.67 to 2.79) | 0.07 (–0.09 to 0.23) |
| TOC_8 (IV) + MTX | | 2.46 (1.04 to 5.55) | 1.93 (1.03 to 3.59) | 0.17 (0.01 to 0.32) |
| GOL_STD (SC) + MTX | | 3.41 (1.35 to 8.29) | 2.34 (1.22 to 4.40) | 0.25 (0.06 to 0.42) |
| GOL_STD (IV) + MTX | | 1.66 (0.53 to 4.84) | 1.47 (0.60 to 3.18) | 0.09 (–0.10 to 0.30) |
| INF_STD + MTX | | 1.71 (0.71 to 3.87) | 1.51 (0.78 to 2.88) | 0.09 (–0.06 to 0.23) |
| CERTO_STD + MTX | | 3.04 (1.34 to 6.69) | 2.19 (1.22 to 4.01) | 0.22 (0.06 to 0.37) |
| RIT_STD | | 2.02 (0.43 to 9.91) | 1.69 (0.50 to 4.35) | 0.13 (–0.12 to 0.48) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| RIT_STD + MTX | | 3.15 (0.69 to 14.86) | 2.22 (0.75 to 5.05) | 0.23 (–0.06 to 0.57) |
| BAR_4 + MTX | | 3.09 (1.29 to 7.25) | 2.21 (1.19 to 4.13) | 0.23 (0.05 to 0.39) |
| HD203 + MTX | | 4.04 (1.41 to 12.12) | 2.53 (1.28 to 4.61) | 0.29 (0.06 to 0.53) |
| SB4 + MTX | | 2.65 (1.02 to 7.18) | 2.01 (1.02 to 3.69) | 0.19 (0.003 to 0.42) |
| ANBAI + MTX | | 4.98 (1.37 to 17.77) | 2.81 (1.25 to 5.56) | 0.34 (0.06 to 0.60) |
| CT-P13 + MTX | | 2.35 (0.79 to 6.82) | 1.86 (0.84 to 3.86) | 0.16 (–0.04 to 0.39) |
| SB2 + MTX | | 1.49 (0.44 to 4.67) | 1.36 (0.51 to 3.09) | 0.07 (–0.13 to 0.30) |
| SB5 + MTX | | 2.13 (0.65 to 6.35) | 1.75 (0.72 to 3.72) | 0.14 (–0.07 to 0.37) |
| ZRC-3197 + MTX | | 2.19 (0.59 to 7.98) | 1.78 (0.66 to 4.06) | 0.15 (–0.08 to 0.43) |
| ABP501 + MTX | ETN_STD + MTX | 2.04 (0.64 to 5.99) | 1.70 (0.70 to 3.58) | 0.13 (–0.08 to 0.36) |
| ABA_STD (IV) + MTX | | 1.05 (0.47 to 2.15) | 1.03 (0.62 to 1.66) | 0.01 (–0.17 to 0.17) |
| ABA_STD (SC) + MTX | | 0.94 (0.30 to 2.56) | 0.96 (0.43 to 1.79) | –0.01 (–0.24 to 0.22) |
| ADA_STD + MTX | | 1.01 (0.48 to 1.91) | 1.01 (0.64 to 1.57) | 0.002 (–0.17 to 0.14) |
| TOF_STD + MTX | | 1.47 (0.64 to 3.09) | 1.27 (0.76 to 2.02) | 0.09 (–0.11 to 0.26) |
| TOC_4 (IV) | | 0.39 (0.12 to 1.16) | 0.49 (0.19 to 1.11) | –0.17 (–0.36 to 0.03) |
| TOC_8 (IV) | | 0.96 (0.40 to 2.13) | 0.98 (0.54 to 1.64) | –0.01 (–0.20 to 0.17) |
| TOC_4 (IV) + MTX | | 0.69 (0.27 to 1.55) | 0.77 (0.40 to 1.35) | –0.08 (–0.27 to 0.09) |
| TOC_8 (IV) + MTX | | 1.09 (0.48 to 2.28) | 1.06 (0.63 to 1.72) | 0.02 (–0.17 to 0.18) |
| GOL_STD (SC) + MTX | | 1.52 (0.63 to 3.43) | 1.29 (0.75 to 2.10) | 0.10 (–0.11 to 0.29) |
| GOL_STD (IV) + MTX | | 0.74 (0.24 to 2.04) | 0.81 (0.36 to 1.58) | –0.06 (–0.28 to 0.16) |
| INF_STD + MTX | | 0.76 (0.34 to 1.59) | 0.83 (0.48 to 1.38) | –0.06 (–0.24 to 0.10) |
| CERTO_STD + MTX | | 1.35 (0.62 to 2.76) | 1.21 (0.75 to 1.91) | 0.07 (–0.11 to 0.23) |
| RIT_STD | | 0.90 (0.20 to 4.23) | 0.94 (0.29 to 2.18) | –0.02 (–0.29 to 0.34) |
| RIT_STD + MTX | | 1.40 (0.31 to 6.30) | 1.23 (0.44 to 2.51) | 0.08 (–0.23 to 0.42) |
| BAR_4 + MTX | | 1.38 (0.60 to 2.98) | 1.22 (0.73 to 1.97) | 0.07 (–0.12 to 0.25) |
| HD203 + MTX | | 1.80 (0.71 to 4.62) | 1.40 (0.79 to 2.12) | 0.14 (–0.07 to 0.36) |
| SB4 + MTX | | 1.18 (0.52 to 2.71) | 1.11 (0.62 to 1.71) | 0.04 (–0.13 to 0.24) |
| ANBAI + MTX | | 2.21 (0.62 to 7.57) | 1.55 (0.74 to 2.71) | 0.19 (–0.11 to 0.46) |
| CT-P13 + MTX | | 1.05 (0.36 to 2.83) | 1.03 (0.50 to 1.87) | 0.01 (–0.21 to 0.24) |
| SB2 + MTX | | 0.66 (0.20 to 1.98) | 0.75 (0.30 to 1.54) | –0.08 (–0.30 to 0.15) |
| SB5 + MTX | | 0.95 (0.30 to 2.67) | 0.97 (0.42 to 1.82) | –0.01 (–0.25 to 0.23) |
| ZRC-3197 + MTX | | 0.98 (0.27 to 3.31) | 0.99 (0.39 to 1.99) | –0.004 (–0.26 to 0.28) |
| ABP501 + MTX | | 0.91 (0.29 to 2.54) | 0.94 (0.42 to 1.78) | –0.02 (–0.25 to 0.21) |
| ABA_STD (SC) + MTX | ABA_STD (IV) + MTX | 0.89 (0.31 to 2.40) | 0.93 (0.44 to 1.69) | –0.02 (–0.23 to 0.21) |
| ADA_STD + MTX | | 0.97 (0.53 to 1.73) | 0.98 (0.67 to 1.45) | –0.01 (–0.15 to 0.12) |
| TOF_STD + MTX | | 1.41 (0.69 to 2.82) | 1.23 (0.79 to 1.87) | 0.08 (–0.09 to 0.24) |
| TOC_4 (IV) | | 0.37 (0.12 to 1.06) | 0.48 (0.19 to 1.04) | –0.18 (–0.34 to 0.01) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| TOC_8 (IV) | | 0.92 (0.43 to 1.96) | 0.95 (0.56 to 1.54) | –0.02 (–0.19 to 0.15) |
| TOC_4 (IV) + MTX | | 0.66 (0.29 to 1.44) | 0.75 (0.41 to 1.27) | –0.09 (–0.25 to 0.08) |
| TOC_8 (IV) + MTX | | 1.05 (0.51 to 2.09) | 1.03 (0.65 to 1.60) | 0.01 (–0.15 to 0.17) |
| GOL_STD (SC) + MTX | | 1.46 (0.66 to 3.18) | 1.25 (0.77 to 1.98) | 0.09 (–0.10 to 0.27) |
| GOL_STD (IV) + MTX | | 0.70 (0.26 to 1.90) | 0.79 (0.37 to 1.49) | –0.07 (–0.26 to 0.15) |
| INF_STD + MTX | | 0.73 (0.39 to 1.36) | 0.80 (0.52 to 1.23) | –0.07 (–0.20 to 0.07) |
| CERTO_STD + MTX | | 1.30 (0.67 to 2.52) | 1.17 (0.78 to 1.78) | 0.06 (–0.09 to 0.21) |
| RIT_STD | | 0.86 (0.20 to 3.98) | 0.91 (0.29 to 2.06) | –0.03 (–0.28 to 0.33) |
| RIT_STD + MTX | | 1.33 (0.33 to 6.01) | 1.19 (0.44 to 2.38) | 0.07 (–0.22 to 0.41) |
| BAR_4 + MTX | | 1.32 (0.63 to 2.78) | 1.19 (0.75 to 1.85) | 0.06 (–0.11 to 0.24) |
| HD203 + MTX | | 1.72 (0.53 to 5.96) | 1.37 (0.66 to 2.40) | 0.13 (–0.14 to 0.41) |
| SB4 + MTX | | 1.13 (0.38 to 3.61) | 1.08 (0.51 to 2.02) | 0.03 (–0.20 to 0.30) |
| ANBAI + MTX | | 2.12 (0.65 to 7.05) | 1.51 (0.76 to 2.54) | 0.18 (–0.10 to 0.45) |
| CT-P13 + MTX | | 1.00 (0.40 to 2.51) | 1.00 (0.53 to 1.72) | 0.0001 (–0.19 to 0.22) |
| SB2 + MTX | | 0.63 (0.22 to 1.78) | 0.73 (0.32 to 1.42) | –0.09 (–0.27 to 0.13) |
| SB5 + MTX | | 0.91 (0.31 to 2.49) | 0.94 (0.43 to 1.72) | –0.02 (–0.23 to 0.22) |
| ZRC-3197 + MTX | | 0.94 (0.28 to 3.12) | 0.96 (0.39 to 1.88) | –0.01 (–0.25 to 0.27) |
| ABP501 + MTX | | 0.87 (0.31 to 2.40) | 0.91 (0.43 to 1.69) | –0.03 (–0.24 to 0.20) |
| ADA_STD + MTX | ABA_STD (SC) + MTX | 1.09 (0.48 to 2.47) | 1.06 (0.66 to 1.97) | 0.02 (–0.18 to 0.17) |
| TOF_STD + MTX | | 1.58 (0.58 to 4.33) | 1.33 (0.74 to 2.72) | 0.11 (–0.13 to 0.31) |
| TOC_4 (IV) | | 0.42 (0.11 to 1.51) | 0.52 (0.19 to 1.37) | –0.15 (–0.39 to 0.07) |
| TOC_8 (IV) | | 1.03 (0.36 to 3.02) | 1.02 (0.53 to 2.20) | 0.01 (–0.23 to 0.22) |
| TOC_4 (IV) + MTX | | 0.74 (0.25 to 2.18) | 0.81 (0.39 to 1.78) | –0.06 (–0.30 to 0.15) |
| TOC_8 (IV) + MTX | | 1.17 (0.43 to 3.28) | 1.11 (0.60 to 2.34) | 0.04 (–0.20 to 0.24) |
| GOL_STD (SC) + MTX | | 1.63 (0.56 to 4.88) | 1.35 (0.72 to 2.86) | 0.11 (–0.14 to 0.34) |
| GOL_STD (IV) + MTX | | 0.79 (0.23 to 2.81) | 0.85 (0.36 to 2.04) | –0.05 (–0.30 to 0.21) |
| INF_STD + MTX | | 0.81 (0.29 to 2.30) | 0.87 (0.45 to 1.85) | –0.04 (–0.27 to 0.16) |
| CERTO_STD + MTX | | 1.45 (0.57 to 3.86) | 1.26 (0.73 to 2.57) | 0.09 (–0.14 to 0.28) |
| RIT_STD | | 0.97 (0.19 to 5.22) | 0.98 (0.30 to 2.68) | –0.01 (–0.31 to 0.37) |
| RIT_STD + MTX | | 1.51 (0.30 to 7.96) | 1.29 (0.44 to 3.20) | 0.09 (–0.24 to 0.46) |
| BAR_4 + MTX | | 1.48 (0.55 to 4.17) | 1.28 (0.71 to 2.63) | 0.09 (–0.14 to 0.30) |
| HD203 + MTX | | 1.92 (0.50 to 8.64) | 1.47 (0.65 to 3.43) | 0.15 (–0.15 to 0.48) |
| SB4 + MTX | | 1.27 (0.35 to 5.17) | 1.16 (0.49 to 2.80) | 0.05 (–0.23 to 0.36) |
| ANBAI + MTX | | 2.37 (0.61 to 9.88) | 1.62 (0.74 to 3.57) | 0.20 (–0.12 to 0.51) |
| CT-P13 + MTX | | 1.12 (0.34 to 3.93) | 1.08 (0.49 to 2.47) | 0.03 (–0.24 to 0.29) |
| SB2 + MTX | | 0.71 (0.19 to 2.66) | 0.79 (0.30 to 1.96) | –0.07 (–0.33 to 0.20) |
| SB5 + MTX | | 1.02 (0.31 to 3.29) | 1.01 (0.45 to 2.22) | 0.003 (–0.25 to 0.25) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ZRC-3197 + MTX | | 1.05 (0.28 to 4.02) | 1.03 (0.41 to 2.43) | 0.01 (–0.26 to 0.31) |
| ABP501 + MTX | | 0.97 (0.30 to 3.13) | 0.98 (0.44 to 2.17) | –0.01 (–0.25 to 0.24) |
| TOF_STD + MTX | ADA_STD + MTX | 1.46 (0.82 to 2.58) | 1.26 (0.88 to 1.74) | 0.09 (–0.04 to 0.23) |
| TOC_4 (IV) | | 0.38 (0.14 to 1.05) | 0.49 (0.20 to 1.04) | –0.17 (–0.30 to 0.01) |
| TOC_8 (IV) | | 0.95 (0.49 to 1.90) | 0.97 (0.60 to 1.49) | –0.01 (–0.15 to 0.15) |
| TOC_4 (IV) + MTX | | 0.68 (0.33 to 1.39) | 0.76 (0.44 to 1.24) | –0.08 (–0.21 to 0.07) |
| TOC_8 (IV) + MTX | | 1.08 (0.59 to 2.01) | 1.05 (0.70 to 1.54) | 0.02 (–0.12 to 0.16) |
| GOL_STD (SC) + MTX | | 1.50 (0.75 to 3.08) | 1.28 (0.83 to 1.89) | 0.10 (–0.06 to 0.27) |
| GOL_STD (IV) + MTX | | 0.73 (0.29 to 1.90) | 0.80 (0.39 to 1.48) | –0.07 (–0.23 to 0.15) |
| INF_STD + MTX | | 0.75 (0.40 to 1.41) | 0.82 (0.52 to 1.25) | –0.06 (–0.18 to 0.08) |
| CERTO_STD + MTX | | 1.34 (0.82 to 2.28) | 1.20 (0.88 to 1.64) | 0.07 (–0.05 to 0.19) |
| RIT_STD | | 0.89 (0.22 to 3.90) | 0.93 (0.31 to 2.02) | –0.02 (–0.25 to 0.33) |
| RIT_STD + MTX | | 1.39 (0.35 to 5.94) | 1.22 (0.46 to 2.31) | 0.08 (–0.20 to 0.41) |
| BAR_4 + MTX | | 1.36 (0.76 to 2.56) | 1.21 (0.84 to 1.73) | 0.07 (–0.06 to 0.22) |
| HD203 + MTX | | 1.78 (0.58 to 6.06) | 1.40 (0.69 to 2.35) | 0.14 (–0.11 to 0.42) |
| SB4 + MTX | | 1.16 (0.42 to 3.59) | 1.10 (0.54 to 1.98) | 0.03 (–0.17 to 0.31) |
| ANBAI + MTX | | 2.19 (0.72 to 6.97) | 1.55 (0.80 to 2.44) | 0.19 (–0.07 to 0.44) |
| CT-P13 + MTX | | 1.04 (0.42 to 2.64) | 1.02 (0.54 to 1.75) | 0.01 (–0.17 to 0.23) |
| SB2 + MTX | | 0.66 (0.23 to 1.85) | 0.74 (0.32 to 1.46) | –0.09 (–0.25 to 0.15) |
| SB5 + MTX | | 0.93 (0.40 to 2.18) | 0.96 (0.50 to 1.55) | –0.01 (–0.17 to 0.19) |
| ZRC-3197 + MTX | | 0.97 (0.34 to 2.77) | 0.98 (0.44 to 1.73) | –0.01 (–0.19 to 0.25) |
| ABP501 + MTX | | 0.90 (0.39 to 2.06) | 0.93 (0.49 to 1.51) | –0.02 (–0.17 to 0.17) |
| TOC_4 (IV) | TOF_STD + MTX | 0.26 (0.09 to 0.77) | 0.39 (0.16 to 0.85) | –0.26 (–0.43 to –0.06) |
| TOC_8 (IV) | | 0.65 (0.30 to 1.43) | 0.77 (0.46 to 1.24) | –0.10 (–0.27 to 0.08) |
| TOC_4 (IV) + MTX | | 0.47 (0.21 to 1.06) | 0.61 (0.34 to 1.04) | –0.17 (–0.33 to 0.01) |
| TOC_8 (IV) + MTX | | 0.74 (0.36 to 1.53) | 0.84 (0.54 to 1.30) | –0.07 (–0.24 to 0.10) |
| GOL_STD (SC) + MTX | | 1.03 (0.46 to 2.34) | 1.02 (0.64 to 1.60) | 0.01 (–0.18 to 0.21) |
| GOL_STD (IV) + MTX | | 0.50 (0.18 to 1.40) | 0.64 (0.30 to 1.22) | –0.16 (–0.35 to 0.08) |
| INF_STD + MTX | | 0.52 (0.25 to 1.08) | 0.65 (0.40 to 1.05) | –0.15 (–0.31 to 0.02) |
| CERTO_STD + MTX | | 0.92 (0.47 to 1.84) | 0.95 (0.65 to 1.43) | –0.02 (–0.18 to 0.15) |
| RIT_STD | | 0.61 (0.14 to 2.82) | 0.74 (0.24 to 1.66) | –0.11 (–0.37 to 0.25) |
| RIT_STD + MTX | | 0.95 (0.23 to 4.29) | 0.97 (0.36 to 1.90) | –0.01 (–0.31 to 0.34) |
| BAR_4 + MTX | | 0.93 (0.45 to 2.01) | 0.96 (0.63 to 1.49) | –0.02 (–0.19 to 0.17) |
| HD203 + MTX | | 1.22 (0.38 to 4.38) | 1.11 (0.54 to 1.95) | 0.05 (–0.22 to 0.34) |
| SB4 + MTX | | 0.80 (0.27 to 2.65) | 0.88 (0.42 to 1.65) | –0.05 (–0.28 to 0.24) |
| ANBAI + MTX | | 1.51 (0.46 to 5.12) | 1.23 (0.62 to 2.04) | 0.10 (–0.18 to 0.38) |
| CT-P13 + MTX | | 0.71 (0.27 to 1.98) | 0.81 (0.42 to 1.45) | –0.08 (–0.29 to 0.17) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| SB2 + MTX | | 0.45 (0.15 to 1.38) | 0.59 (0.25 to 1.20) | –0.18 (–0.37 to 0.08) |
| SB5 + MTX | | 0.64 (0.23 to 1.79) | 0.76 (0.36 to 1.38) | –0.10 (–0.31 to 0.14) |
| ZRC-3197 + MTX | | 0.67 (0.20 to 2.22) | 0.78 (0.33 to 1.52) | –0.09 (–0.32 to 0.19) |
| ABP501 + MTX | | 0.61 (0.22 to 1.68) | 0.74 (0.36 to 1.34) | –0.11 (–0.31 to 0.13) |
| TOC_8 (IV) | TOC_4 (IV) | 2.48 (0.96 to 6.59) | 1.98 (0.97 to 4.54) | 0.16 (–0.01 to 0.31) |
| TOC_4 (IV) + MTX | | 1.77 (0.65 to 4.83) | 1.56 (0.73 to 3.65) | 0.09 (–0.08 to 0.24) |
| TOC_8 (IV) + MTX | | 2.81 (1.11 to 7.36) | 2.15 (1.07 to 4.92) | 0.19 (0.02 to 0.33) |
| GOL_STD (SC) + MTX | | 3.93 (1.27 to 12.39) | 2.62 (1.17 to 6.60) | 0.27 (0.05 to 0.46) |
| GOL_STD (IV) + MTX | | 1.90 (0.52 to 7.18) | 1.65 (0.60 to 4.68) | 0.11 (–0.11 to 0.34) |
| INF_STD + MTX | | 1.96 (0.66 to 6.06) | 1.68 (0.74 to 4.34) | 0.11 (–0.08 to 0.27) |
| CERTO_STD + MTX | | 3.49 (1.24 to 10.43) | 2.46 (1.15 to 6.12) | 0.24 (0.05 to 0.40) |
| RIT_STD | | 2.32 (0.45 to 13.30) | 1.88 (0.52 to 6.06) | 0.14 (–0.13 to 0.51) |
| RIT_STD + MTX | | 3.65 (0.70 to 19.99) | 2.48 (0.76 to 7.27) | 0.25 (–0.06 to 0.59) |
| BAR_4 + MTX | | 3.56 (1.19 to 11.20) | 2.48 (1.12 to 6.30) | 0.25 (0.04 to 0.42) |
| HD203 + MTX | | 4.66 (1.11 to 21.40) | 2.84 (1.08 to 7.72) | 0.31 (0.02 to 0.60) |
| SB4 + MTX | | 3.05 (0.78 to 13.14) | 2.25 (0.83 to 6.38) | 0.21 (–0.05 to 0.49) |
| ANBAI + MTX | | 5.72 (1.35 to 25.23) | 3.13 (1.22 to 8.27) | 0.36 (0.06 to 0.63) |
| CT-P13 + MTX | | 2.71 (0.76 to 10.18) | 2.09 (0.82 to 5.74) | 0.18 (–0.05 to 0.42) |
| SB2 + MTX | | 1.71 (0.43 to 6.97) | 1.52 (0.51 to 4.57) | 0.08 (–0.14 to 0.33) |
| SB5 + MTX | | 2.44 (0.65 to 9.32) | 1.95 (0.72 to 5.44) | 0.16 (–0.08 to 0.40) |
| ZRC-3197 + MTX | | 2.52 (0.59 to 11.18) | 1.99 (0.67 to 5.81) | 0.16 (–0.09 to 0.46) |
| ABP501 + MTX | | 2.34 (0.63 to 8.77) | 1.89 (0.71 to 5.23) | 0.15 (–0.08 to 0.39) |
| TOC_4 (IV) + MTX | TOC_8 (IV) | 0.71 (0.35 to 1.42) | 0.79 (0.47 to 1.27) | –0.07 (–0.21 to 0.07) |
| TOC_8 (IV) + MTX | | 1.14 (0.70 to 1.86) | 1.09 (0.80 to 1.52) | 0.03 (–0.08 to 0.13) |
| GOL_STD (SC) + MTX | | 1.58 (0.68 to 3.77) | 1.32 (0.78 to 2.26) | 0.11 (–0.09 to 0.30) |
| GOL_STD (IV) + MTX | | 0.77 (0.26 to 2.25) | 0.83 (0.38 to 1.70) | –0.06 (–0.26 to 0.18) |
| INF_STD + MTX | | 0.79 (0.35 to 1.75) | 0.85 (0.49 to 1.48) | –0.05 (–0.22 to 0.12) |
| CERTO_STD + MTX | | 1.41 (0.68 to 3.00) | 1.24 (0.79 to 2.05) | 0.08 (–0.09 to 0.25) |
| RIT_STD | | 0.94 (0.21 to 4.47) | 0.96 (0.30 to 2.28) | –0.01 (–0.28 to 0.35) |
| RIT_STD + MTX | | 1.46 (0.34 to 6.80) | 1.26 (0.46 to 2.64) | 0.09 (–0.21 to 0.44) |
| BAR_4 + MTX | | 1.43 (0.64 to 3.27) | 1.25 (0.76 to 2.12) | 0.08 (–0.10 to 0.27) |
| HD203 + MTX | | 1.87 (0.55 to 6.98) | 1.44 (0.67 to 2.74) | 0.15 (–0.13 to 0.44) |
| SB4 + MTX | | 1.23 (0.39 to 4.17) | 1.14 (0.52 to 2.26) | 0.05 (–0.19 to 0.33) |
| ANBAI + MTX | | 2.31 (0.68 to 7.99) | 1.60 (0.78 to 2.85) | 0.20 (–0.09 to 0.47) |
| CT-P13 + MTX | | 1.09 (0.39 to 3.13) | 1.06 (0.52 to 2.03) | 0.02 (–0.20 to 0.26) |
| SB2 + MTX | | 0.69 (0.22 to 2.20) | 0.77 (0.32 to 1.66) | –0.08 (–0.28 to 0.17) |
| SB5 + MTX | | 0.98 (0.33 to 2.91) | 0.99 (0.45 to 1.94) | –0.004 (–0.22 to 0.24) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ZRC-3197 + MTX | | 1.02 (0.29 to 3.55) | 1.01 (0.41 to 2.10) | 0.004 (–0.24 to 0.30) |
| ABP501 + MTX | | 0.94 (0.32 to 2.76) | 0.96 (0.44 to 1.89) | –0.01 (–0.23 to 0.23) |
| TOC_8 (IV) + MTX | TOC_4 (IV) + MTX | 1.59 (0.88 to 2.98) | 1.37 (0.92 to 2.19) | 0.10 (–0.03 to 0.22) |
| GOL_STD (SC) + MTX | | 2.21 (0.93 to 5.48) | 1.67 (0.96 to 3.08) | 0.18 (–0.02 to 0.37) |
| GOL_STD (IV) + MTX | | 1.08 (0.36 to 3.26) | 1.05 (0.47 to 2.28) | 0.01 (–0.18 to 0.25) |
| INF_STD + MTX | | 1.11 (0.49 to 2.56) | 1.08 (0.60 to 2.01) | 0.02 (–0.15 to 0.18) |
| CERTO_STD + MTX | | 1.98 (0.92 to 4.41) | 1.57 (0.95 to 2.79) | 0.15 (–0.02 to 0.31) |
| RIT_STD | | 1.31 (0.30 to 6.44) | 1.21 (0.38 to 3.04) | 0.05 (–0.20 to 0.42) |
| RIT_STD + MTX | | 2.04 (0.47 to 9.72) | 1.59 (0.57 to 3.54) | 0.15 (–0.14 to 0.51) |
| BAR_4 + MTX | | 2.00 (0.88 to 4.83) | 1.58 (0.92 to 2.89) | 0.15 (–0.03 to 0.33) |
| HD203 + MTX | | 2.62 (0.77 to 10.15) | 1.82 (0.83 to 3.72) | 0.22 (–0.05 to 0.51) |
| SB4 + MTX | | 1.72 (0.55 to 6.08) | 1.44 (0.65 to 3.09) | 0.11 (–0.12 to 0.40) |
| ANBAI + MTX | | 3.24 (0.95 to 11.58) | 2.02 (0.96 to 3.85) | 0.27 (–0.01 to 0.54) |
| CT-P13 + MTX | | 1.53 (0.54 to 4.59) | 1.34 (0.64 to 2.74) | 0.09 (–0.12 to 0.33) |
| SB2 + MTX | | 0.97 (0.30 to 3.16) | 0.97 (0.39 to 2.21) | –0.01 (–0.21 to 0.24) |
| SB5 + MTX | | 1.38 (0.45 to 4.23) | 1.25 (0.56 to 2.62) | 0.07 (–0.15 to 0.31) |
| ZRC-3197 + MTX | | 1.44 (0.41 to 5.16) | 1.29 (0.50 to 2.81) | 0.07 (–0.16 to 0.36) |
| ABP501 + MTX | | 1.32 (0.44 to 4.01) | 1.22 (0.54 to 2.54) | 0.06 (–0.15 to 0.30) |
| GOL_STD (SC) + MTX | TOC_8 (IV) + MTX | 1.39 (0.63 to 3.11) | 1.22 (0.75 to 1.94) | 0.08 (–0.11 to 0.27) |
| GOL_STD (IV) + MTX | | 0.68 (0.24 to 1.88) | 0.77 (0.35 to 1.48) | –0.08 (–0.27 to 0.15) |
| INF_STD + MTX | | 0.70 (0.33 to 1.45) | 0.78 (0.47 to 1.29) | –0.08 (–0.24 to 0.08) |
| CERTO_STD + MTX | | 1.24 (0.63 to 2.47) | 1.14 (0.76 to 1.75) | 0.05 (–0.11 to 0.21) |
| RIT_STD | | 0.82 (0.19 to 3.81) | 0.88 (0.29 to 2.01) | –0.04 (–0.29 to 0.32) |
| RIT_STD + MTX | | 1.28 (0.31 to 5.75) | 1.16 (0.43 to 2.32) | 0.06 (–0.23 to 0.40) |
| BAR_4 + MTX | | 1.26 (0.60 to 2.71) | 1.15 (0.73 to 1.83) | 0.05 (–0.12 to 0.23) |
| HD203 + MTX | | 1.64 (0.50 to 5.83) | 1.33 (0.64 to 2.38) | 0.12 (–0.15 to 0.41) |
| SB4 + MTX | | 1.08 (0.36 to 3.51) | 1.05 (0.49 to 1.99) | 0.02 (–0.21 to 0.30) |
| ANBAI + MTX | | 2.02 (0.63 to 6.82) | 1.47 (0.74 to 2.49) | 0.17 (–0.11 to 0.44) |
| CT-P13 + MTX | | 0.96 (0.36 to 2.66) | 0.97 (0.49 to 1.77) | –0.01 (–0.21 to 0.23) |
| SB2 + MTX | | 0.61 (0.20 to 1.82) | 0.71 (0.30 to 1.45) | –0.10 (–0.30 to 0.14) |
| SB5 + MTX | | 0.87 (0.30 to 2.43) | 0.91 (0.42 to 1.69) | –0.03 (–0.24 to 0.21) |
| ZRC-3197 + MTX | | 0.89 (0.27 to 3.02) | 0.93 (0.38 to 1.86) | –0.03 (–0.25 to 0.26) |
| ABP501 + MTX | | 0.83 (0.29 to 2.31) | 0.89 (0.41 to 1.65) | –0.04 (–0.25 to 0.20) |
| GOL_STD (IV) + MTX | GOL_STD (SC) + MTX | 0.48 (0.16 to 1.42) | 0.63 (0.29 to 1.23) | –0.16 (–0.37 to 0.08) |
| INF_STD + MTX | | 0.50 (0.22 to 1.12) | 0.64 (0.38 to 1.08) | –0.16 (–0.34 to 0.03) |
| CERTO_STD + MTX | | 0.89 (0.41 to 1.95) | 0.94 (0.61 to 1.49) | –0.03 (–0.22 to 0.16) |
| RIT_STD | | 0.59 (0.13 to 2.85) | 0.73 (0.23 to 1.68) | –0.12 (–0.39 to 0.25) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| RIT_STD + MTX | | 0.92 (0.21 to 4.32) | 0.96 (0.35 to 1.94) | –0.02 (–0.33 to 0.34) |
| BAR_4 + MTX | | 0.91 (0.40 to 2.09) | 0.95 (0.59 to 1.53) | –0.02 (–0.22 to 0.18) |
| HD203 + MTX | | 1.19 (0.34 to 4.32) | 1.10 (0.52 to 1.96) | 0.04 (–0.25 to 0.34) |
| SB4 + MTX | | 0.78 (0.25 to 2.64) | 0.86 (0.40 to 1.65) | –0.06 (–0.31 to 0.23) |
| ANBAI + MTX | | 1.46 (0.43 to 5.08) | 1.21 (0.61 to 2.08) | 0.09 (–0.20 to 0.37) |
| CT-P13 + MTX | | 0.69 (0.24 to 1.99) | 0.80 (0.40 to 1.47) | –0.09 (–0.31 to 0.17) |
| SB2 + MTX | | 0.43 (0.14 to 1.37) | 0.58 (0.24 to 1.21) | –0.18 (–0.40 to 0.07) |
| SB5 + MTX | | 0.62 (0.20 to 1.86) | 0.75 (0.34 to 1.42) | –0.11 (–0.34 to 0.15) |
| ZRC-3197 + MTX | | 0.64 (0.18 to 2.30) | 0.77 (0.31 to 1.56) | –0.10 (–0.35 to 0.20) |
| ABP501 + MTX | GOL_STD (IV) + MTX | 0.60 (0.20 to 1.76) | 0.73 (0.34 to 1.38) | –0.12 (–0.35 to 0.13) |
| INF_STD + MTX | | 1.03 (0.37 to 2.88) | 1.03 (0.52 to 2.24) | 0.01 (–0.22 to 0.19) |
| CERTO_STD + MTX | | 1.84 (0.68 to 5.00) | 1.49 (0.80 to 3.15) | 0.13 (–0.09 to 0.32) |
| RIT_STD | | 1.23 (0.24 to 6.61) | 1.15 (0.34 to 3.24) | 0.04 (–0.26 to 0.41) |
| RIT_STD + MTX | | 1.91 (0.38 to 10.13) | 1.51 (0.50 to 3.85) | 0.14 (–0.19 to 0.50) |
| BAR_4 + MTX | | 1.87 (0.66 to 5.34) | 1.51 (0.78 to 3.24) | 0.14 (–0.10 to 0.34) |
| HD203 + MTX | | 2.44 (0.61 to 10.74) | 1.72 (0.73 to 4.12) | 0.20 (–0.11 to 0.51) |
| SB4 + MTX | | 1.60 (0.44 to 6.46) | 1.36 (0.56 to 3.40) | 0.10 (–0.18 to 0.40) |
| ANBAI + MTX | | 3.01 (0.76 to 12.22) | 1.91 (0.84 to 4.31) | 0.25 (–0.06 to 0.54) |
| CT-P13 + MTX | | 1.42 (0.43 to 4.88) | 1.27 (0.56 to 3.01) | 0.07 (–0.18 to 0.33) |
| SB2 + MTX | | 0.90 (0.24 to 3.34) | 0.93 (0.35 to 2.37) | –0.02 (–0.27 to 0.24) |
| SB5 + MTX | | 1.28 (0.36 to 4.56) | 1.19 (0.48 to 2.87) | 0.05 (–0.21 to 0.31) |
| ZRC-3197 + MTX | | 1.33 (0.32 to 5.43) | 1.21 (0.45 to 3.06) | 0.06 (–0.22 to 0.36) |
| ABP501 + MTX | | 1.23 (0.34 to 4.34) | 1.15 (0.47 to 2.79) | 0.04 (–0.22 to 0.30) |
| CERTO_STD + MTX | INF_STD + MTX | 1.78 (0.89 to 3.61) | 1.46 (0.93 to 2.35) | 0.13 (–0.03 to 0.28) |
| RIT_STD | | 1.19 (0.28 to 5.58) | 1.13 (0.36 to 2.65) | 0.04 (–0.21 to 0.40) |
| RIT_STD + MTX | | 1.84 (0.44 to 8.32) | 1.48 (0.54 to 3.04) | 0.14 (–0.15 to 0.48) |
| BAR_4 + MTX | | 1.82 (0.86 to 3.92) | 1.47 (0.90 to 2.42) | 0.13 (–0.03 to 0.31) |
| HD203 + MTX | | 2.37 (0.73 to 8.43) | 1.70 (0.80 to 3.13) | 0.20 (–0.07 to 0.48) |
| SB4 + MTX | | 1.55 (0.52 to 5.05) | 1.34 (0.62 to 2.62) | 0.10 (–0.13 to 0.37) |
| ANBAI + MTX | | 2.90 (0.89 to 9.88) | 1.87 (0.93 to 3.31) | 0.25 (–0.02 to 0.51) |
| CT-P13 + MTX | | 1.38 (0.72 to 2.73) | 1.24 (0.79 to 1.85) | 0.07 (–0.06 to 0.23) |
| SB2 + MTX | | 0.87 (0.38 to 1.99) | 0.90 (0.46 to 1.56) | –0.03 (–0.16 to 0.16) |
| SB5 + MTX | | 1.24 (0.43 to 3.53) | 1.16 (0.53 to 2.24) | 0.05 (–0.16 to 0.28) |
| ZRC-3197 + MTX | | 1.29 (0.38 to 4.42) | 1.19 (0.48 to 2.44) | 0.05 (–0.17 to 0.34) |
| ABP501 + MTX | | 1.19 (0.42 to 3.39) | 1.13 (0.52 to 2.20) | 0.04 (–0.16 to 0.27) |
| RIT_STD | CERTO_STD + MTX | 0.66 (0.16 to 3.05) | 0.77 (0.25 to 1.72) | –0.09 (–0.34 to 0.27) |
| RIT_STD + MTX | | 1.03 (0.25 to 4.50) | 1.02 (0.38 to 1.96) | 0.01 (–0.28 to 0.35) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| BAR_4 + MTX | | 1.02 (0.50 to 2.06) | 1.01 (0.66 to 1.51) | 0.004 (–0.16 to 0.18) |
| HD203 + MTX | | 1.33 (0.42 to 4.56) | 1.17 (0.56 to 1.98) | 0.07 (–0.20 to 0.35) |
| SB4 + MTX | | 0.87 (0.30 to 2.73) | 0.92 (0.44 to 1.67) | –0.03 (–0.26 to 0.24) |
| ANBAI + MTX | | 1.63 (0.51 to 5.41) | 1.29 (0.65 to 2.10) | 0.12 (–0.16 to 0.39) |
| CT-P13 + MTX | | 0.77 (0.30 to 2.06) | 0.85 (0.44 to 1.49) | –0.06 (–0.26 to 0.18) |
| SB2 + MTX | | 0.49 (0.16 to 1.44) | 0.62 (0.26 to 1.24) | –0.15 (–0.34 to 0.09) |
| SB5 + MTX | | 0.70 (0.26 to 1.85) | 0.80 (0.38 to 1.41) | –0.08 (–0.28 to 0.15) |
| ZRC-3197 + MTX | | 0.73 (0.22 to 2.31) | 0.82 (0.34 to 1.54) | –0.07 (–0.30 to 0.20) |
| ABP501 + MTX | | 0.67 (0.24 to 1.73) | 0.78 (0.37 to 1.36) | –0.09 (–0.29 to 0.13) |
| RIT_STD + MTX | RIT_STD | 1.56 (0.47 to 5.23) | 1.29 (0.62 to 3.03) | 0.09 (–0.16 to 0.35) |
| BAR_4 + MTX | | 1.53 (0.33 to 6.74) | 1.31 (0.57 to 4.06) | 0.10 (–0.27 to 0.36) |
| HD203 + MTX | | 2.01 (0.33 to 12.22) | 1.50 (0.55 to 4.96) | 0.16 (–0.26 to 0.52) |
| SB4 + MTX | | 1.31 (0.23 to 7.61) | 1.19 (0.43 to 4.06) | 0.06 (–0.33 to 0.41) |
| ANBAI + MTX | | 2.45 (0.42 to 13.97) | 1.65 (0.64 to 5.27) | 0.21 (–0.20 to 0.55) |
| CT-P13 + MTX | | 1.16 (0.22 to 5.91) | 1.10 (0.42 to 3.63) | 0.03 (–0.35 to 0.34) |
| SB2 + MTX | | 0.73 (0.13 to 3.93) | 0.80 (0.26 to 2.84) | –0.06 (–0.43 to 0.25) |
| SB5 + MTX | | 1.04 (0.19 to 5.31) | 1.03 (0.37 to 3.42) | 0.01 (–0.37 to 0.32) |
| ZRC-3197 + MTX | | 1.09 (0.18 to 6.29) | 1.06 (0.34 to 3.62) | 0.02 (–0.38 to 0.37) |
| ABP501 + MTX | | 1.00 (0.18 to 5.08) | 1.00 (0.36 to 3.30) | 0.001 (–0.38 to 0.31) |
| BAR_4 + MTX | RIT_STD + MTX | 0.98 (0.22 to 4.19) | 0.99 (0.49 to 2.69) | –0.004 (–0.36 to 0.30) |
| HD203 + MTX | | 1.28 (0.22 to 7.58) | 1.14 (0.47 to 3.33) | 0.06 (–0.35 to 0.45) |
| SB4 + MTX | | 0.84 (0.15 to 4.72) | 0.90 (0.36 to 2.71) | –0.04 (–0.42 to 0.34) |
| ANBAI + MTX | | 1.58 (0.27 to 8.82) | 1.26 (0.54 to 3.52) | 0.11 (–0.30 to 0.48) |
| CT-P13 + MTX | | 0.75 (0.15 to 3.68) | 0.84 (0.36 to 2.43) | –0.07 (–0.44 to 0.27) |
| SB2 + MTX | | 0.47 (0.08 to 2.48) | 0.61 (0.22 to 1.90) | –0.16 (–0.53 to 0.18) |
| SB5 + MTX | | 0.67 (0.13 to 3.43) | 0.78 (0.31 to 2.33) | –0.09 (–0.46 to 0.25) |
| ZRC-3197 + MTX | | 0.70 (0.11 to 4.01) | 0.81 (0.28 to 2.50) | –0.08 (–0.48 to 0.30) |
| ABP501 + MTX | | 0.65 (0.12 to 3.25) | 0.77 (0.30 to 2.28) | –0.10 (–0.47 to 0.24) |
| HD203 + MTX | BAR_4 + MTX | 1.31 (0.39 to 4.67) | 1.16 (0.55 to 2.06) | 0.07 (–0.21 to 0.36) |
| SB4 + MTX | | 0.85 (0.28 to 2.82) | 0.91 (0.43 to 1.72) | –0.04 (–0.27 to 0.25) |
| ANBAI + MTX | | 1.61 (0.48 to 5.49) | 1.28 (0.64 to 2.16) | 0.12 (–0.17 to 0.39) |
| CT-P13 + MTX | | 0.76 (0.28 to 2.09) | 0.84 (0.43 to 1.51) | –0.06 (–0.28 to 0.18) |
| SB2 + MTX | | 0.48 (0.15 to 1.46) | 0.62 (0.26 to 1.26) | –0.16 (–0.37 to 0.09) |
| SB5 + MTX | | 0.69 (0.24 to 1.90) | 0.79 (0.37 to 1.44) | –0.09 (–0.30 to 0.15) |
| ZRC-3197 + MTX | | 0.71 (0.21 to 2.35) | 0.81 (0.33 to 1.57) | –0.08 (–0.32 to 0.21) |
| ABP501 + MTX | | 0.66 (0.23 to 1.80) | 0.77 (0.36 to 1.40) | –0.10 (–0.31 to 0.14) |
| SB4 + MTX | HD203 + MTX | 0.66 (0.19 to 2.27) | 0.79 (0.39 to 1.61) | –0.10 (–0.38 to 0.19) |

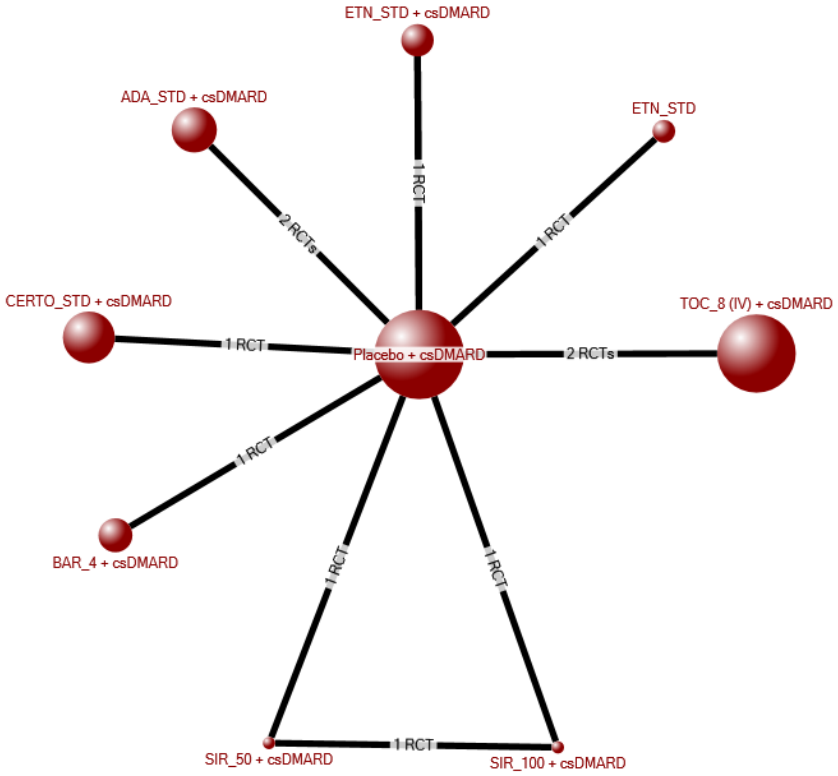
| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ANBAI + MTX | | 1.23 (0.25 to 5.68) | 1.10 (0.50 to 2.41) | 0.05 (–0.32 to 0.40) |
| CT-P13 + MTX | | 0.58 (0.14 to 2.27) | 0.74 (0.34 to 1.67) | –0.13 (–0.44 to 0.19) |
| SB2 + MTX | | 0.37 (0.08 to 1.55) | 0.54 (0.21 to 1.32) | –0.22 (–0.53 to 0.09) |
| SB5 + MTX | | 0.53 (0.12 to 2.13) | 0.69 (0.29 to 1.60) | –0.15 (–0.48 to 0.17) |
| ZRC-3197 + MTX | | 0.54 (0.11 to 2.51) | 0.71 (0.26 to 1.72) | –0.14 (–0.48 to 0.21) |
| ABP501 + MTX | | 0.51 (0.11 to 2.00) | 0.67 (0.28 to 1.55) | –0.16 (–0.48 to 0.15) |
| ANBAI + MTX | SB4 + MTX | 1.88 (0.41 to 8.02) | 1.40 (0.61 to 3.10) | 0.15 (–0.21 to 0.47) |
| CT-P13 + MTX | | 0.89 (0.23 to 3.20) | 0.93 (0.41 to 2.14) | –0.03 (–0.33 to 0.25) |
| SB2 + MTX | | 0.56 (0.13 to 2.20) | 0.68 (0.25 to 1.71) | –0.12 (–0.42 to 0.17) |
| SB5 + MTX | | 0.80 (0.19 to 2.98) | 0.87 (0.35 to 2.04) | –0.05 (–0.36 to 0.24) |
| ZRC-3197 + MTX | | 0.83 (0.18 to 3.52) | 0.89 (0.32 to 2.19) | –0.04 (–0.37 to 0.28) |
| ABP501 + MTX | | 0.77 (0.19 to 2.83) | 0.85 (0.34 to 2.00) | –0.06 (–0.37 to 0.23) |
| CT-P13 + MTX | ANBAI + MTX | 0.47 (0.12 to 1.86) | 0.66 (0.32 to 1.44) | –0.18 (–0.48 to 0.15) |
| SB2 + MTX | | 0.30 (0.07 to 1.27) | 0.49 (0.20 to 1.16) | –0.27 (–0.56 to 0.05) |
| SB5 + MTX | | 0.43 (0.10 to 1.71) | 0.62 (0.28 to 1.38) | –0.20 (–0.50 to 0.12) |
| ZRC-3197 + MTX | | 0.44 (0.09 to 2.06) | 0.64 (0.25 to 1.50) | –0.19 (–0.51 to 0.17) |
| ABP501 + MTX | | 0.41 (0.10 to 1.62) | 0.60 (0.27 to 1.34) | –0.21 (–0.51 to 0.11) |
| SB2 + MTX | CT-P13 + MTX | 0.63 (0.21 to 1.80) | 0.73 (0.33 to 1.48) | –0.09 (–0.31 to 0.13) |
| SB5 + MTX | | 0.90 (0.25 to 3.08) | 0.94 (0.40 to 2.08) | –0.02 (–0.29 to 0.25) |
| ZRC-3197 + MTX | | 0.94 (0.23 to 3.70) | 0.96 (0.36 to 2.23) | –0.01 (–0.30 to 0.30) |
| ABP501 + MTX | | 0.87 (0.25 to 2.95) | 0.91 (0.39 to 2.04) | –0.03 (–0.30 to 0.24) |
| SB5 + MTX | SB2 + MTX | 1.43 (0.36 to 5.45) | 1.28 (0.50 to 3.39) | 0.07 (–0.21 to 0.34) |
| ZRC-3197 + MTX | | 1.48 (0.35 to 6.51) | 1.31 (0.47 to 3.61) | 0.08 (–0.21 to 0.39) |
| ABP501 + MTX | | 1.37 (0.36 to 5.23) | 1.25 (0.49 to 3.29) | 0.06 (–0.21 to 0.32) |
| ZRC-3197 + MTX | SB5 + MTX | 1.04 (0.27 to 4.02) | 1.02 (0.41 to 2.44) | 0.01 (–0.27 to 0.31) |
| ABP501 + MTX | | 0.96 (0.29 to 3.20) | 0.97 (0.44 to 2.20) | –0.01 (–0.26 to 0.24) |
| ABP501 + MTX | ZRC-3197 + MTX | 0.92 (0.24 to 3.50) | 0.95 (0.40 to 2.40) | –0.02 (–0.32 to 0.26) |
| | | | | |
| Random-Effects Model | Residual Deviance | 129.8 vs. 125 data points | | |
| | Deviance Information Criteria | 833.475 | | |
| Fixed-Effects Model | Residual Deviance | 220.8 vs 140 data points | | |
| | Deviance Information Criteria | 1,015.2 | | |

ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; ANBAI = Anbainuo (biosimilar adalimumab); BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; CrI = credible interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar of infliximab; ETN = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; HD203 = etanercept biosimilar; INF = infliximab; IV = intravenous; MTX = methotrexate; OR = odds ratio; RD = risk difference; RIT = rituximab; RR = relative risk; SB2 = biosimilar infliximab 3mg/kg; SB4 = biosimilar etanercept 50 mg; SB5 = biosimilar adalimumab; SC = subcutaneous; SSZ = sulfasalazine; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; vs. = versus; ZRC-3197 = biosimilar of adalimumab.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator.

### *Conventional Synthetic DMARD Background Therapy*

Nine studies (seven two-arm studies and two three-arm studies)[143,151,158,162,163,172,217,241,249] were included that used a csDMARD as the common comparator. The evidence network involved 4,264 participants and 10 treatments, forming 13 direct comparisons. Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in Figure 4. The odds ratios for all treatment comparisons with csDMARD monotherapy as the common comparator are available in Table 8. Staircase tables for ACR 20, ACR 50, and ACR 70 with csDMARD as a common comparator are reported in Appendix 10 (Tables 88 to 90).

## Figure 4: Evidence Network: ACR 50 (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




ADA = adalimumab; BAR_4 = 4 mg baricitinib 4 mg; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; IV = intravenous; RCT = randomized controlled trial; SIR_50 = 50 mg sirukumab; SIR_100 = 100 mg sirukumab; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab.

Participants receiving a combination of csDMARD with adalimumab, 8 mg/kg tocilizumab, and 50 mg or 100 mg sirukumab had statistically significantly higher odds of achieving ACR 50 disease response compared with those receiving csDMARD monotherapy (Table 8). However, the 95% CrIs for the comparisons of both 50 mg and 100 mg of sirukumab were very wide. It should also be noted that submissions for regulatory approval were withdrawn globally for sirukumab after the analysis was completed.[57] There were no other statistically significant results when comparing any biologic or tsDMARD inhibitor with another.

## Table 8: ACR 50 (Placebo + csDMARD): Odds Ratios, Relative Risks, and Risk Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ETN_STD | Placebo + csDMARD | 4.10 (0.89 to 23.63) | 3.14 (0.90 to 7.66) | 0.21 (– 0.01 to 0.62) |
| ETN_STD + csDMARD | | 4.72 (1.40 to 16.87) | 3.45 (1.34 to 6.87) | 0.24 (0.03 to 0.54) |
| ADA_STD + csDMARD | | 4.05 (1.24 to 13.53) | 3.11 (1.21 to 6.25) | 0.21 (0.02 to 0.50) |
| TOC_8 (IV) + csDMARD | | 3.59 (1.13 to 10.97) | 2.85 (1.11 to 5.67) | 0.18 (0.01 to 0.45) |
| CERTO_STD + csDMARD | | 4.32 (0.82 to 23.02) | 3.25 (0.84 to 7.53) | 0.22 (– 0.02 to 0.61) |
| BAR_4 + csDMARD | | 3.09 (0.61 to 15.65) | 2.56 (0.64 to 6.52) | 0.15 (– 0.04 to 0.53) |
| SIR_100 + csDMARD | | *13.12 (1.10 to 465.50)* | 5.90 (1.08 to 13.66) | 0.49 (0.01 to 0.90) |
| SIR_50 + csDMARD | | *15.90 (1.28 to 571.60)* | 6.36 (1.24 to 13.78) | 0.54 (0.03 to 0.90) |
| ETN_STD + csDMARD | ETN_STD | 1.15 (0.23 to 5.12) | 1.10 (0.42 to 3.28) | 0.03 (– 0.32 to 0.31) |
| ADA_STD + csDMARD | | 0.99 (0.12 to 6.76) | 0.99 (0.27 to 4.01) | 0.00 (– 0.45 to 0.35) |
| TOC_8 (IV) + csDMARD | | 0.88 (0.11 to 5.67) | 0.91 (0.25 to 3.67) | – 0.03 (– 0.46 to 0.31) |
| CERTO_STD + csDMARD | | 1.06 (0.09 to 9.83) | 1.04 (0.21 to 4.53) | 0.01 (– 0.46 to 0.45) |
| BAR_4 + csDMARD | | 0.76 (0.07 to 6.71) | 0.82 (0.16 to 3.71) | – 0.05 (– 0.50 to 0.36) |
| SIR_100 + csDMARD | | *3.26 (0.15 to 145.90)* | 1.83 (0.29 to 8.20) | 0.26 (– 0.38 to 0.79) |
| SIR_50 + csDMARD | | *3.95 (0.17 to 179.00)* | 1.95 (0.34 to 8.45) | 0.30 (– 0.35 to 0.80) |
| ADA_STD + csDMARD | ETN_STD + csDMARD | 0.86 (0.15 to 4.64) | 0.90 (0.28 to 2.80) | – 0.03 (– 0.39 to 0.32) |
| TOC_8 (IV) + csDMARD | | 0.76 (0.13 to 3.93) | 0.83 (0.26 to 2.56) | – 0.06 (– 0.41 to 0.27) |
| CERTO_STD + csDMARD | | 0.92 (0.11 to 7.14) | 0.95 (0.21 to 3.25) | – 0.02 (– 0.41 to 0.42) |
| BAR_4 + csDMARD | | 0.66 (0.08 to 4.86) | 0.75 (0.16 to 2.69) | – 0.08 (– 0.44 to 0.33) |
| SIR_100 + csDMARD | | *2.82 (0.17 to 114.70)* | 1.69 (0.29 to 5.76) | 0.24 (– 0.35 to 0.75) |
| SIR_50 + csDMARD | | *3.42 (0.20 to 143.00)* | 1.80 (0.34 to 5.95) | 0.28 (– 0.32 to 0.76) |
| TOC_8 (IV) + csDMARD | ADA_STD + csDMARD | 0.88 (0.16 to 4.54) | 0.92 (0.29 to 2.88) | – 0.02 (– 0.36 to 0.30) |
| CERTO_STD + csDMARD | | 1.07 (0.14 to 8.28) | 1.04 (0.24 to 3.64) | 0.01 (– 0.36 to 0.44) |
| BAR_4 + csDMARD | | 0.76 (0.10 to 5.70) | 0.83 (0.18 to 3.06) | – 0.05 (– 0.39 to 0.36) |
| SIR_100 + csDMARD | | *3.28 (0.21 to 137.00)* | 1.87 (0.32 to 6.56) | 0.27 (– 0.30 to 0.77) |
| SIR_50 + csDMARD | | *4.00 (0.24 to 168.10)* | 2.00 (0.37 to 6.70) | 0.32 (– 0.28 to 0.78) |
| CERTO_STD + csDMARD | TOC_8 (IV) + csDMARD | 1.21 (0.16 to 9.39) | 1.14 (0.26 to 4.00) | 0.04 (– 0.32 to 0.46) |
| BAR_4 + csDMARD | | 0.86 (0.12 to 6.35) | 0.89 (0.20 to 3.36) | – 0.03 (– 0.35 to 0.38) |
| SIR_100 + csDMARD | | *3.72 (0.23 to 159.40)* | 2.03 (0.35 to 7.25) | 0.30 (– 0.26 to 0.79) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| SIR_50 + csDMARD | | *4.47 (0.28 to 190.60)* | 2.18 (0.41 to 7.43) | 0.34 (– 0.24 to 0.80) |
| BAR_4 + csDMARD | CERTO_STD + csDMARD | 0.71 (0.07 to 7.36) | 0.79 (0.16 to 4.02) | – 0.06 (– 0.50 to 0.37) |
| SIR_100 + csDMARD | | *3.10 (0.16 to 151.60)* | 1.76 (0.30 to 8.63) | 0.25 (– 0.38 to 0.79) |
| SIR_50 + csDMARD | | *3.75 (0.18 to 186.00)* | 1.89 (0.34 to 8.93) | 0.29 (– 0.35 to 0.80) |
| SIR_100 + csDMARD | BAR_4 + csDMARD | *4.32 (0.21 to 211.90)* | 2.23 (0.36 to 11.46) | 0.32 (– 0.29 to 0.83) |
| SIR_50 + csDMARD | | *5.26 (0.26 to 260.60)* | 2.39 (0.41 to 11.88) | 0.36 (– 0.26 to 0.83) |
| SIR_50 + csDMARD | SIR_100 + csDMARD | 1.20 (0.17 to 8.47) | 1.04 (0.42 to 3.01) | 0.03 (– 0.34 to 0.41) |
| | | | | |
| Random-Effects Model | Residual Deviance | 21.4 vs. 20 data points | | |
| | Deviance Information Criteria | 137.79 | | |
| Fixed-Effect Model | Residual Deviance | 38.94 vs 20 data points | | |
| | Deviance Information Criteria | 152.64 | | |

ADA = adalimumab; BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; CrI = credible interval; csDMARD = disease-modifying antirheumatic drug; ETN = etanercept; IV = intravenous; OR = odds ratio; RD = risk difference; RR = relative risk; SIR_100 = 100 mg sirukumab; SIR_50 = 50 mg sirukumab; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator. Italicized results indicate wide credible intervals.

## Disease Activity Score

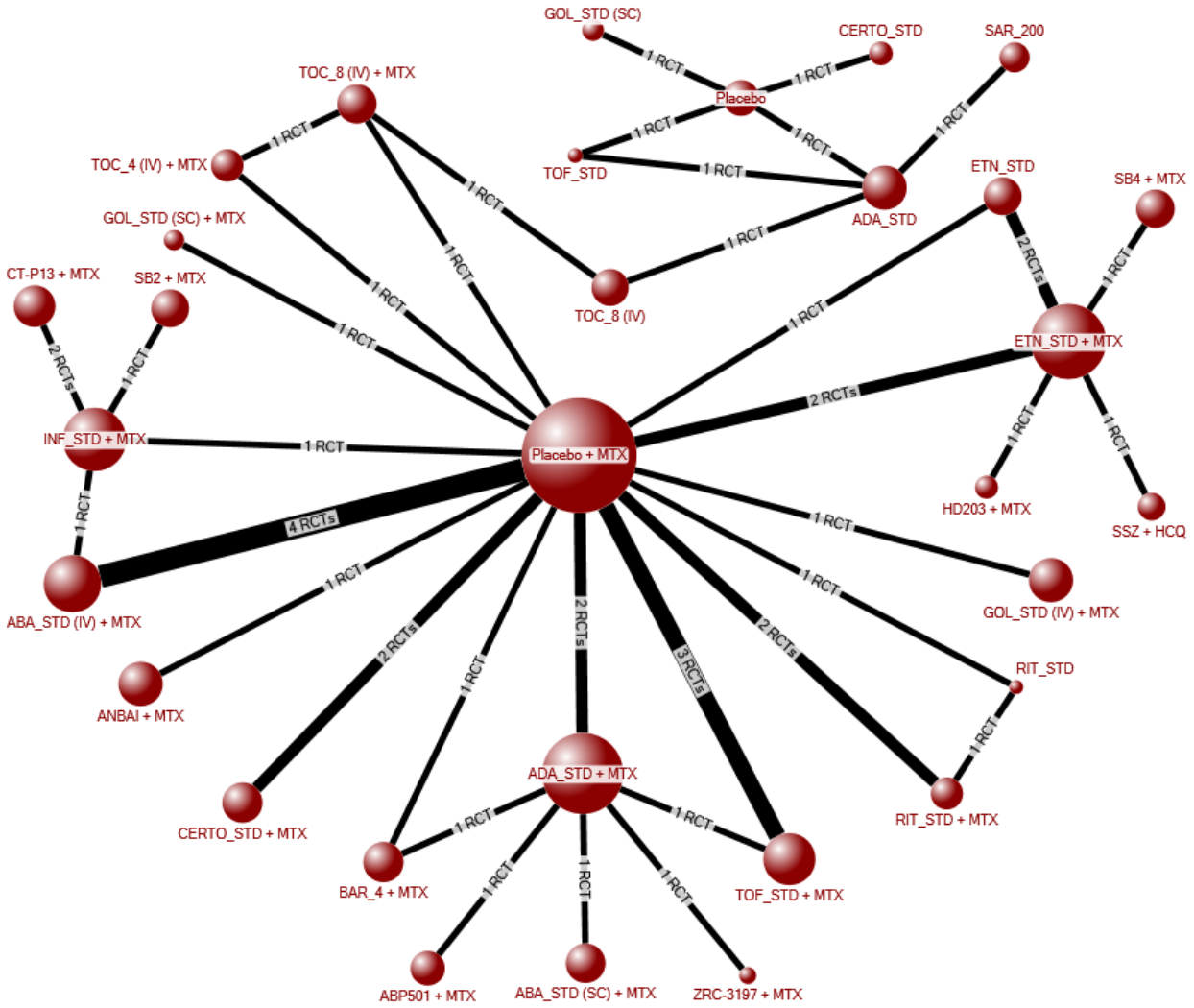
The DAS-28 was analyzed using the SMD to account for differences in scales (i.e., DAS28-ESR and DAS28-CRP).

### *Methotrexate as a Common Comparator*

Thirty-four studies[94,95,97,99,100,102,130,132,135,137,138,145,152,153,155,165,167,169,188,195,207,214,215,223,224,226,229,230,232,234,240,247,248,251] were included for the evidence network of DAS28 with MTX monotherapy as the common comparator (placebo + MTX). The DAS28 ESR and CRP scales were both included and SMDs were calculated. There were 48 direct comparisons in the evidence network based on 31 treatments with 27 two-arm studies and seven three-arm studies. The total number of participants contributing to the evidence network was 13,022.

Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in Figure 5. The SMDs for all treatment comparisons with placebo as the common comparator are available in Table 9.

## Figure 5: Evidence Network: Disease Activity Score 28-Joint Count (Placebo + Methotrexate)




ABA = abatacept; ABP501 = biosimilar of adalimumab; ADA = adalimumab; ANBAI = Anbainuo (biosimilar of etanercept); BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; CT-P13 = biosimilar of infliximab; ETN = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; HD203 = biosimilar of etanercept; INF = infliximab; LFN = leflunomide; MTX = methotrexate; RCT = randomized controlled trial; RIT = rituximab; SAR_200 = 200 mg sarilumab; SB2 = biosimilar of infliximab; SB4 = biosimilar of etanercept; SSZ = sulfasalazine; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; ZRC-3197 = biosimilar adalimumab.

Compared with MTX monotherapy, abatacept (IV), certolizumab pegol, and rituximab, all in combination with MTX, achieved statistically significant improvements in the DAS28 (SMD = –1.43 [95% CrI, –2.73 to –0.16], –2.23 [95% CrI, –4.04 to –0.43], and –2.65 [95% CrI, –4.44 to –0.81], respectively). In addition, tocilizumab at a dose of 8 mg/kg (IV) both as monotherapy and in combination with MTX statistically significantly improved DAS28 scores compared with MTX monotherapy (SMD = –3.68 [95% CrI, –7.23 to –0.004] and –3.67 [95% CrI, –6.22 to –1.11], respectively). Of the head-to-head comparisons of drugs, the odds of

an improvement in DAS28 was higher for 8 mg/kg tocilizumab in combination with MTX compared with etanercept monotherapy (odds ratio = –3.57; 95% CrI, –6.83 to –0.29). None of the remaining comparisons of one drug with another had any statistically significant results (Table 9).

## Table 9: Disease Activity Score 28-Joint Count (Placebo + MTX): Standardized Mean Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| Placebo | Placebo + MTX | –1.06 (–6.13 to 4.17) |
| SSZ + HCQ | | –0.77 (–3.86 to 2.33) |
| ETN_STD | | –0.10 (–2.18 to 1.95) |
| ETN_STD + MTX | | –0.98 (–2.72 to 0.75) |
| ABA_STD (IV) + MTX | | **–1.43 (–2.73 to –0.16)** |
| ABA_STD (SC) + MTX | | –1.05 (–4.09 to 2.01) |
| ADA_STD | | –1.80 (–6.18 to 2.74) |
| ADA_STD + MTX | | –1.03 (–2.74 to 0.66) |
| TOF_STD | | –1.20 (–6.30 to 4.02) |
| TOF_STD + MTX | | –1.27 (–2.76 to 0.16) |
| TOC_8 (IV) | | **–3.68 (–7.23 to –0.004)** |
| TOC_4 (IV) + MTX | | –2.17 (–4.72 to 0.36) |
| TOC_8 (IV) + MTX | | **–3.67 (–6.22 to –1.11)** |
| GOL_STD (SC) | | –2.02 (–7.70 to 3.76) |
| GOL_STD (SC) + MTX | | –1.26 (–3.80 to 1.28) |
| GOL_STD (IV) + MTX | | –1.03 (–3.54 to 1.51) |
| INF_STD + MTX | | –0.78 (–3.06 to 1.52) |
| CERTO_STD | | –2.67 (–8.27 to 3.17) |
| CERTO_STD + MTX | | **–2.23 (–4.04 to –0.43)** |
| RIT_STD | | –1.49 (–3.89 to 0.90) |
| RIT_STD + MTX | | **–2.65 (–4.44 to –0.81)** |
| SAR_200 | | –1.25 (–6.32 to 3.91) |
| BAR_4 + MTX | | –0.83 (–3.21 to 1.53) |
| HD203 + MTX | | –1.10 (–4.19 to 1.97) |
| SB4 + MTX | | –1.16 (–4.19 to 1.92) |
| ANBAI + MTX | | –1.38 (–3.93 to 1.16) |
| CT-P13 + MTX | | –1.01 (–3.92 to 1.92) |
| SB2 + MTX | | –0.76 (–4.20 to 2.66) |
| ZRC-3197 + MTX | | –0.95 (–4.00 to 2.11) |
| ABP501 + MTX | | –1.03 (–4.06 to 1.99) |
| SSZ + HCQ | Placebo | 0.28 (–5.75 to 6.21) |
| ETN_STD | | 0.95 (–4.64 to 6.44) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| ETN_STD + MTX | | 0.08 (–5.39 to 5.45) |
| ABA_STD (IV) + MTX | | –0.37 (–5.76 to 4.84) |
| ABA_STD (SC) + MTX | | 0.01 (–6.03 to 5.88) |
| ADA_STD | | –0.73 (–3.29 to 1.84) |
| ADA_STD + MTX | | 0.03 (–5.46 to 5.40) |
| TOF_STD | | –0.14 (–2.68 to 2.42) |
| TOF_STD + MTX | | –0.21 (–5.65 to 5.04) |
| TOC_8 (IV) | | –2.61 (–6.27 to 0.97) |
| TOC_4 (IV) + MTX | | –1.10 (–6.33 to 4.00) |
| TOC_8 (IV) + MTX | | –2.61 (–7.11 to 1.79) |
| GOL_STD (SC) | | –0.96 (–3.51 to 1.58) |
| GOL_STD (SC) + MTX | | –0.20 (–6.02 to 5.46) |
| GOL_STD (IV) + MTX | | 0.05 (–5.78 to 5.64) |
| INF_STD + MTX | | 0.29 (–5.46 to 5.83) |
| CERTO_STD | | –1.60 (–4.17 to 0.97) |
| CERTO_STD + MTX | | –1.16 (–6.73 to 4.21) |
| RIT_STD | | –0.44 (–6.18 to 5.14) |
| RIT_STD + MTX | | –1.60 (–7.10 to 3.75) |
| SAR_200 | | –0.18 (–3.79 to 3.43) |
| BAR_4 + MTX | | 0.24 (–5.50 to 5.80) |
| HD203 + MTX | | –0.06 (–6.07 to 5.87) |
| SB4 + MTX | | –0.10 (–6.12 to 5.83) |
| ANBAI + MTX | | –0.32 (–6.14 to 5.32) |
| CT-P13 + MTX | | 0.04 (–5.97 to 5.88) |
| SB2 + MTX | | 0.29 (–6.01 to 6.44) |
| ZRC-3197 + MTX | | 0.11 (–5.98 to 6.06) |
| ABP501 + MTX | | 0.04 (–5.98 to 5.94) |
| ETN_STD | SSZ + HCQ | 0.67 (–2.44 to 3.76) |
| ETN_STD + MTX | | –0.21 (–2.76 to 2.33) |
| ABA_STD (IV) + MTX | | –0.67 (–4.01 to 2.66) |
| ABA_STD (SC) + MTX | | –0.28 (–4.62 to 4.07) |
| ADA_STD | | –1.01 (–6.38 to 4.43) |
| ADA_STD + MTX | | –0.26 (–3.80 to 3.24) |
| TOF_STD | | –0.43 (–6.35 to 5.63) |
| TOF_STD + MTX | | –0.50 (–3.95 to 2.86) |
| TOC_8 (IV) | | –2.91 (–7.58 to 1.87) |
| TOC_4 (IV) + MTX | | –1.41 (–5.43 to 2.61) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| TOC_8 (IV) + MTX | | –2.90 (–6.91 to 1.09) |
| GOL_STD (SC) | | –1.25 (–7.68 to 5.29) |
| GOL_STD (SC) + MTX | | –0.49 (–4.50 to 3.49) |
| GOL_STD (IV) + MTX | | –0.25 (–4.22 to 3.74) |
| INF_STD + MTX | | 0.0004 (–3.85 to 3.80) |
| CERTO_STD | | –1.89 (–8.28 to 4.67) |
| CERTO_STD + MTX | | –1.47 (–5.07 to 2.09) |
| RIT_STD | | –0.73 (–4.65 to 3.21) |
| RIT_STD + MTX | | –1.88 (–5.48 to 1.70) |
| SAR_200 | | –0.47 (–6.43 to 5.53) |
| BAR_4 + MTX | | –0.06 (–3.98 to 3.79) |
| HD203 + MTX | | –0.34 (–3.97 to 3.29) |
| SB4 + MTX | | –0.39 (–3.97 to 3.23) |
| ANBAI + MTX | | –0.61 (–4.60 to 3.37) |
| CT-P13 + MTX | | –0.24 (–4.48 to 3.96) |
| SB2 + MTX | | 0.002 (–4.60 to 4.61) |
| ZRC-3197 + MTX | | –0.18 (–4.51 to 4.18) |
| ABP501 + MTX | | –0.26 (–4.62 to 4.05) |
| ETN_STD + MTX | ETN_STD | –0.88 (–2.60 to 0.85) |
| ABA_STD (IV) + MTX | | –1.33 (–3.75 to 1.10) |
| ABA_STD (SC) + MTX | | –0.94 (–4.64 to 2.73) |
| ADA_STD | | –1.69 (–6.56 to 3.25) |
| ADA_STD + MTX | | –0.93 (–3.60 to 1.73) |
| TOF_STD | | –1.10 (–6.57 to 4.52) |
| TOF_STD + MTX | | –1.18 (–3.71 to 1.34) |
| TOC_8 (IV) | | –3.57 (–7.71 to 0.65) |
| TOC_4 (IV) + MTX | | –2.07 (–5.33 to 1.22) |
| TOC_8 (IV) + MTX | | **–3.57 (–6.83 to –0.29)** |
| GOL_STD (SC) | | –1.92 (–7.95 to 4.22) |
| GOL_STD (SC) + MTX | | –1.16 (–4.42 to 2.13) |
| GOL_STD (IV) + MTX | | –0.93 (–4.20 to 2.34) |
| INF_STD + MTX | | –0.67 (–3.74 to 2.38) |
| CERTO_STD | | –2.57 (–8.57 to 3.61) |
| CERTO_STD + MTX | | –2.13 (–4.87 to 0.61) |
| RIT_STD | | –1.40 (–4.56 to 1.77) |
| RIT_STD + MTX | | –2.56 (–5.27 to 0.22) |
| SAR_200 | | –1.14 (–6.64 to 4.44) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| BAR_4 + MTX | | –0.73 (–3.86 to 2.40) |
| HD203 + MTX | | –1.02 (–4.07 to 2.06) |
| SB4 + MTX | | –1.06 (–4.08 to 2.04) |
| ANBAI + MTX | | –1.29 (–4.52 to 2.00) |
| CT-P13 + MTX | | –0.91 (–4.45 to 2.66) |
| SB2 + MTX | | –0.65 (–4.66 to 3.33) |
| ZRC-3197 + MTX | | –0.85 (–4.52 to 2.82) |
| ABP501 + MTX | | –0.93 (–4.60 to 2.76) |
| ABA_STD (IV) + MTX | ETN_STD + MTX | –0.45 (–2.61 to 1.69) |
| ABA_STD (SC) + MTX | | –0.06 (–3.58 to 3.45) |
| ADA_STD | | –0.80 (–5.55 to 4.02) |
| ADA_STD + MTX | | –0.05 (–2.50 to 2.36) |
| TOF_STD | | –0.22 (–5.59 to 5.28) |
| TOF_STD + MTX | | –0.30 (–2.55 to 1.95) |
| TOC_8 (IV) | | –2.68 (–6.69 to 1.33) |
| TOC_4 (IV) + MTX | | –1.19 (–4.30 to 1.90) |
| TOC_8 (IV) + MTX | | –2.69 (–5.77 to 0.43) |
| GOL_STD (SC) | | –1.03 (–6.97 to 4.96) |
| GOL_STD (SC) + MTX | | –0.28 (–3.36 to 2.81) |
| GOL_STD (IV) + MTX | | –0.04 (–3.11 to 3.00) |
| INF_STD + MTX | | 0.21 (–2.67 to 3.05) |
| CERTO_STD | | –1.69 (–7.55 to 4.39) |
| CERTO_STD + MTX | | –1.25 (–3.75 to 1.24) |
| RIT_STD | | –0.50 (–3.47 to 2.46) |
| RIT_STD + MTX | | –1.67 (–4.17 to 0.85) |
| SAR_200 | | –0.26 (–5.63 to 5.16) |
| BAR_4 + MTX | | 0.16 (–2.77 to 3.06) |
| HD203 + MTX | | –0.13 (–2.68 to 2.40) |
| SB4 + MTX | | –0.18 (–2.67 to 2.38) |
| ANBAI + MTX | | –0.40 (–3.47 to 2.66) |
| CT-P13 + MTX | | –0.02 (–3.40 to 3.32) |
| SB2 + MTX | | 0.22 (–3.63 to 4.04) |
| ZRC-3197 + MTX | | 0.04 (–3.46 to 3.56) |
| ABP501 + MTX | | –0.06 (–3.53 to 3.46) |
| ABA_STD (SC) + MTX | ABA_STD (IV) + MTX | 0.38 (–2.92 to 3.68) |
| ADA_STD | | –0.37 (–4.93 to 4.35) |
| ADA_STD + MTX | | 0.40 (–1.73 to 2.55) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| TOF_STD | | 0.23 (–5.01 to 5.63) |
| TOF_STD + MTX | | 0.16 (–1.79 to 2.06) |
| TOC_8 (IV) | | –2.25 (–6.02 to 1.65) |
| TOC_4 (IV) + MTX | | –0.75 (–3.60 to 2.11) |
| TOC_8 (IV) + MTX | | –2.24 (–5.09 to 0.65) |
| GOL_STD (SC) | | –0.58 (–6.39 to 5.33) |
| GOL_STD (SC) + MTX | | 0.18 (–2.66 to 3.01) |
| GOL_STD (IV) + MTX | | 0.40 (–2.41 to 3.27) |
| INF_STD + MTX | | 0.66 (–1.64 to 2.94) |
| CERTO_STD | | –1.24 (–7.02 to 4.71) |
| CERTO_STD + MTX | | –0.80 (–3.01 to 1.41) |
| RIT_STD | | –0.06 (–2.76 to 2.66) |
| RIT_STD + MTX | | –1.23 (–3.42 to 1.06) |
| SAR_200 | | 0.18 (–5.02 to 5.50) |
| BAR_4 + MTX | | 0.60 (–2.09 to 3.28) |
| HD203 + MTX | | 0.32 (–3.01 to 3.65) |
| SB4 + MTX | | 0.28 (–3.01 to 3.59) |
| ANBAI + MTX | | 0.05 (–2.76 to 2.87) |
| CT-P13 + MTX | | 0.42 (–2.51 to 3.34) |
| SB2 + MTX | | 0.67 (–2.77 to 4.12) |
| ZRC-3197 + MTX | | 0.49 (–2.80 to 3.84) |
| ABP501 + MTX | | 0.40 (–2.87 to 3.70) |
| ADA_STD | ABA_STD (SC) + MTX | –0.74 (–6.04 to 4.68) |
| ADA_STD + MTX | | 0.02 (–2.53 to 2.56) |
| TOF_STD | | –0.15 (–5.99 to 5.86) |
| TOF_STD + MTX | | –0.23 (–3.46 to 2.96) |
| TOC_8 (IV) | | –2.63 (–7.24 to 2.18) |
| TOC_4 (IV) + MTX | | –1.13 (–5.08 to 2.82) |
| TOC_8 (IV) + MTX | | –2.62 (–6.55 to 1.36) |
| GOL_STD (SC) | | –0.98 (–7.37 to 5.54) |
| GOL_STD (SC) + MTX | | –0.21 (–4.17 to 3.75) |
| GOL_STD (IV) + MTX | | 0.02 (–3.93 to 4.01) |
| INF_STD + MTX | | 0.28 (–3.55 to 4.09) |
| CERTO_STD | | –1.62 (–7.98 to 4.93) |
| CERTO_STD + MTX | | –1.18 (–4.76 to 2.35) |
| RIT_STD | | –0.44 (–4.32 to 3.44) |
| RIT_STD + MTX | | –1.61 (–5.15 to 1.99) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| SAR_200 | | –0.20 (–6.06 to 5.85) |
| BAR_4 + MTX | | 0.22 (–3.25 to 3.69) |
| HD203 + MTX | | –0.06 (–4.40 to 4.20) |
| SB4 + MTX | | –0.11 (–4.41 to 4.21) |
| ANBAI + MTX | | –0.34 (–4.30 to 3.64) |
| CT-P13 + MTX | | 0.05 (–4.17 to 4.28) |
| SB2 + MTX | | 0.28 (–4.35 to 4.91) |
| ZRC-3197 + MTX | | 0.10 (–3.48 to 3.70) |
| ABP501 + MTX | | 0.02 (–3.57 to 3.59) |
| ADA_STD + MTX | ADA_STD | 0.76 (–4.06 to 5.45) |
| TOF_STD | | 0.60 (–1.97 to 3.17) |
| TOF_STD + MTX | | 0.52 (–4.22 to 5.11) |
| TOC_8 (IV) | | –1.89 (–4.42 to 0.64) |
| TOC_4 (IV) + MTX | | –0.37 (–4.91 to 3.99) |
| TOC_8 (IV) + MTX | | –1.89 (–5.58 to 1.65) |
| GOL_STD (SC) | | –0.23 (–3.89 to 3.33) |
| GOL_STD (SC) + MTX | | 0.54 (–4.63 to 5.60) |
| GOL_STD (IV) + MTX | | 0.77 (–4.41 to 5.80) |
| INF_STD + MTX | | 1.02 (–4.05 to 5.97) |
| CERTO_STD | | –0.87 (–4.50 to 2.77) |
| CERTO_STD + MTX | | –0.44 (–5.35 to 4.30) |
| RIT_STD | | 0.31 (–4.82 to 5.27) |
| RIT_STD + MTX | | –0.86 (–5.74 to 3.87) |
| SAR_200 | | 0.55 (–1.98 to 3.10) |
| BAR_4 + MTX | | 0.96 (–4.14 to 5.90) |
| HD203 + MTX | | 0.67 (–4.81 to 6.04) |
| SB4 + MTX | | 0.63 (–4.77 to 5.98) |
| ANBAI + MTX | | 0.41 (–4.75 to 5.50) |
| CT-P13 + MTX | | 0.78 (–4.64 to 6.06) |
| SB2 + MTX | | 1.02 (–4.70 to 6.59) |
| ZRC-3197 + MTX | | 0.84 (–4.60 to 6.17) |
| ABP501 + MTX | | 0.76 (–4.69 to 6.01) |
| TOF_STD | ADA_STD + MTX | –0.17 (–5.53 to 5.32) |
| TOF_STD + MTX | | –0.25 (–2.20 to 1.70) |
| TOC_8 (IV) | | –2.64 (–6.58 to 1.45) |
| TOC_4 (IV) + MTX | | –1.14 (–4.16 to 1.91) |
| TOC_8 (IV) + MTX | | –2.63 (–5.67 to 0.44) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| GOL_STD (SC) | | –0.99 (–6.90 to 5.04) |
| GOL_STD (SC) + MTX | | –0.22 (–3.27 to 2.82) |
| GOL_STD (IV) + MTX | | 0.004 (–3.04 to 3.06) |
| INF_STD + MTX | | 0.25 (–2.58 to 3.13) |
| CERTO_STD | | –1.63 (–7.51 to 4.45) |
| CERTO_STD + MTX | | –1.19 (–3.68 to 1.28) |
| RIT_STD | | –0.46 (–3.41 to 2.47) |
| RIT_STD + MTX | | –1.62 (–4.09 to 0.89) |
| SAR_200 | | –0.22 (–5.56 to 5.19) |
| BAR_4 + MTX | | 0.20 (–2.17 to 2.57) |
| HD203 + MTX | | –0.08 (–3.62 to 3.43) |
| SB4 + MTX | | –0.13 (–3.60 to 3.37) |
| ANBAI + MTX | | –0.36 (–3.40 to 2.71) |
| CT-P13 + MTX | | 0.02 (–3.31 to 3.41) |
| SB2 + MTX | | 0.26 (–3.59 to 4.16) |
| ZRC-3197 + MTX | | 0.09 (–2.44 to 2.64) |
| ABP501 + MTX | | –0.001 (–2.52 to 2.53) |
| TOF_STD + MTX | TOF_STD | –0.09 (–5.48 to 5.18) |
| TOC_8 (IV) | | –2.49 (–6.11 to 1.10) |
| TOC_4 (IV) + MTX | | –0.96 (–6.21 to 4.09) |
| TOC_8 (IV) + MTX | | –2.48 (–6.98 to 1.88) |
| GOL_STD (SC) | | –0.82 (–4.45 to 2.78) |
| GOL_STD (SC) + MTX | | –0.05 (–5.87 to 5.62) |
| GOL_STD (IV) + MTX | | 0.18 (–5.65 to 5.82) |
| INF_STD + MTX | | 0.43 (–5.30 to 5.99) |
| CERTO_STD | | –1.46 (–5.09 to 2.14) |
| CERTO_STD + MTX | | –1.03 (–6.60 to 4.33) |
| RIT_STD | | –0.30 (–6.04 to 5.31) |
| RIT_STD + MTX | | –1.45 (–6.91 to 3.94) |
| SAR_200 | | –0.05 (–3.66 to 3.59) |
| BAR_4 + MTX | | 0.37 (–5.36 to 5.93) |
| HD203 + MTX | | 0.07 (–5.99 to 6.02) |
| SB4 + MTX | | 0.04 (–5.97 to 5.93) |
| ANBAI + MTX | | –0.18 (–5.97 to 5.48) |
| CT-P13 + MTX | | 0.19 (–5.84 to 6.06) |
| SB2 + MTX | | 0.44 (–5.81 to 6.58) |
| ZRC-3197 + MTX | | 0.26 (–5.82 to 6.19) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| ABP501 + MTX | | 0.19 (–5.87 to 6.05) |
| TOC_8 (IV) | TOF_STD + MTX | –2.40 (–6.24 to 1.56) |
| TOC_4 (IV) + MTX | | –0.89 (–3.80 to 2.04) |
| TOC_8 (IV) + MTX | | –2.40 (–5.31 to 0.57) |
| GOL_STD (SC) | | –0.75 (–6.57 to 5.22) |
| GOL_STD (SC) + MTX | | 0.01 (–2.89 to 2.97) |
| GOL_STD (IV) + MTX | | 0.25 (–2.66 to 3.21) |
| INF_STD + MTX | | 0.50 (–2.17 to 3.21) |
| CERTO_STD | | –1.39 (–7.16 to 4.64) |
| CERTO_STD + MTX | | –0.96 (–3.24 to 1.38) |
| RIT_STD | | –0.21 (–3.00 to 2.60) |
| RIT_STD + MTX | | –1.38 (–3.68 to 0.98) |
| SAR_200 | | 0.02 (–5.20 to 5.40) |
| BAR_4 + MTX | | 0.45 (–2.19 to 3.11) |
| HD203 + MTX | | 0.16 (–3.22 to 3.59) |
| SB4 + MTX | | 0.12 (–3.25 to 3.51) |
| ANBAI + MTX | | –0.11 (–3.02 to 2.83) |
| CT-P13 + MTX | | 0.26 (–2.95 to 3.54) |
| SB2 + MTX | | 0.51 (–3.19 to 4.26) |
| ZRC-3197 + MTX | | 0.33 (–2.84 to 3.57) |
| ABP501 + MTX | | 0.25 (–2.94 to 3.44) |
| TOC_4 (IV) + MTX | TOC_8 (IV) | 1.50 (–2.18 to 5.08) |
| TOC_8 (IV) + MTX | | 0.01 (–2.60 to 2.55) |
| GOL_STD (SC) | | 1.65 (–2.81 to 6.11) |
| GOL_STD (SC) + MTX | | 2.42 (–2.03 to 6.82) |
| GOL_STD (IV) + MTX | | 2.66 (–1.82 to 7.00) |
| INF_STD + MTX | | 2.90 (–1.48 to 7.15) |
| CERTO_STD | | 1.01 (–3.37 to 5.47) |
| CERTO_STD + MTX | | 1.45 (–2.67 to 5.43) |
| RIT_STD | | 2.18 (–2.25 to 6.46) |
| RIT_STD + MTX | | 1.02 (–3.06 to 5.03) |
| SAR_200 | | 2.44 (–1.15 to 6.07) |
| BAR_4 + MTX | | 2.85 (–1.55 to 7.09) |
| HD203 + MTX | | 2.56 (–2.26 to 7.24) |
| SB4 + MTX | | 2.51 (–2.27 to 7.28) |
| ANBAI + MTX | | 2.29 (–2.17 to 6.67) |
| CT-P13 + MTX | | 2.66 (–2.04 to 7.31) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| SB2 + MTX | | 2.89 (–2.16 to 7.88) |
| ZRC-3197 + MTX | | 2.73 (–2.06 to 7.42) |
| ABP501 + MTX | | 2.66 (–2.15 to 7.29) |
| TOC_8 (IV) + MTX | TOC_4 (IV) + MTX | –1.50 (–4.03 to 1.07) |
| GOL_STD (SC) | | 0.15 (–5.50 to 5.96) |
| GOL_STD (SC) + MTX | | 0.91 (–2.70 to 4.47) |
| GOL_STD (IV) + MTX | | 1.14 (–2.44 to 4.70) |
| INF_STD + MTX | | 1.39 (–2.02 to 4.82) |
| CERTO_STD | | –0.49 (–6.14 to 5.35) |
| CERTO_STD + MTX | | –0.07 (–3.18 to 3.05) |
| RIT_STD | | 0.68 (–2.75 to 4.18) |
| RIT_STD + MTX | | –0.49 (–3.59 to 2.64) |
| SAR_200 | | 0.92 (–4.13 to 6.12) |
| BAR_4 + MTX | | 1.33 (–2.12 to 4.82) |
| HD203 + MTX | | 1.05 (–2.94 to 5.08) |
| SB4 + MTX | | 1.01 (–2.94 to 4.99) |
| ANBAI + MTX | | 0.79 (–2.77 to 4.37) |
| CT-P13 + MTX | | 1.17 (–2.70 to 5.01) |
| SB2 + MTX | | 1.40 (–2.90 to 5.69) |
| ZRC-3197 + MTX | | 1.23 (–2.75 to 5.23) |
| ABP501 + MTX | | 1.15 (–2.85 to 5.07) |
| GOL_STD (SC) | TOC_8 (IV) + MTX | 1.66 (–3.41 to 6.81) |
| GOL_STD (SC) + MTX | | 2.42 (–1.22 to 6.00) |
| GOL_STD (IV) + MTX | | 2.65 (–0.94 to 6.22) |
| INF_STD + MTX | | 2.90 (–0.59 to 6.33) |
| CERTO_STD | | 1.01 (–4.04 to 6.15) |
| CERTO_STD + MTX | | 1.45 (–1.72 to 4.53) |
| RIT_STD | | 2.18 (–1.32 to 5.65) |
| RIT_STD + MTX | | 1.03 (–2.12 to 4.13) |
| SAR_200 | | 2.44 (–1.95 to 6.93) |
| BAR_4 + MTX | | 2.85 (–0.65 to 6.30) |
| HD203 + MTX | | 2.57 (–1.49 to 6.58) |
| SB4 + MTX | | 2.51 (–1.47 to 6.51) |
| ANBAI + MTX | | 2.29 (–1.33 to 5.87) |
| CT-P13 + MTX | | 2.66 (–1.29 to 6.54) |
| SB2 + MTX | | 2.90 (–1.43 to 7.16) |
| ZRC-3197 + MTX | | 2.73 (–1.31 to 6.67) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| ABP501 + MTX | | 2.65 (–1.39 to 6.57) |
| GOL_STD (SC) + MTX | GOL_STD (SC) | 0.77 (–5.56 to 6.95) |
| GOL_STD (IV) + MTX | | 1.00 (–5.37 to 7.18) |
| INF_STD + MTX | | 1.24 (–5.00 to 7.38) |
| CERTO_STD | | –0.63 (–4.23 to 2.97) |
| CERTO_STD + MTX | | –0.21 (–6.27 to 5.72) |
| RIT_STD | | 0.52 (–5.74 to 6.66) |
| RIT_STD + MTX | | –0.63 (–6.69 to 5.31) |
| SAR_200 | | 0.78 (–3.66 to 5.22) |
| BAR_4 + MTX | | 1.20 (–5.04 to 7.28) |
| HD203 + MTX | | 0.90 (–5.61 to 7.35) |
| SB4 + MTX | | 0.86 (–5.63 to 7.28) |
| ANBAI + MTX | | 0.64 (–5.68 to 6.82) |
| CT-P13 + MTX | | 1.01 (–5.49 to 7.40) |
| SB2 + MTX | | 1.23 (–5.55 to 7.91) |
| ZRC-3197 + MTX | | 1.08 (–5.48 to 7.52) |
| ABP501 + MTX | | 0.99 (–5.48 to 7.43) |
| GOL_STD (IV) + MTX | GOL_STD (SC) + MTX | 0.23 (–3.36 to 3.83) |
| INF_STD + MTX | | 0.49 (–2.93 to 3.88) |
| CERTO_STD | | –1.40 (–7.57 to 4.93) |
| CERTO_STD + MTX | | –0.97 (–4.07 to 2.12) |
| RIT_STD | | –0.24 (–3.71 to 3.29) |
| RIT_STD + MTX | | –1.40 (–4.50 to 1.73) |
| SAR_200 | | 0.01 (–5.64 to 5.78) |
| BAR_4 + MTX | | 0.43 (–3.04 to 3.84) |
| HD203 + MTX | | 0.15 (–3.83 to 4.11) |
| SB4 + MTX | | 0.10 (–3.87 to 4.07) |
| ANBAI + MTX | | –0.13 (–3.70 to 3.45) |
| CT-P13 + MTX | | 0.26 (–3.61 to 4.15) |
| SB2 + MTX | | 0.49 (–3.77 to 4.77) |
| ZRC-3197 + MTX | | 0.31 (–3.66 to 4.24) |
| ABP501 + MTX | | 0.23 (–3.72 to 4.19) |
| INF_STD + MTX | GOL_STD (IV) + MTX | 0.26 (–3.17 to 3.63) |
| CERTO_STD | | –1.63 (–7.79 to 4.73) |
| CERTO_STD + MTX | | –1.21 (–4.32 to 1.89) |
| RIT_STD | | –0.47 (–3.96 to 3.03) |
| RIT_STD + MTX | | –1.63 (–4.72 to 1.50) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| SAR_200 | | –0.23 (–5.88 to 5.55) |
| BAR_4 + MTX | | 0.19 (–3.29 to 3.65) |
| HD203 + MTX | | –0.09 (–4.06 to 3.85) |
| SB4 + MTX | | –0.14 (–4.05 to 3.82) |
| ANBAI + MTX | | –0.36 (–3.94 to 3.24) |
| CT-P13 + MTX | | 0.02 (–3.85 to 3.85) |
| SB2 + MTX | | 0.27 (–4.01 to 4.54) |
| ZRC-3197 + MTX | | 0.09 (–3.91 to 4.03) |
| ABP501 + MTX | | –0.001 (–3.98 to 3.93) |
| CERTO_STD | INF_STD + MTX | –1.88 (–8.01 to 4.42) |
| CERTO_STD + MTX | | –1.46 (–4.38 to 1.44) |
| RIT_STD | | –0.71 (–4.02 to 2.62) |
| RIT_STD + MTX | | –1.88 (–4.78 to 1.07) |
| SAR_200 | | –0.48 (–6.01 to 5.20) |
| BAR_4 + MTX | | –0.05 (–3.37 to 3.25) |
| HD203 + MTX | | –0.34 (–4.15 to 3.51) |
| SB4 + MTX | | –0.39 (–4.17 to 3.43) |
| ANBAI + MTX | | –0.61 (–3.98 to 2.82) |
| CT-P13 + MTX | | –0.23 (–2.02 to 1.56) |
| SB2 + MTX | | 0.01 (–2.55 to 2.58) |
| ZRC-3197 + MTX | | –0.17 (–3.97 to 3.65) |
| ABP501 + MTX | | –0.26 (–4.07 to 3.58) |
| CERTO_STD + MTX | CERTO_STD | 0.43 (–5.74 to 6.32) |
| RIT_STD | | 1.17 (–5.10 to 7.31) |
| RIT_STD + MTX | | 0.01 (–6.09 to 5.93) |
| SAR_200 | | 1.41 (–3.00 to 5.83) |
| BAR_4 + MTX | | 1.84 (–4.45 to 7.89) |
| HD203 + MTX | | 1.55 (–5.04 to 7.93) |
| SB4 + MTX | | 1.51 (–5.03 to 7.93) |
| ANBAI + MTX | | 1.27 (–5.09 to 7.45) |
| CT-P13 + MTX | | 1.65 (–4.85 to 8.08) |
| SB2 + MTX | | 1.88 (–4.91 to 8.56) |
| ZRC-3197 + MTX | | 1.73 (–4.88 to 8.18) |
| ABP501 + MTX | | 1.65 (–4.93 to 7.99) |
| RIT_STD | CERTO_STD + MTX | 0.74 (–2.28 to 3.74) |
| RIT_STD + MTX | | –0.42 (–2.98 to 2.16) |
| SAR_200 | | 0.98 (–4.39 to 6.46) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| BAR_4 + MTX | | 1.40 (–1.55 to 4.38) |
| HD203 + MTX | | 1.11 (–2.44 to 4.72) |
| SB4 + MTX | | 1.08 (–2.43 to 4.63) |
| ANBAI + MTX | | 0.85 (–2.28 to 3.95) |
| CT-P13 + MTX | | 1.23 (–2.19 to 4.66) |
| SB2 + MTX | | 1.46 (–2.42 to 5.36) |
| ZRC-3197 + MTX | | 1.29 (–2.26 to 4.85) |
| ABP501 + MTX | | 1.20 (–2.36 to 4.74) |
| RIT_STD + MTX | RIT_STD | –1.16 (–3.56 to 1.23) |
| SAR_200 | | 0.24 (–5.33 to 5.98) |
| BAR_4 + MTX | | 0.66 (–2.69 to 4.04) |
| HD203 + MTX | | 0.38 (–3.56 to 4.24) |
| SB4 + MTX | | 0.33 (–3.56 to 4.24) |
| ANBAI + MTX | | 0.10 (–3.36 to 3.63) |
| CT-P13 + MTX | | 0.48 (–3.28 to 4.22) |
| SB2 + MTX | | 0.72 (–3.47 to 4.93) |
| ZRC-3197 + MTX | | 0.54 (–3.35 to 4.43) |
| ABP501 + MTX | | 0.46 (–3.39 to 4.34) |
| SAR_200 | RIT_STD + MTX | 1.40 (–3.96 to 6.90) |
| BAR_4 + MTX | | 1.82 (–1.16 to 4.79) |
| HD203 + MTX | | 1.53 (–2.06 to 5.13) |
| SB4 + MTX | | 1.49 (–2.04 to 5.08) |
| ANBAI + MTX | | 1.28 (–1.86 to 4.37) |
| CT-P13 + MTX | | 1.65 (–1.82 to 5.08) |
| SB2 + MTX | | 1.89 (–2.03 to 5.76) |
| ZRC-3197 + MTX | | 1.71 (–1.84 to 5.26) |
| ABP501 + MTX | | 1.62 (–1.94 to 5.10) |
| BAR_4 + MTX | SAR_200 | 0.42 (–5.27 to 5.99) |
| HD203 + MTX | | 0.12 (–5.92 to 6.07) |
| SB4 + MTX | | 0.08 (–5.91 to 5.97) |
| ANBAI + MTX | | –0.14 (–5.95 to 5.56) |
| CT-P13 + MTX | | 0.23 (–5.75 to 6.12) |
| SB2 + MTX | | 0.47 (–5.78 to 6.54) |
| ZRC-3197 + MTX | | 0.29 (–5.68 to 6.22) |
| ABP501 + MTX | | 0.22 (–5.82 to 6.12) |
| HD203 + MTX | BAR_4 + MTX | –0.29 (–4.12 to 3.56) |
| SB4 + MTX | | –0.33 (–4.18 to 3.53) |

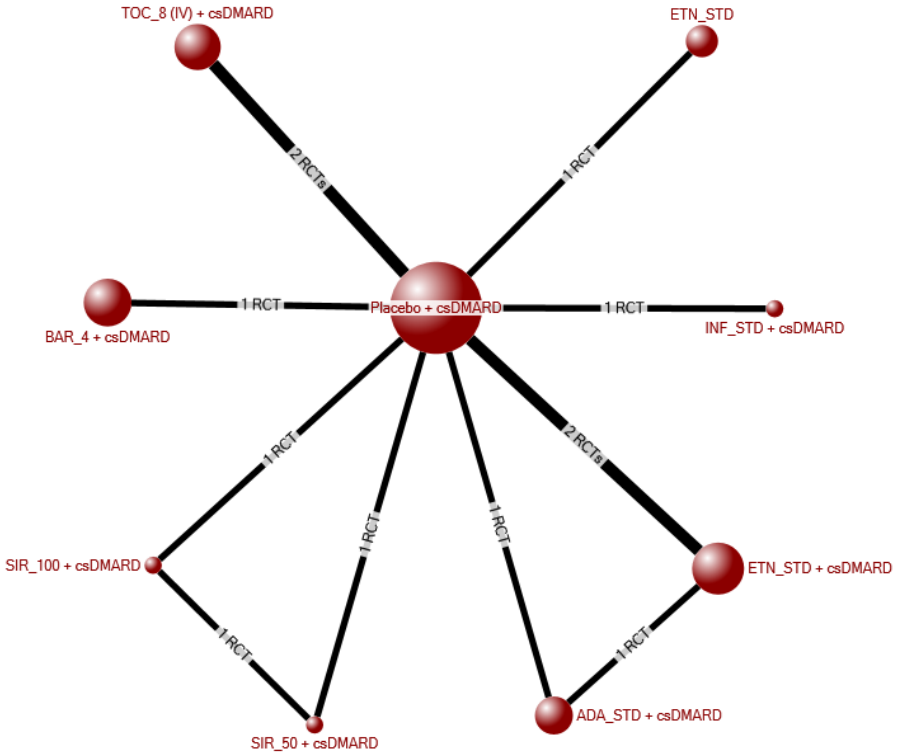
| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| ANBAI + MTX | | –0.56 (–4.01 to 2.92) |
| CT-P13 + MTX | | –0.18 (–3.96 to 3.56) |
| SB2 + MTX | | 0.06 (–4.11 to 4.23) |
| ZRC-3197 + MTX | | –0.12 (–3.55 to 3.39) |
| ABP501 + MTX | | –0.20 (–3.65 to 3.21) |
| SB4 + MTX | HD203 + MTX | –0.05 (–3.58 to 3.55) |
| ANBAI + MTX | | –0.27 (–4.23 to 3.69) |
| CT-P13 + MTX | | 0.11 (–4.16 to 4.31) |
| SB2 + MTX | | 0.35 (–4.28 to 4.96) |
| ZRC-3197 + MTX | | 0.16 (–4.12 to 4.52) |
| ABP501 + MTX | | 0.07 (–4.23 to 4.41) |
| ANBAI + MTX | SB4 + MTX | –0.23 (–4.19 to 3.73) |
| CT-P13 + MTX | | 0.15 (–4.07 to 4.34) |
| SB2 + MTX | | 0.39 (–4.23 to 4.95) |
| ZRC-3197 + MTX | | 0.21 (–4.11 to 4.52) |
| ABP501 + MTX | | 0.12 (–4.17 to 4.40) |
| CT-P13 + MTX | ANBAI + MTX | 0.38 (–3.50 to 4.19) |
| SB2 + MTX | | 0.63 (–3.67 to 4.85) |
| ZRC-3197 + MTX | | 0.44 (–3.52 to 4.36) |
| ABP501 + MTX | | 0.35 (–3.60 to 4.29) |
| SB2 + MTX | CT-P13 + MTX | 0.24 (–2.87 to 3.38) |
| ZRC-3197 + MTX | | 0.06 (–4.16 to 4.26) |
| ABP501 + MTX | | –0.02 (–4.23 to 4.18) |
| ZRC-3197 + MTX | SB2 + MTX | –0.18 (–4.78 to 4.41) |
| ABP501 + MTX | | –0.26 (–4.88 to 4.39) |
| ABP501 + MTX | ZRC-3197 + MTX | –0.09 (–3.64 to 3.47) |
| | | |
| Random-Effects Model | Residual Deviance | 41.17 vs. 75 data points |
| | Deviance Information Criteria | –9.225 |
| Fixed-Effects Model | Residual Deviance | 316.4 vs. 75 data points |
| | Deviance Information Criteria | 255.289 |

ABA = abatacept; ABP501 = biosimilar of adalimumab; ADA = adalimumab; ANBAI = Anbainuo (biosimilar of etanercept); BAR_4 = 4 mg baricitinib once daily (oral); CERTO = certolizumab pegol; CrI = credible interval; CT-P13 = biosimilar of infliximab; ETN = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; HD203 = biosimilar etanercept; INF = infliximab; IV = intravenous; LFN = leflunomide; MTX = methotrexate; RIT = rituximab; SAR_200 = 200 mg sarilumab; SB4 = biosimilar of etanercept; SB2 = biosimilar of infliximab; SC = subcutaneous; SMD = standardized mean difference; SSZ = sulfasalazine; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; ZRC-3197 = biosimilar adalimumab; vs. = versus; ZRC-3197 = biosimilar of adalimumab.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator. Bold results represent large effect sizes.

*Conventional Synthetic DMARD as a Common Comparator*

A total of nine RCTs[101,143,151,163,172,184,211,217,249] were included for the evidence network of DAS28 with monotherapy of a csDMARD other than MTX as the common comparator (placebo + csDMARD). The DAS28 ESR and CRP scales were both included and SMDs were calculated. Thirteen direct comparisons from nine treatments were available in the evidence network; there were seven two-arm studies and two three-arm studies. The total number of participants contributing to the evidence network was 2,131. Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in Figure 6. The SMDs for all treatment comparisons with placebo as the common comparator are available in Table 10. A staircase table of the results as SMDs is also presented in Appendix 10 (Table 91).

## Figure 6: Evidence Network: Disease Activity Score 28-Joint Count (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




ADA = adalimumab; BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; INF = infliximab; IV = intravenous; RCT = randomized controlled trial; SIR_50 = 50 mg sirukumab; SIR_100 = 100 mg sirukumab; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab.

There were no statistically significant differences between treatments and csDMARD monotherapy or any head-to-head comparisons of biologics or tsDMARDs.

## Table 10: Disease Activity Score 28-Joint Count (Placebo + csDMARD): Standardized Mean Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| ETN_STD | Placebo + csDMARD | –1.88 (–5.79 to 1.98) |
| ETN_STD + csDMARD | | –1.53 (–4.20 to 1.14) |
| ADA_STD + csDMARD | | –1.05 (–4.34 to 2.20) |
| TOC_8 (IV) + csDMARD | | –1.50 (–4.47 to 1.46) |
| INF_STD + csDMARD | | –0.95 (–5.16 to 3.27) |
| BAR_4 + csDMARD | | –1.49 (–5.68 to 2.73) |
| SIR_100 + csDMARD | | –0.93 (–5.15 to 3.25) |
| SIR_50 + csDMARD | | –1.14 (–5.40 to 3.04) |
| ETN_STD + csDMARD | ETN_STD | 0.34 (–3.54 to 4.21) |
| ADA_STD + csDMARD | | 0.82 (–3.88 to 5.52) |
| TOC_8 (IV) + csDMARD | | 0.38 (–4.49 to 5.25) |
| INF_STD + csDMARD | | 0.93 (–4.82 to 6.71) |
| BAR_4 + csDMARD | | 0.39 (–5.34 to 6.09) |
| SIR_100 + csDMARD | | 0.94 (–4.83 to 6.63) |
| SIR_50 + csDMARD | | 0.73 (–5.01 to 6.46) |
| ADA_STD + csDMARD | ETN_STD + csDMARD | 0.47 (–2.78 to 3.70) |
| TOC_8 (IV) + csDMARD | | 0.03 (–3.94 to 4.02) |
| INF_STD + csDMARD | | 0.58 (–4.41 to 5.57) |
| BAR_4 + csDMARD | | 0.04 (–4.94 to 5.00) |
| SIR_100 + csDMARD | | 0.60 (–4.37 to 5.59) |
| SIR_50 + csDMARD | | 0.40 (–4.59 to 5.36) |
| TOC_8 (IV) + csDMARD | ADA_STD + csDMARD | –0.45 (–4.86 to 4.01) |
| INF_STD + csDMARD | | 0.10 (–5.25 to 5.45) |
| BAR_4 + csDMARD | | –0.44 (–5.75 to 4.89) |
| SIR_100 + csDMARD | | 0.12 (–5.12 to 5.43) |
| SIR_50 + csDMARD | | –0.09 (–5.42 to 5.23) |
| INF_STD + csDMARD | TOC_8 (IV) + csDMARD | 0.55 (–4.64 to 5.73) |
| BAR_4 + csDMARD | | –0.001 (–5.11 to 5.16) |
| SIR_100 + csDMARD | | 0.57 (–4.61 to 5.74) |
| SIR_50 + csDMARD | | 0.36 (–4.84 to 5.47) |
| BAR_4 + csDMARD | INF_STD + csDMARD | –0.54 (–6.48 to 5.42) |
| SIR_100 + csDMARD | | 0.01 (–5.93 to 5.91) |
| SIR_50 + csDMARD | | –0.19 (–6.14 to 5.76) |
| SIR_100 + csDMARD | BAR_4 + csDMARD | 0.57 (–5.40 to 6.48) |
| SIR_50 + csDMARD | | 0.35 (–5.58 to 6.29) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| SIR_50 + csDMARD | SIR_100 + csDMARD | –0.20 (–4.47 to 3.95) |
| | | |
| Random-Effects Model | Total Residual Deviance | 11.03 vs. 20 data points |
| | Deviance Information Criteria | 6.368 |
| Fixed-Effects Model | Total Residual Deviance | 89.19 vs. 20 data points |
| | Deviance Information Criteria | 81.571 |

ADA = adalimumab; BAR_4 = 4 mg baricitinib; CrI = credible interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; INF = infliximab; IV = intravenous; SIR_50 = 50 mg sirukumab; SIR_100 = 100 mg sirukumab; SMD = standardized mean difference; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator. Bold results represent large effect sizes.

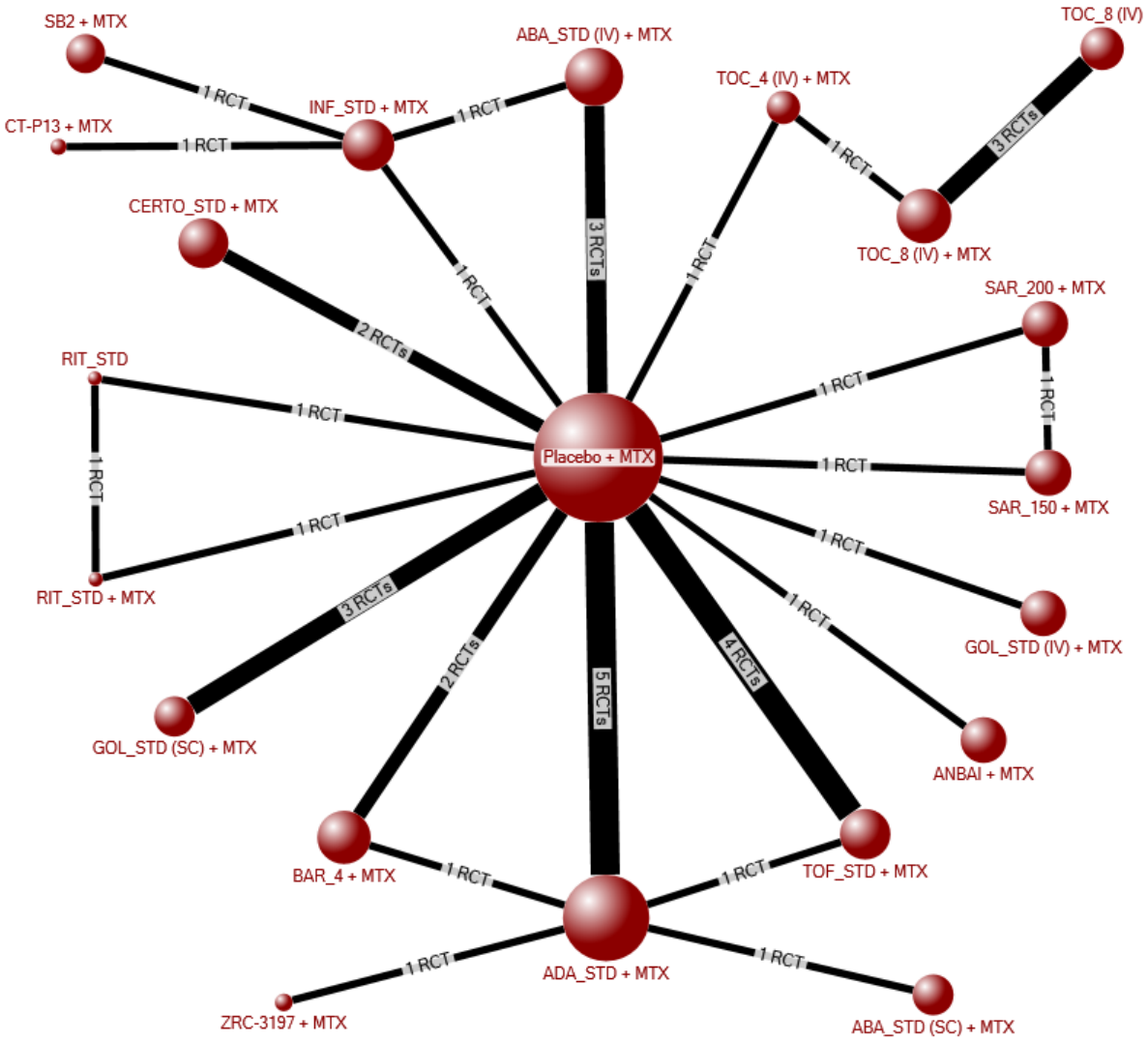
## Disability

Disability was extracted and analyzed in terms of the HAQ-DI.

### *Methotrexate as a Common Comparator*

A total of 28 studies[95,99,102,134,136-138,150,165,169,175,176,178,186,188,193,215,218-220,222,224,226,229,230,234,245,248] reported the change from baseline data for disability in the evidence network with MTX monotherapy as the common comparator (placebo + MTX) and were included in the reference case NMA. The evidence network had 21 treatments, 40 direct treatment comparisons, 22 two-arm studies, and six three-arm studies. The total number of participants contributing to the evidence network was 10,410. Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in Figure 7. The mean differences for all treatment comparisons with placebo as the common comparator are available in Table 11.

## Figure 7: Evidence Network: Health Assessment Questionnaire Disability Index (Placebo + Methotrexate)




ABA = abatacept; ADA = adalimumab; ANBAI = Anbainuo (biosimilar of etanercept); BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; CT-P13 = biosimilar infliximab; GOL = golimumab; INF = infliximab; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; RIT = rituximab; SAR 150 = 150 mg sarilumab; SAR_200 = 200 mg sarilumab; SB2 = biosimilar infliximab; SC = subcutaneous; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; ZRC-3197 = biosimilar adalimumab; ZRC-3197 = biosimilar adalimumab.

Overall, 15 of the 18 treatments were found to result in a reduction in disability that was statistically significant compared with MTX monotherapy. The 15 treatments were as follows: abatacept (IV), adalimumab, tofacitinib, 4 mg/kg tocilizumab (IV), 8 mg/kg tocilizumab, golimumab (SC), golimumab (IV), infliximab, certolizumab pegol, 150 mg and 200 mg sarilumab, baricitinib, Anbainuo (biosimilar etanercept), CT-P13 (biosimilar infliximab), all in combination with MTX; and monotherapy with 8 mg/kg tocilizumab (IV) and rituximab. There

was insufficient evidence to determine whether rituximab, SB2 (biosimilar infliximab), and ZRC-3197 (biosimilar adalimumab), all in combination with MTX, had statistically significant reductions in disability compared with MTX monotherapy.

Anbainuo (biosimilar etanercept) in combination with MTX had a statistically significant reduction in disability compared with: abatacept (SC) in combination with MTX (mean difference: –0.36; 95% CrI, –0.67 to –0.06); adalimumab in combination with MTX (mean difference: –0.38; 95% CrI, –0.62 to –0.15); tofacitinib in combination with MTX (mean difference: –0.32; 95% CrI, –0.56 to –0.08); 4 mg/kg of tocilizumab (IV) in combination with MTX (mean difference: –0.32; 95% CrI, –0.60 to –0.04); golimumab (SC) in combination with MTX (mean difference: –0.32; 95% CrI, –0.57 to –0.08); golimumab (IV) in combination with MTX (mean difference: –0.35; 95% CrI, –0.64 to –0.06); infliximab in combination with MTX (mean difference: –0.39; 95% CrI, –0.67 to –0.09); certolizumab pegol in combination with MTX (mean difference: –0.27; 95% CrI, –0.52 to –0.02); rituximab in combination with MTX (mean difference: –0.43; 95% CrI, –0.74 to –0.12); 150 mg sarilumab in combination with MTX (mean difference: –0.40; 95% CrI, –0.68 to –0.13); 200 mg sarilumab in combination with MTX (mean difference: 95% CrI, –0.34; –0.62 to –0.06); and 4 mg baricitinib in combination with MTX (mean difference: –0.33; 95% CrI, –0.58 to –0.09). However, no comparison could be made between Anbainuo in combination with MTX and its reference product etanercept (either as monotherapy or in combination with MTX) because none of the included studies with HAQ-DI data involved etanercept. Both SB2 (biosimilar infliximab) in combination with MTX and ZRC–3197 (biosimilar adalimumab) in combination with MTX demonstrated worsening in disability compared with Anbainuo in combination with MTX (mean differences: 0.39; 95% CrI, 0.03 to 0.73 and 0.39, 95% CrI, 0.03 to 0.74, respectively).

CT-P13 (biosimilar infliximab) in combination with MTX had a greater reduction in disability compared with infliximab in combination with MTX (mean difference: –0.29; 95% CrI, –0.55 to –0.03).

## Table 11: Health Assessment Questionnaire Disability Index (Placebo + MTX): Mean Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| ABA_STD (IV) + MTX | Placebo + MTX | –0.28 (–0.40 to –0.16) |
| ABA_STD (SC) + MTX | | –0.27 (–0.48 to –0.04) |
| ADA_STD + MTX | | –0.25 (–0.34 to –0.15) |
| TOF_STD + MTX | | –0.31 (–0.42 to –0.20) |
| TOC_8 (IV) | | –0.47 (–0.72 to –0.24) |
| TOC_4 (IV) + MTX | | –0.31 (–0.50 to –0.12) |
| TOC_8 (IV) + MTX | | –0.44 (–0.63 to –0.25) |
| GOL_STD (SC) + MTX | | –0.31 (–0.43 to –0.19) |
| GOL_STD (IV) + MTX | | –0.28 (–0.47 to –0.09) |
| INF_STD + MTX | | –0.24 (–0.45 to –0.05) |
| CERTO_STD + MTX | | –0.36 (–0.50 to –0.22) |
| RIT_STD | | –0.40 (–0.63 to –0.17) |
| RIT_STD + MTX | | –0.20 (–0.43 to 0.03) |

| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| SAR_150 + MTX | | –0.23 (–0.41 to –0.05) |
| SAR_200 + MTX | | –0.29 (–0.46 to –0.11) |
| BAR_4 + MTX | | –0.30 (–0.42 to –0.17) |
| ANBAI + MTX | | –0.63 (–0.84 to –0.42) |
| CT-P13 + MTX | | –0.53 (–0.87 to –0.21) |
| SB2 + MTX | | –0.24 (–0.52 to 0.03) |
| ZRC-3197 + MTX | | –0.24 (–0.53 to 0.04) |
| ABA_STD (SC) + MTX | ABA_STD (IV) + MTX | 0.01 (–0.23 to 0.27) |
| ADA_STD + MTX | | 0.03 (–0.12 to 0.19) |
| TOF_STD + MTX | | –0.03 (–0.19 to 0.13) |
| TOC_8 (IV) | | –0.20 (–0.47 to 0.08) |
| TOC_4 (IV) + MTX | | –0.03 (–0.25 to 0.20) |
| TOC_8 (IV) + MTX | | –0.16 (–0.39 to 0.07) |
| GOL_STD (SC) + MTX | | –0.03 (–0.20 to 0.15) |
| GOL_STD (IV) + MTX | | –0.003 (–0.23 to 0.23) |
| INF_STD + MTX | | 0.03 (–0.16 to 0.23) |
| CERTO_STD + MTX | | –0.09 (–0.26 to 0.11) |
| RIT_STD | | –0.12 (–0.38 to 0.14) |
| RIT_STD + MTX | | 0.08 (–0.18 to 0.34) |
| SAR_150 + MTX | | 0.05 (–0.16 to 0.27) |
| SAR_200 + MTX | | –0.01 (–0.22 to 0.21) |
| BAR_4 + MTX | | –0.02 (–0.19 to 0.17) |
| ANBAI + MTX | | –0.35 (–0.60 to –0.10) |
| CT-P13 + MTX | | –0.26 (–0.59 to 0.07) |
| SB2 + MTX | | 0.03 (–0.24 to 0.31) |
| ZRC-3197 + MTX | | 0.03 (–0.28 to 0.35) |
| ADA_STD + MTX | ABA_STD (SC) + MTX | 0.02 (–0.18 to 0.22) |
| TOF_STD + MTX | | –0.04 (–0.28 to 0.19) |
| TOC_8 (IV) | | –0.21 (–0.54 to 0.11) |
| TOC_4 (IV) + MTX | | –0.04 (–0.33 to 0.24) |
| TOC_8 (IV) + MTX | | –0.17 (–0.47 to 0.12) |
| GOL_STD (SC) + MTX | | –0.04 (–0.29 to 0.21) |
| GOL_STD (IV) + MTX | | –0.01 (–0.31 to 0.27) |
| INF_STD + MTX | | 0.02 (–0.28 to 0.31) |
| CERTO_STD + MTX | | –0.10 (–0.35 to 0.16) |
| RIT_STD | | –0.14 (–0.45 to 0.18) |
| RIT_STD + MTX | | 0.07 (–0.25 to 0.38) |

| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| SAR_150 + MTX | | 0.04 (–0.25 to 0.32) |
| SAR_200 + MTX | | –0.02 (–0.31 to 0.26) |
| BAR_4 + MTX | | –0.03 (–0.28 to 0.21) |
| ANBAI + MTX | | –0.36 (–0.67 to –0.06) |
| CT-P13 + MTX | | –0.27 (–0.67 to 0.12) |
| SB2 + MTX | | 0.02 (–0.34 to 0.37) |
| ZRC-3197 + MTX | | 0.02 (–0.32 to 0.35) |
| TOF_STD + MTX | ADA_STD + MTX | –0.06 (–0.19 to 0.06) |
| TOC_8 (IV) | | –0.23 (–0.49 to 0.02) |
| TOC_4 (IV) + MTX | | –0.06 (–0.28 to 0.14) |
| TOC_8 (IV) + MTX | | –0.19 (–0.41 to 0.02) |
| GOL_STD (SC) + MTX | | –0.06 (–0.21 to 0.09) |
| GOL_STD (IV) + MTX | | –0.03 (–0.25 to 0.18) |
| INF_STD + MTX | | 0.001 (–0.22 to 0.22) |
| CERTO_STD + MTX | | –0.12 (–0.28 to 0.05) |
| RIT_STD | | –0.16 (–0.40 to 0.09) |
| RIT_STD + MTX | | 0.05 (–0.20 to 0.29) |
| SAR_150 + MTX | | 0.02 (–0.18 to 0.21) |
| SAR_200 + MTX | | –0.04 (–0.24 to 0.15) |
| BAR_4 + MTX | | –0.05 (–0.19 to 0.09) |
| ANBAI + MTX | | –0.38 (–0.62 to –0.15) |
| CT-P13 + MTX | | –0.29 (–0.63 to 0.05) |
| SB2 + MTX | | 0.0004 (–0.29 to 0.29) |
| ZRC-3197 + MTX | | 0.0002 (–0.27 to 0.27) |
| TOC_8 (IV) | TOF_STD + MTX | –0.17 (–0.43 to 0.10) |
| TOC_4 (IV) + MTX | | –0.002 (–0.22 to 0.22) |
| TOC_8 (IV) + MTX | | –0.13 (–0.35 to 0.09) |
| GOL_STD (SC) + MTX | | 0.002 (–0.16 to 0.17) |
| GOL_STD (IV) + MTX | | 0.03 (–0.19 to 0.25) |
| INF_STD + MTX | | 0.06 (–0.16 to 0.29) |
| CERTO_STD + MTX | | –0.06 (–0.22 to 0.13) |
| RIT_STD | | –0.09 (–0.34 to 0.16) |
| RIT_STD + MTX | | 0.11 (–0.14 to 0.36) |
| SAR_150 + MTX | | 0.08 (–0.12 to 0.29) |
| SAR_200 + MTX | | 0.02 (–0.18 to 0.23) |
| BAR_4 + MTX | | 0.01 (–0.15 to 0.18) |
| ANBAI + MTX | | –0.32 (–0.56 to –0.08) |

| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| CT-P13 + MTX | | –0.23 (–0.57 to 0.12) |
| SB2 + MTX | | 0.06 (–0.23 to 0.36) |
| ZRC-3197 + MTX | | 0.06 (–0.24 to 0.37) |
| TOC_4 (IV) + MTX | TOC_8 (IV) | 0.16 (–0.08 to 0.41) |
| TOC_8 (IV) + MTX | | 0.03 (–0.11 to 0.19) |
| GOL_STD (SC) + MTX | | 0.17 (–0.10 to 0.44) |
| GOL_STD (IV) + MTX | | 0.19 (–0.11 to 0.51) |
| INF_STD + MTX | | 0.23 (–0.08 to 0.54) |
| CERTO_STD + MTX | | 0.11 (–0.16 to 0.40) |
| RIT_STD | | 0.07 (–0.25 to 0.41) |
| RIT_STD + MTX | | 0.27 (–0.05 to 0.60) |
| SAR_150 + MTX | | 0.24 (–0.05 to 0.55) |
| SAR_200 + MTX | | 0.18 (–0.11 to 0.49) |
| BAR_4 + MTX | | 0.17 (–0.09 to 0.46) |
| ANBAI + MTX | | –0.16 (–0.48 to 0.17) |
| CT-P13 + MTX | | –0.06 (–0.47 to 0.35) |
| SB2 + MTX | | 0.23 (–0.14 to 0.60) |
| ZRC-3197 + MTX | | 0.23 (–0.14 to 0.61) |
| TOC_8 (IV) + MTX | TOC_4 (IV) + MTX | –0.13 (–0.32 to 0.06) |
| GOL_STD (SC) + MTX | | 0.004 (–0.22 to 0.23) |
| GOL_STD (IV) + MTX | | 0.03 (–0.24 to 0.30) |
| INF_STD + MTX | | 0.07 (–0.21 to 0.34) |
| CERTO_STD + MTX | | –0.05 (–0.28 to 0.19) |
| RIT_STD | | –0.09 (–0.39 to 0.21) |
| RIT_STD + MTX | | 0.11 (–0.19 to 0.40) |
| SAR_150 + MTX | | 0.08 (–0.18 to 0.34) |
| SAR_200 + MTX | | 0.02 (–0.24 to 0.28) |
| BAR_4 + MTX | | 0.01 (–0.22 to 0.24) |
| ANBAI + MTX | | –0.32 (–0.60 to –0.04) |
| CT-P13 + MTX | | –0.23 (–0.60 to 0.15) |
| SB2 + MTX | | 0.07 (–0.27 to 0.39) |
| ZRC-3197 + MTX | | 0.07 (–0.28 to 0.41) |
| GOL_STD (SC) + MTX | TOC_8 (IV) + MTX | 0.14 (–0.09 to 0.36) |
| GOL_STD (IV) + MTX | | 0.16 (–0.11 to 0.43) |
| INF_STD + MTX | | 0.20 (–0.08 to 0.47) |
| CERTO_STD + MTX | | 0.08 (–0.15 to 0.32) |
| RIT_STD | | 0.04 (–0.26 to 0.34) |

| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| RIT_STD + MTX | | 0.24 (–0.06 to 0.53) |
| SAR_150 + MTX | | 0.21 (–0.05 to 0.47) |
| SAR_200 + MTX | | 0.15 (–0.11 to 0.41) |
| BAR_4 + MTX | | 0.14 (–0.09 to 0.37) |
| ANBAI + MTX | | –0.19 (–0.48 to 0.09) |
| CT-P13 + MTX | | –0.09 (–0.47 to 0.29) |
| SB2 + MTX | | 0.20 (–0.14 to 0.53) |
| ZRC-3197 + MTX | | 0.20 (–0.15 to 0.54) |
| GOL_STD (IV) + MTX | GOL_STD (SC) + MTX | 0.03 (–0.20 to 0.25) |
| INF_STD + MTX | | 0.06 (–0.17 to 0.29) |
| CERTO_STD + MTX | | –0.06 (–0.23 to 0.13) |
| RIT_STD | | –0.10 (–0.35 to 0.16) |
| RIT_STD + MTX | | 0.10 (–0.15 to 0.36) |
| SAR_150 + MTX | | 0.08 (–0.14 to 0.29) |
| SAR_200 + MTX | | 0.02 (–0.20 to 0.23) |
| BAR_4 + MTX | | 0.01 (–0.16 to 0.19) |
| ANBAI + MTX | | –0.32 (–0.57 to –0.08) |
| CT-P13 + MTX | | –0.23 (–0.58 to 0.12) |
| SB2 + MTX | | 0.06 (–0.24 to 0.36) |
| ZRC-3197 + MTX | | 0.06 (–0.25 to 0.37) |
| INF_STD + MTX | GOL_STD (IV) + MTX | 0.04 (–0.24 to 0.31) |
| CERTO_STD + MTX | | –0.08 (–0.31 to 0.16) |
| RIT_STD | | –0.12 (–0.42 to 0.18) |
| RIT_STD + MTX | | 0.08 (–0.22 to 0.37) |
| SAR_150 + MTX | | 0.05 (–0.21 to 0.31) |
| SAR_200 + MTX | | –0.01 (–0.27 to 0.25) |
| BAR_4 + MTX | | –0.02 (–0.25 to 0.21) |
| ANBAI + MTX | | –0.35 (–0.64 to –0.06) |
| CT-P13 + MTX | | –0.25 (–0.64 to 0.12) |
| SB2 + MTX | | 0.04 (–0.31 to 0.37) |
| ZRC-3197 + MTX | | 0.03 (–0.31 to 0.38) |
| CERTO_STD + MTX | INF_STD + MTX | –0.12 (–0.35 to 0.13) |
| RIT_STD | | –0.16 (–0.46 to 0.15) |
| RIT_STD + MTX | | 0.04 (–0.25 to 0.35) |
| SAR_150 + MTX | | 0.01 (–0.25 to 0.28) |
| SAR_200 + MTX | | –0.05 (–0.31 to 0.23) |
| BAR_4 + MTX | | –0.06 (–0.29 to 0.19) |

| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| ANBAI + MTX | | –0.39 (–0.67 to –0.09) |
| CT-P13 + MTX | | –0.29 (–0.55 to –0.03) |
| SB2 + MTX | | 0.00002 (–0.19 to 0.19) |
| ZRC-3197 + MTX | | –0.00004 (–0.35 to 0.35) |
| RIT_STD | CERTO_STD + MTX | –0.04 (–0.31 to 0.22) |
| RIT_STD + MTX | | 0.16 (–0.11 to 0.42) |
| SAR_150 + MTX | | 0.13 (–0.09 to 0.35) |
| SAR_200 + MTX | | 0.07 (–0.15 to 0.29) |
| BAR_4 + MTX | | 0.06 (–0.13 to 0.25) |
| ANBAI + MTX | | –0.27 (–0.52 to –0.02) |
| CT-P13 + MTX | | –0.17 (–0.53 to 0.18) |
| SB2 + MTX | | 0.12 (–0.20 to 0.42) |
| ZRC-3197 + MTX | | 0.12 (–0.20 to 0.43) |
| RIT_STD + MTX | RIT_STD | 0.20 (–0.03 to 0.44) |
| SAR_150 + MTX | | 0.17 (–0.11 to 0.46) |
| SAR_200 + MTX | | 0.11 (–0.18 to 0.40) |
| BAR_4 + MTX | | 0.10 (–0.16 to 0.37) |
| ANBAI + MTX | | –0.23 (–0.54 to 0.08) |
| CT-P13 + MTX | | –0.13 (–0.54 to 0.26) |
| SB2 + MTX | | 0.16 (–0.21 to 0.51) |
| ZRC-3197 + MTX | | 0.16 (–0.21 to 0.52) |
| SAR_150 + MTX | RIT_STD + MTX | –0.03 (–0.32 to 0.26) |
| SAR_200 + MTX | | –0.09 (–0.38 to 0.20) |
| BAR_4 + MTX | | –0.10 (–0.35 to 0.16) |
| ANBAI + MTX | | –0.43 (–0.74 to –0.12) |
| CT-P13 + MTX | | –0.33 (–0.73 to 0.06) |
| SB2 + MTX | | –0.04 (–0.41 to 0.31) |
| ZRC-3197 + MTX | | –0.04 (–0.41 to 0.32) |
| SAR_200 + MTX | SAR_150 + MTX | –0.06 (–0.24 to 0.12) |
| BAR_4 + MTX | | –0.07 (–0.29 to 0.15) |
| ANBAI + MTX | | –0.40 (–0.68 to –0.13) |
| CT-P13 + MTX | | –0.31 (–0.68 to 0.06) |
| SB2 + MTX | | –0.01 (–0.35 to 0.31) |
| ZRC-3197 + MTX | | –0.02 (–0.35 to 0.32) |
| BAR_4 + MTX | SAR_200 + MTX | –0.01 (–0.22 to 0.21) |
| ANBAI + MTX | | –0.34 (–0.62 to –0.06) |
| CT-P13 + MTX | | –0.24 (–0.62 to 0.12) |

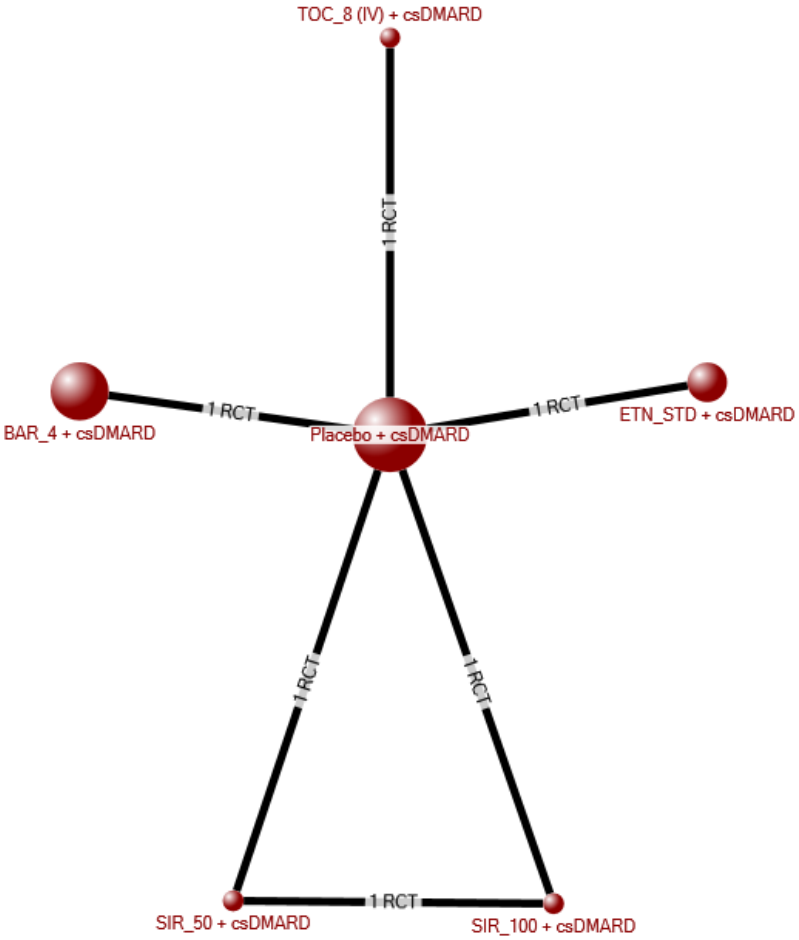
| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| SB2 + MTX | | 0.05 (–0.28 to 0.37) |
| ZRC-3197 + MTX | | 0.05 (–0.29 to 0.38) |
| ANBAI + MTX | BAR_4 + MTX | –0.33 (–0.58 to –0.09) |
| CT-P13 + MTX | | –0.24 (–0.59 to 0.11) |
| SB2 + MTX | | 0.06 (–0.26 to 0.35) |
| ZRC-3197 + MTX | | 0.05 (–0.25 to 0.36) |
| CT-P13 + MTX | ANBAI + MTX | 0.09 (–0.30 to 0.48) |
| SB2 + MTX | | 0.39 (0.03 to 0.73) |
| ZRC-3197 + MTX | | 0.39 (0.03 to 0.74) |
| SB2 + MTX | CT-P13 + MTX | 0.29 (–0.04 to 0.61) |
| ZRC-3197 + MTX | | 0.29 (–0.15 to 0.73) |
| ZRC-3197 + MTX | SB2 + MTX | –0.001 (–0.39 to 0.40) |
| | | |
| Random-Effects Model | Residual Deviance | 62.4 vs. 62 data points |
| | Deviance Information Criteria | –153.112 |
| Fixed-Effect Model | Residual Deviance | 77.9 vs 62 data points |
| | Deviance Information Criteria | -145.656 |

ABA = abatacept; ADA = adalimumab; ANBAI = Anbainuo (biosimilar of etanercept); BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; CrI = credible interval; CT-P13 = biosimilar infliximab; GOL = golimumab; INF = infliximab; IV = intravenous; MD = mean difference; MTX = methotrexate; RIT = rituximab; SAR 150 = 150 mg sarilumab; SAR_200 = 200 mg sarilumab; SB2 = biosimilar infliximab; SC = subcutaneous; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; ZRC-3197 = biosimilar adalimumab; vs. = versus; ZRC-3197 = biosimilar adalimumab.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator.

### *Conventional Synthetic DMARD as a Common Comparator*

Four studies[151,163,211,217] were included in the evidence network for the HAQ-DI outcome with monotherapy of a csDMARD other than MTX as the common comparator (placebo + csDMARD). There were six direct comparisons in the evidence network based on six treatments with two two-arm studies, one three-arm study, and one five-arm study. The total number of participants contributing to the evidence network was 1,086 (Figure 8). Assessment for consistency demonstrated that the model was consistent. The mean differences for all treatment comparisons with placebo as the common comparator are available in Table 12. A staircase table of the results as mean differences is also presented in Appendix 10 (Table 92).

## Figure 8: Evidence Network: Health Assessment Questionnaire, Disability Index (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; RCT = randomized controlled trial; SIR_50 = 50 mg sirukumab; SIR 100 = 100 mg sirukumab; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab.

There were no statistically significant results for any of the treatment comparisons.

## Table 12: Health Assessment Questionnaire Disability Index (Placebo + csDMARD): Mean Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| ETN_STD + csDMARD | Placebo + csDMARD | *–0.19 (–6.44 to 6.13)* |
| TOC_8 (IV) + csDMARD | | *–0.63 (–6.91 to 5.62)* |
| BAR_4 + csDMARD | | *–0.24 (–6.53 to 6.05)* |
| SIR_100 + csDMARD | | *–0.14 (–6.35 to 6.12)* |
| SIR_50 + csDMARD | | *–0.37 (–6.67 to 5.85)* |
| TOC_8 (IV) + csDMARD | ETN_STD + csDMARD | *–0.44 (–9.34 to 8.44)* |
| BAR_4 + csDMARD | | *–0.05 (–8.91 to 8.72)* |
| SIR_100 + csDMARD | | *0.05 (–8.84 to 8.85)* |
| SIR_50 + csDMARD | | *–0.19 (–9.02 to 8.69)* |
| BAR_4 + csDMARD | TOC_8 (IV) + csDMARD | *0.40 (–8.55 to 9.30)* |
| SIR_100 + csDMARD | | *0.49 (–8.29 to 9.47)* |
| SIR_50 + csDMARD | | *0.26 (–8.61 to 9.07)* |
| SIR_100 + csDMARD | BAR_4 + csDMARD | *0.10 (–8.76 to 9.02)* |
| SIR_50 + csDMARD | | *–0.13 (–9.10 to 8.79)* |
| SIR_50 + csDMARD | SIR_100 + csDMARD | *–0.24 (–6.51 to 6.07)* |
| | | |
| Random-Effects Model | Residual Deviance | 9.014 vs. 9 data points |
| | Deviance Information Criteria | –17.679 |
| Fixed-Effects Model | Residual Deviance | 9.017 vs. 9 data points |
| | Deviance Information Criteria | –17.671 |

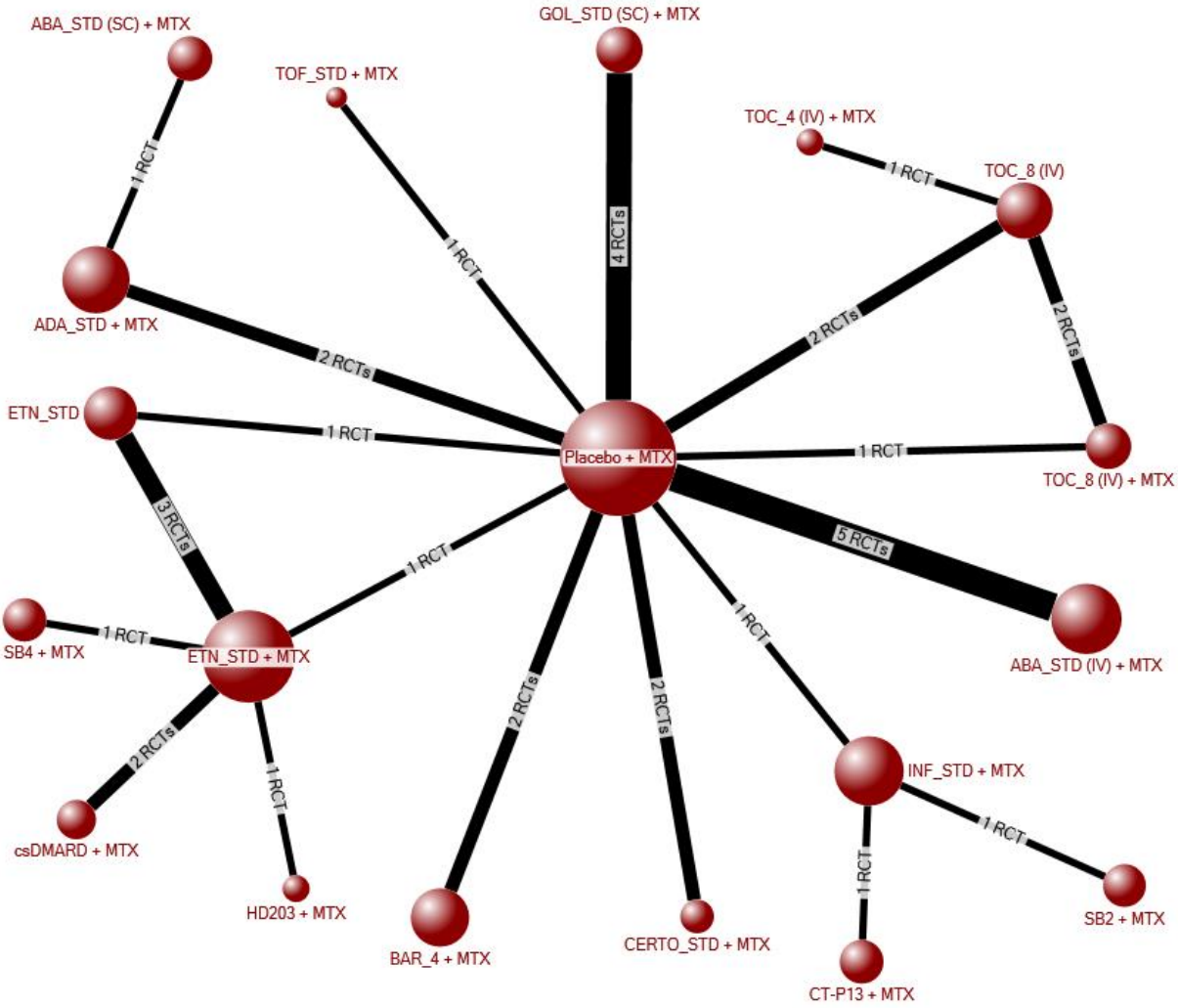
BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CrI = credible interval; ETN = etanercept; IV = intravenous; MD = mean difference; SIR_50 = 50 mg sirukumab; SIR 100 = 100 mg sirukumab; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator. Italicized results indicate wide credible intervals.

### Remission

#### *Methotrexate as a Common Comparator*

There were 29 studies (25 two-arm studies and four three-arm studies)[95,99,102,132,138,139,145,150,155,167,169,171,175,178,179,186-188,193,195,199,204,224,229,233,236,245,248,250] included with MTX monotherapy as the common comparator that reported on remission outcomes using DAS28 scores of less than 2.6. The evidence network involved 9,821 participants and 19 treatments, forming 37 direct comparisons. Assessment for consistency demonstrated that the model was fairly consistent. A geometric illustration of the evidence network is presented in Figure 9. The odds ratios for all treatment comparisons with MTX monotherapy as the common comparator are available in Table 13. A staircase table of the results is presented in Appendix 10 (Table 103).

## Figure 9: Evidence Network: Remission (Placebo + Methotrexate)




ABA = abatacept; ADA = adalimumab; BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; csDMARDs = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; GOL = golimumab; HD203 = etanercept biosimilar; INF = infliximab; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib.

Compared with MTX monotherapy, there was a statistically significantly higher odds of achieving remission for participants receiving combination therapy with MTX and either etanercept, abatacept (IV and SC), tocilizumab (4 mg/kg or 8 mg/kg), golimumab (SC), infliximab, certolizumab pegol, 4 mg baricitinib, CT-P13 (biosimilar infliximab), or SB2 (biosimilar infliximab) as well as monotherapy of 8 mg/kg tocilizumab (Table 13).

The results indicate that all treatments except for etanercept monotherapy and tofacitinib in combination with MTX offer higher odds of achieving remission compared with combination therapy with a csDMARD and MTX. However, the 95% CrIs were very wide for abatacept (SC) in combination with MTX; 8 mg/kg tocilizumab monotherapy; 4 mg/kg and 8 mg/kg tocilizumab in combination with MTX; golimumab (SC) in combination with MTX;

certolizumab pegol in combination with MTX; and CT-P13 (biosimilar infliximab) in combination with MTX (Table 13).

When the comparator was etanercept monotherapy, the following biologics in combination with MTX resulted in higher odds of disease remission: etanercept, abatacept (IV and SC), adalimumab, tocilizumab (4 mg/kg or 8 mg/kg), golimumab (SC), infliximab, certolizumab pegol, and 4 mg baricitinib (Table 13). Monotherapy with 8 mg/kg tocilizumab also resulted in statistically significantly higher odds of disease remission compared with etanercept monotherapy (Table 13).

Only treatment with 8 mg/kg tocilizumab in combination with MTX demonstrated higher odds of remission compared with etanercept in combination with MTX (odds ratio = 5.33; 95% CrI, 1.05 to 27.81) (Table 13). There were no other statistically significant results for the remaining comparisons of biologics and biosimilars with one another.

## Table 13: Remission (Placebo + Methotrexate): Odds Ratios, Relative Risks, and Risk Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| csDMARD + MTX | Placebo + MTX | 0.60 (0.15 to 2.27) | 0.61 (0.15 to 2.20) | –0.01 (–0.02 to 0.03) |
| ETN_STD | | 1.40 (0.52 to 3.77) | 1.39 (0.52 to 3.53) | 0.01 (–0.01 to 0.06) |
| ETN_STD + MTX | | 2.86 (1.03 to 7.36) | 2.73 (1.03 to 6.38) | 0.04 (0.001 to 0.13) |
| ABA_STD (IV) + MTX | | 6.20 (3.20 to 13.49) | 5.49 (3.02 to 10.62) | 0.11 (0.05 to 0.22) |
| ABA_STD (SC) + MTX | | 7.95 (2.10 to 38.43) | 6.78 (2.04 to 20.79) | 0.14 (0.03 to 0.46) |
| ADA_STD + MTX | | 8.87 (3.57 to 27.29) | 7.42 (3.34 to 17.28) | 0.16 (0.06 to 0.37) |
| TOF_STD + MTX | | 3.46 (0.79 to 17.21) | 3.26 (0.79 to 12.52) | 0.06 (–0.01 to 0.27) |
| TOC_8 (IV) | | 10.93 (3.43 to 36.90) | 8.77 (3.23 to 20.82) | 0.19 (0.05 to 0.44) |
| TOC_4 (IV) + MTX | | 12.10 (2.42 to 63.41) | 9.48 (2.34 to 26.64) | 0.21 (0.03 to 0.58) |
| TOC_8 (IV) + MTX | | 15.05 (4.14 to 56.70) | 11.14 (3.84 to 25.57) | 0.25 (0.07 to 0.55) |
| GOL_STD (SC) + MTX | | 11.19 (4.19 to 33.16) | 8.93 (3.85 to 20.09) | 0.20 (0.08 to 0.40) |
| INF_STD + MTX | | 6.58 (1.98 to 23.28) | 5.78 (1.94 to 15.63) | 0.12 (0.02 to 0.33) |
| CERTO_STD + MTX | | 9.85 (2.36 to 64.72) | 8.08 (2.28 to 27.89) | 0.17 (0.03 to 0.56) |
| BAR_4 + MTX | | 8.72 (3.77 to 27.68) | 7.32 (3.51 to 17.33) | 0.16 (0.06 to 0.37) |
| HD203 + MTX | | 3.22 (0.68 to 13.62) | 3.05 (0.69 to 10.47) | 0.05 (–0.01 to 0.23) |
| SB4 + MTX | | 2.98 (0.67 to 12.17) | 2.84 (0.67 to 9.64) | 0.04 (–0.01 to 0.21) |
| CT-P13 + MTX | | 9.20 (1.77 to 52.39) | 7.64 (1.73 to 24.29) | 0.16 (0.02 to 0.53) |
| SB2 + MTX | | 5.85 (1.17 to 31.03) | 5.22 (1.17 to 18.53) | 0.10 (0.004 to 0.40) |
| ETN_STD | csDMARD + MTX | 2.35 (0.78 to 7.51) | 2.30 (0.78 to 7.20) | 0.02 (–0.01 to 0.06) |
| ETN_STD + MTX | | 4.73 (1.92 to 12.20) | 4.46 (1.84 to 11.42) | 0.05 (0.02 to 0.12) |
| ABA_STD (IV) + MTX | | 10.34 (2.42 to 52.42) | 9.06 (2.25 to 43.14) | 0.12 (0.05 to 0.23) |
| ABA_STD (SC) + MTX | | *13.36 (2.07 to 111.20)* | *11.13 (1.97 to 67.90)* | *0.15 (0.03 to 0.46)* |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ADA_STD + MTX | | 14.96 (3.04 to 91.54) | 12.24 (2.77 to 63.80) | 0.16 (0.06 to 0.37) |
| TOF_STD + MTX | | 5.77 (0.78 to 49.82) | 5.36 (0.79 to 37.91) | 0.06 (–0.01 to 0.28) |
| TOC_8 (IV) | | *18.62 (3.08 to 114.60)* | *14.53 (2.81 to 72.93)* | *0.20 (0.06 to 0.45)* |
| TOC_4 (IV) + MTX | | *20.54 (2.46 to 175.40)* | *15.51 (2.31 to 87.20)* | *0.22 (0.03 to 0.59)* |
| TOC_8 (IV) + MTX | | *25.57 (3.90 to 170.80)* | *18.30 (3.46 to 91.00)* | *0.26 (0.07 to 0.56)* |
| GOL_STD (SC) + MTX | | *18.85 (3.58 to 103.80)* | *14.75 (3.18 to 70.16)* | *0.20 (0.08 to 0.40)* |
| INF_STD + MTX | | 10.92 (1.89 to 72.19) | 9.40 (1.82 to 52.36) | 0.12 (0.02 to 0.34) |
| CERTO_STD + MTX | | *16.98 (2.35 to 158.00)* | *13.52 (2.21 to 82.30)* | *0.18 (0.04 to 0.57)* |
| BAR_4 + MTX | | 14.68 (3.18 to 95.35) | 12.05 (2.88 to 65.84) | 0.16 (0.06 to 0.38) |
| HD203 + MTX | | 5.37 (1.23 to 23.31) | 4.99 (1.22 to 19.32) | 0.06 (0.003 to 0.22) |
| SB4 + MTX | | 4.96 (1.21 to 20.83) | 4.64 (1.20 to 17.73) | 0.05 (0.003 to 0.20) |
| CT-P13 + MTX | | *15.32 (1.87 to 140.00)* | *12.33 (1.81 to 75.77)* | *0.17 (0.02 to 0.53)* |
| SB2 + MTX | | 9.70 (1.22 to 85.97) | 8.47 (1.21 to 55.46) | 0.11 (0.01 to 0.41) |
| ETN_STD + MTX | ETN_STD | 2.03 (1.03 to 3.83) | 1.95 (1.03 to 3.57) | 0.03 (0.001 to 0.09) |
| ABA_STD (IV) + MTX | | 4.42 (1.40 to 16.06) | 3.94 (1.36 to 13.18) | 0.10 (0.02 to 0.21) |
| ABA_STD (SC) + MTX | | 5.69 (1.09 to 37.25) | 4.85 (1.08 to 22.09) | 0.13 (0.004 to 0.44) |
| ADA_STD + MTX | | 6.34 (1.71 to 28.68) | 5.32 (1.63 to 19.80) | 0.15 (0.04 to 0.36) |
| TOF_STD + MTX | | 2.46 (0.43 to 16.67) | 2.33 (0.44 to 12.47) | 0.04 (–0.03 to 0.26) |
| TOC_8 (IV) | | 7.83 (1.69 to 37.56) | 6.28 (1.61 to 23.08) | 0.18 (0.03 to 0.43) |
| TOC_4 (IV) + MTX | | 8.63 (1.29 to 60.17) | 6.75 (1.27 to 28.25) | 0.20 (0.01 to 0.57) |
| TOC_8 (IV) + MTX | | 10.79 (2.06 to 55.87) | 7.96 (1.92 to 28.71) | 0.24 (0.05 to 0.54) |
| GOL_STD (SC) + MTX | | 8.04 (1.95 to 33.66) | 6.44 (1.82 to 22.35) | 0.18 (0.05 to 0.39) |
| INF_STD + MTX | | 4.69 (1.03 to 23.50) | 4.14 (1.03 to 16.74) | 0.11 (0.001 to 0.32) |
| CERTO_STD + MTX | | 7.13 (1.25 to 56.14) | 5.84 (1.23 to 26.79) | 0.16 (0.01 to 0.55) |
| BAR_4 + MTX | | 6.20 (1.80 to 29.92) | 5.22 (1.70 to 20.48) | 0.14 (0.04 to 0.36) |
| HD203 + MTX | | 2.29 (0.58 to 8.22) | 2.18 (0.60 to 6.71) | 0.04 (–0.02 to 0.20) |
| SB4 + MTX | | 2.12 (0.58 to 7.40) | 2.03 (0.59 to 6.13) | 0.03 (–0.02 to 0.18) |
| CT-P13 + MTX | | 6.53 (0.98 to 46.37) | 5.42 (0.98 to 24.50) | 0.15 (–0.001 to 0.51) |
| SB2 + MTX | | 4.16 (0.63 to 29.22) | 3.72 (0.65 to 18.45) | 0.09 (–0.02 to 0.39) |
| ABA_STD (IV) + MTX | ETN_STD + MTX | 2.18 (0.72 to 8.14) | 2.02 (0.75 to 6.76) | 0.07 (–0.03 to 0.18) |
| ABA_STD (SC) + MTX | | 2.79 (0.56 to 18.87) | 2.47 (0.59 to 11.29) | 0.10 (–0.04 to 0.41) |
| ADA_STD + MTX | | 3.12 (0.85 to 14.49) | 2.71 (0.87 to 10.06) | 0.11 (–0.01 to 0.33) |
| TOF_STD + MTX | | 1.21 (0.21 to 8.33) | 1.20 (0.23 to 6.35) | 0.01 (–0.09 to 0.23) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| TOC_8 (IV) | | 3.88 (0.85 to 18.51) | 3.22 (0.87 to 11.55) | 0.15 (–0.01 to 0.40) |
| TOC_4 (IV) + MTX | | 4.27 (0.65 to 29.58) | 3.46 (0.67 to 14.18) | 0.16 (–0.03 to 0.54) |
| TOC_8 (IV) + MTX | | 5.33 (1.05 to 27.81) | 4.06 (1.04 to 14.44) | 0.20 (0.004 to 0.51) |
| GOL_STD (SC) + MTX | | 3.96 (0.98 to 16.57) | 3.28 (0.99 to 11.13) | 0.15 (–0.002 to 0.36) |
| INF_STD + MTX | | 2.32 (0.52 to 11.88) | 2.12 (0.56 to 8.58) | 0.07 (–0.05 to 0.29) |
| CERTO_STD + MTX | | 3.55 (0.63 to 28.02) | 3.01 (0.66 to 13.47) | 0.13 (–0.04 to 0.52) |
| BAR_4 + MTX | | 3.05 (0.90 to 15.13) | 2.66 (0.91 to 10.50) | 0.11 (–0.01 to 0.33) |
| HD203 + MTX | | 1.13 (0.36 to 3.52) | 1.12 (0.37 to 2.99) | 0.01 (–0.05 to 0.14) |
| SB4 + MTX | | 1.04 (0.36 to 3.06) | 1.04 (0.37 to 2.67) | 0.002 (–0.05 to 0.12) |
| CT-P13 + MTX | | 3.22 (0.51 to 23.85) | 2.77 (0.54 to 12.58) | 0.12 (–0.05 to 0.48) |
| SB2 + MTX | | 2.05 (0.33 to 14.58) | 1.90 (0.36 to 9.38) | 0.06 (–0.07 to 0.36) |
| ABA_STD (SC) + MTX | ABA_STD (IV) + MTX | 1.29 (0.27 to 6.66) | 1.24 (0.31 to 4.09) | 0.03 (–0.13 to 0.34) |
| ADA_STD + MTX | | 1.44 (0.44 to 5.10) | 1.35 (0.49 to 3.64) | 0.05 (–0.10 to 0.26) |
| TOF_STD + MTX | | 0.56 (0.10 to 3.04) | 0.59 (0.12 to 2.47) | –0.05 (–0.18 to 0.16) |
| TOC_8 (IV) | | 1.77 (0.41 to 7.11) | 1.60 (0.47 to 4.43) | 0.08 (–0.10 to 0.34) |
| TOC_4 (IV) + MTX | | 1.97 (0.31 to 11.45) | 1.73 (0.35 to 5.50) | 0.10 (–0.12 to 0.47) |
| TOC_8 (IV) + MTX | | 2.43 (0.50 to 10.72) | 2.02 (0.55 to 5.51) | 0.14 (–0.08 to 0.45) |
| GOL_STD (SC) + MTX | | 1.81 (0.50 to 6.29) | 1.63 (0.57 to 4.23) | 0.08 (–0.09 to 0.30) |
| INF_STD + MTX | | 1.07 (0.34 to 3.19) | 1.06 (0.38 to 2.49) | 0.01 (–0.10 to 0.19) |
| CERTO_STD + MTX | | 1.60 (0.30 to 11.25) | 1.48 (0.35 to 5.51) | 0.06 (–0.13 to 0.46) |
| BAR_4 + MTX | | 1.41 (0.46 to 5.05) | 1.33 (0.51 to 3.59) | 0.04 (–0.10 to 0.27) |
| HD203 + MTX | | 0.52 (0.09 to 2.36) | 0.56 (0.10 to 2.04) | –0.06 (–0.18 to 0.12) |
| SB4 + MTX | | 0.48 (0.08 to 2.17) | 0.52 (0.10 to 1.91) | –0.06 (–0.19 to 0.10) |
| CT-P13 + MTX | | 1.49 (0.29 to 7.23) | 1.40 (0.33 to 3.97) | 0.05 (–0.10 to 0.39) |
| SB2 + MTX | | 0.95 (0.19 to 4.38) | 0.95 (0.22 to 2.98) | –0.01 (–0.13 to 0.27) |
| ADA_STD + MTX | ABA_STD (SC) + MTX | 1.11 (0.39 to 3.21) | 1.09 (0.52 to 2.75) | 0.01 (–0.19 to 0.14) |
| TOF_STD + MTX | | 0.43 (0.05 to 3.39) | 0.48 (0.08 to 2.82) | –0.08 (–0.39 to 0.15) |
| TOC_8 (IV) | | 1.39 (0.19 to 7.98) | 1.30 (0.29 to 5.43) | 0.05 (–0.30 to 0.33) |
| TOC_4 (IV) + MTX | | 1.52 (0.15 to 12.20) | 1.39 (0.23 to 6.54) | 0.06 (–0.30 to 0.45) |
| TOC_8 (IV) + MTX | | 1.91 (0.24 to 11.90) | 1.64 (0.35 to 6.82) | 0.10 (–0.26 to 0.43) |
| GOL_STD (SC) + MTX | | 1.42 (0.22 to 7.50) | 1.33 (0.33 to 5.28) | 0.05 (–0.29 to 0.29) |
| INF_STD + MTX | | 0.83 (0.11 to 5.26) | 0.85 (0.18 to 4.00) | –0.02 (–0.35 to 0.22) |
| CERTO_STD + MTX | | 1.25 (0.14 to 12.62) | 1.20 (0.22 to 6.53) | 0.03 (–0.32 to 0.45) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| BAR_4 + MTX | | 1.08 (0.27 to 4.92) | 1.06 (0.39 to 3.87) | 0.01 (–0.24 to 0.21) |
| HD203 + MTX | | 0.40 (0.04 to 2.81) | 0.45 (0.07 to 2.44) | –0.09 (–0.40 to 0.11) |
| SB4 + MTX | | 0.37 (0.04 to 2.53) | 0.42 (0.07 to 2.23) | –0.09 (–0.41 to 0.10) |
| CT-P13 + MTX | | 1.15 (0.12 to 10.15) | 1.12 (0.17 to 5.84) | 0.02 (–0.32 to 0.39) |
| SB2 + MTX | | 0.73 (0.08 to 6.02) | 0.77 (0.12 to 4.22) | –0.04 (–0.36 to 0.27) |
| TOF_STD + MTX | ADA_STD + MTX | 0.39 (0.06 to 2.39) | 0.44 (0.08 to 2.03) | –0.10 (–0.32 to 0.13) |
| TOC_8 (IV) | | 1.23 (0.24 to 5.43) | 1.18 (0.32 to 3.63) | 0.03 (–0.23 to 0.30) |
| TOC_4 (IV) + MTX | | 1.36 (0.18 to 8.61) | 1.27 (0.24 to 4.44) | 0.05 (–0.23 to 0.43) |
| TOC_8 (IV) + MTX | | 1.70 (0.30 to 8.13) | 1.50 (0.38 to 4.54) | 0.09 (–0.19 to 0.40) |
| GOL_STD (SC) + MTX | | 1.26 (0.28 to 5.12) | 1.20 (0.38 to 3.59) | 0.04 (–0.22 to 0.27) |
| INF_STD + MTX | | 0.74 (0.14 to 3.48) | 0.78 (0.19 to 2.70) | –0.04 (–0.27 to 0.20) |
| CERTO_STD + MTX | | 1.11 (0.17 to 9.20) | 1.09 (0.24 to 4.78) | 0.01 (–0.25 to 0.43) |
| BAR_4 + MTX | | 0.98 (0.38 to 2.86) | 0.98 (0.47 to 2.30) | –0.003 (–0.16 to 0.17) |
| HD203 + MTX | | 0.36 (0.05 to 1.90) | 0.41 (0.07 to 1.69) | –0.10 (–0.32 to 0.09) |
| SB4 + MTX | | 0.34 (0.05 to 1.72) | 0.39 (0.07 to 1.57) | –0.11 (–0.32 to 0.07) |
| CT-P13 + MTX | | 1.03 (0.14 to 7.08) | 1.02 (0.18 to 4.06) | 0.004 (–0.26 to 0.38) |
| SB2 + MTX | | 0.66 (0.09 to 4.23) | 0.70 (0.12 to 2.96) | –0.05 (–0.29 to 0.25) |
| TOC_8 (IV) | TOF_STD + MTX | 3.21 (0.43 to 22.00) | 2.70 (0.50 to 14.18) | 0.13 (–0.12 to 0.40) |
| TOC_4 (IV) + MTX | | 3.51 (0.35 to 32.68) | 2.86 (0.42 to 16.97) | 0.14 (–0.13 to 0.52) |
| TOC_8 (IV) + MTX | | 4.38 (0.55 to 32.07) | 3.39 (0.62 to 17.64) | 0.18 (–0.09 to 0.50) |
| GOL_STD (SC) + MTX | | 3.25 (0.49 to 20.74) | 2.73 (0.57 to 14.46) | 0.13 (–0.11 to 0.35) |
| INF_STD + MTX | | 1.91 (0.27 to 13.94) | 1.77 (0.33 to 10.28) | 0.06 (–0.16 to 0.28) |
| CERTO_STD + MTX | | 2.92 (0.33 to 29.37) | 2.50 (0.39 to 15.71) | 0.11 (–0.14 to 0.51) |
| BAR_4 + MTX | | 2.56 (0.42 to 16.95) | 2.26 (0.50 to 12.15) | 0.10 (–0.13 to 0.32) |
| HD203 + MTX | | 0.93 (0.10 to 7.31) | 0.94 (0.13 to 5.97) | –0.005 (–0.23 to 0.18) |
| SB4 + MTX | | 0.86 (0.09 to 6.58) | 0.87 (0.12 to 5.52) | –0.01 (–0.23 to 0.16) |
| CT-P13 + MTX | | 2.65 (0.28 to 26.26) | 2.30 (0.33 to 14.51) | 0.10 (–0.14 to 0.47) |
| SB2 + MTX | | 1.67 (0.18 to 15.97) | 1.58 (0.22 to 10.78) | 0.04 (–0.18 to 0.34) |
| TOC_4 (IV) + MTX | TOC_8 (IV) | 1.10 (0.36 to 3.44) | 1.07 (0.42 to 2.30) | 0.01 (–0.14 to 0.26) |
| TOC_8 (IV) + MTX | | 1.37 (0.61 to 3.02) | 1.26 (0.68 to 2.26) | 0.05 (–0.08 to 0.22) |
| GOL_STD (SC) + MTX | | 1.01 (0.22 to 5.03) | 1.01 (0.32 to 3.63) | 0.002 (–0.28 to 0.26) |
| INF_STD + MTX | | 0.60 (0.11 to 3.57) | 0.66 (0.17 to 2.80) | –0.07 (–0.35 to 0.19) |
| CERTO_STD + MTX | | 0.91 (0.14 to 8.32) | 0.93 (0.21 to 4.50) | –0.01 (–0.32 to 0.41) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| BAR_4 + MTX | | 0.80 (0.18 to 4.29) | 0.84 (0.28 to 3.20) | –0.03 (–0.30 to 0.23) |
| HD203 + MTX | | 0.29 (0.04 to 1.91) | 0.35 (0.06 to 1.70) | –0.13 (–0.40 to 0.09) |
| SB4 + MTX | | 0.27 (0.04 to 1.72) | 0.32 (0.06 to 1.58) | –0.14 (–0.40 to 0.07) |
| CT-P13 + MTX | | 0.82 (0.11 to 7.05) | 0.86 (0.16 to 4.05) | –0.03 (–0.33 to 0.37) |
| SB2 + MTX | | 0.52 (0.07 to 4.32) | 0.59 (0.11 to 3.05) | –0.08 (–0.36 to 0.25) |
| TOC_8 (IV) + MTX | TOC_4 (IV) + MTX | 1.25 (0.30 to 4.87) | 1.17 (0.45 to 3.55) | 0.04 (–0.24 to 0.27) |
| GOL_STD (SC) + MTX | | 0.92 (0.14 to 6.57) | 0.94 (0.26 to 4.73) | –0.01 (–0.41 to 0.27) |
| INF_STD + MTX | | 0.54 (0.07 to 4.50) | 0.61 (0.14 to 3.53) | –0.09 (–0.47 to 0.20) |
| CERTO_STD + MTX | | 0.83 (0.09 to 9.74) | 0.87 (0.18 to 5.56) | –0.03 (–0.44 to 0.40) |
| BAR_4 + MTX | | 0.72 (0.12 to 5.79) | 0.78 (0.22 to 4.26) | –0.05 (–0.42 to 0.24) |
| HD203 + MTX | | 0.26 (0.03 to 2.36) | 0.33 (0.05 to 2.08) | –0.15 (–0.53 to 0.09) |
| SB4 + MTX | | 0.24 (0.03 to 2.11) | 0.30 (0.05 to 1.90) | –0.16 (–0.53 to 0.08) |
| CT-P13 + MTX | | 0.75 (0.07 to 8.37) | 0.81 (0.14 to 5.09) | –0.04 (–0.45 to 0.37) |
| SB2 + MTX | | 0.48 (0.05 to 5.22) | 0.55 (0.09 to 3.77) | –0.10 (–0.48 to 0.25) |
| GOL_STD (SC) + MTX | TOC_8 (IV) + MTX | 0.74 (0.15 to 4.09) | 0.80 (0.26 to 3.02) | –0.05 (–0.39 to 0.24) |
| INF_STD + MTX | | 0.43 (0.07 to 2.88) | 0.52 (0.13 to 2.31) | –0.13 (–0.45 to 0.16) |
| CERTO_STD + MTX | | 0.67 (0.09 to 6.48) | 0.74 (0.17 to 3.70) | –0.07 (–0.42 to 0.37) |
| BAR_4 + MTX | | 0.58 (0.13 to 3.46) | 0.66 (0.22 to 2.67) | –0.09 (–0.40 to 0.20) |
| HD203 + MTX | | 0.21 (0.03 to 1.53) | 0.28 (0.05 to 1.41) | –0.19 (–0.50 to 0.05) |
| SB4 + MTX | | 0.19 (0.03 to 1.38) | 0.25 (0.05 to 1.30) | –0.20 (–0.50 to 0.04) |
| CT-P13 + MTX | | 0.60 (0.07 to 5.54) | 0.68 (0.13 to 3.33) | –0.08 (–0.43 to 0.33) |
| SB2 + MTX | | 0.38 (0.05 to 3.38) | 0.47 (0.09 to 2.50) | –0.14 (–0.46 to 0.21) |
| INF_STD + MTX | GOL_STD (SC) + MTX | 0.59 (0.12 to 2.89) | 0.65 (0.17 to 2.29) | –0.07 (–0.31 to 0.18) |
| CERTO_STD + MTX | | 0.89 (0.15 to 7.32) | 0.91 (0.21 to 3.87) | –0.02 (–0.29 to 0.40) |
| BAR_4 + MTX | | 0.79 (0.20 to 3.59) | 0.83 (0.28 to 2.68) | –0.04 (–0.27 to 0.22) |
| HD203 + MTX | | 0.28 (0.04 to 1.67) | 0.34 (0.06 to 1.51) | –0.14 (–0.36 to 0.07) |
| SB4 + MTX | | 0.26 (0.04 to 1.52) | 0.32 (0.06 to 1.41) | –0.14 (–0.36 to 0.06) |
| CT-P13 + MTX | | 0.82 (0.12 to 6.02) | 0.85 (0.17 to 3.45) | –0.03 (–0.29 to 0.36) |
| SB2 + MTX | | 0.52 (0.08 to 3.63) | 0.58 (0.11 to 2.58) | –0.09 (–0.32 to 0.24) |
| CERTO_STD + MTX | INF_STD + MTX | 1.52 (0.22 to 13.47) | 1.41 (0.28 to 7.00) | 0.06 (–0.21 to 0.46) |
| BAR_4 + MTX | | 1.33 (0.31 to 7.25) | 1.27 (0.39 to 5.22) | 0.04 (–0.19 to 0.27) |
| HD203 + MTX | | 0.49 (0.07 to 3.03) | 0.53 (0.09 to 2.60) | –0.06 (–0.28 to 0.12) |
| SB4 + MTX | | 0.45 (0.06 to 2.78) | 0.50 (0.09 to 2.43) | –0.07 (–0.29 to 0.11) |

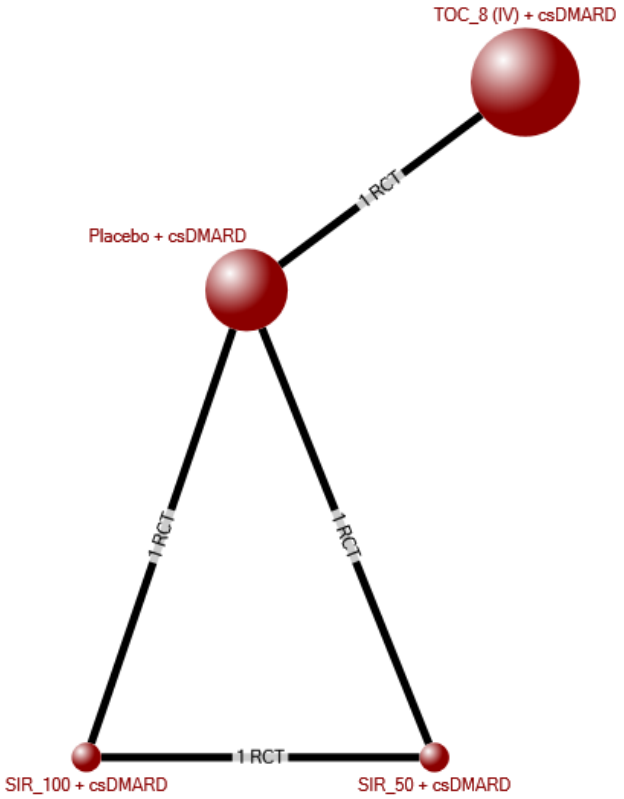
| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| CT-P13 + MTX | | 1.40 (0.45 to 4.29) | 1.31 (0.50 to 2.89) | 0.04 (–0.08 to 0.28) |
| SB2 + MTX | | 0.89 (0.29 to 2.61) | 0.90 (0.33 to 2.08) | –0.01 (–0.13 to 0.17) |
| BAR_4 + MTX | CERTO_STD + MTX | 0.89 (0.11 to 5.72) | 0.91 (0.22 to 4.22) | –0.02 (–0.43 to 0.25) |
| HD203 + MTX | | 0.32 (0.03 to 2.49) | 0.37 (0.06 to 2.18) | –0.12 (–0.51 to 0.11) |
| SB4 + MTX | | 0.29 (0.03 to 2.23) | 0.35 (0.06 to 1.99) | –0.12 (–0.51 to 0.09) |
| CT-P13 + MTX | | 0.90 (0.08 to 8.86) | 0.92 (0.15 to 5.11) | –0.01 (–0.43 to 0.39) |
| SB2 + MTX | | 0.57 (0.05 to 5.48) | 0.64 (0.10 to 3.81) | –0.07 (–0.47 to 0.27) |
| HD203 + MTX | BAR_4 + MTX | 0.37 (0.05 to 1.83) | 0.42 (0.07 to 1.64) | –0.10 (–0.32 to 0.08) |
| SB4 + MTX | | 0.34 (0.05 to 1.65) | 0.39 (0.07 to 1.50) | –0.11 (–0.33 to 0.06) |
| CT-P13 + MTX | | 1.05 (0.14 to 6.67) | 1.04 (0.18 to 3.82) | 0.01 (–0.26 to 0.37) |
| SB2 + MTX | | 0.67 (0.09 to 3.95) | 0.72 (0.12 to 2.79) | –0.05 (–0.29 to 0.24) |
| SB4 + MTX | HD203 + MTX | 0.92 (0.19 to 4.51) | 0.93 (0.22 to 3.96) | –0.005 (–0.15 to 0.12) |
| CT-P13 + MTX | | 2.86 (0.34 to 28.68) | 2.47 (0.39 to 16.38) | 0.11 (–0.11 to 0.47) |
| SB2 + MTX | | 1.82 (0.22 to 17.56) | 1.70 (0.26 to 11.86) | 0.05 (–0.14 to 0.34) |
| CT-P13 + MTX | SB4 + MTX | 3.07 (0.37 to 29.75) | 2.65 (0.42 to 16.84) | 0.11 (–0.09 to 0.47) |
| SB2 + MTX | | 1.97 (0.24 to 18.80) | 1.83 (0.28 to 12.53) | 0.05 (–0.13 to 0.35) |
| SB2 + MTX | CT-P13 + MTX | 0.63 (0.13 to 3.02) | 0.69 (0.19 to 2.42) | –0.05 (–0.33 to 0.15) |
| | | | | |
| Random-Effects Model | Residual Deviance | 67.25 vs. 62 data points | | |
| | Deviance Information Criteria | 379.715 | | |
| Fixed-Effect Model | Residual Deviance | 77.29 vs 62 data points | | |
| | Deviance Information Criteria | 383.975 | | |

ABA = abatacept; ADA = adalimumab; BAR_4 = 4 mg baricitinib 4 mg; CERTO = certolizumab pegol; CrI = credible interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; GOL = golimumab; HD203 = biosimilar etanercept; INF = infliximab; IV = intravenous; MTX = methotrexate; OR = odds ratio; RD = risk difference; RR = relative risk; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; vs. = versus.
Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator. Italicized results indicate wide credible intervals.

### *Conventional Synthetic DMARD as a Common Comparator*

There were two RCTs[217,249] that permitted concomitant treatment with a csDMARD and reported data on remission outcomes. An NMA could not be conducted, since there were too few studies and each study presented different treatment comparisons (Figure 10). Thus, a descriptive analysis follows; event data are in Table 14.

## Figure 10: Evidence Network: Remission (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




csDMARDs = conventional synthetic disease-modifying antirheumatic drug; IV = intravenous; RCT = random controlled trial; SIR_50 = 50 mg sirukumab; SIR_100 = 100 mg sirukumab; TOC_8 = 8 mg/kg tocilizumab.

In the study by Yacizi et al.,[249] many more participants receiving 8 mg/kg tocilizumab in combination with a csDMARD achieved disease remission during the 16 weeks of treatment prior to study adaptation compared with participants receiving csDMARD monotherapy. There was no noticeable difference in the number of participants achieving disease remission in the study comparing 100 mg and 50 mg sirukumab in combination with a csDMARD versus csDMARD monotherapy during the 12 weeks of treatment prior to the adaptation in treatment (Table 14).[217] It should be noted that submissions for regulatory approval were withdrawn globally for sirukumab after the analysis was completed.[57]

## Table 14: Remission Events, Concomitant Conventional Synthetic DMARD

| Author | Treatment 1 | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Yazici 2012 | Placebo + csDMARD | 4 | 205 | TOC_8 (IV) + csDMARD | 98 | 409 | | | |
| Smolen 2014 | Placebo + csDMARD | 0 | 30 | SIR_100 + csDMARD | 1 | 30 | SIR_50 + csDMARD | 4 | 30 |

csDMARD = conventional synthetic disease-modifying antirheumatic drug; IV = intravenous; SIR_50 = 50 mg sirukumab; SIR_100 = 100 mg sirukumab; TOC_8 = 8 mg/kg tocilizumab.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

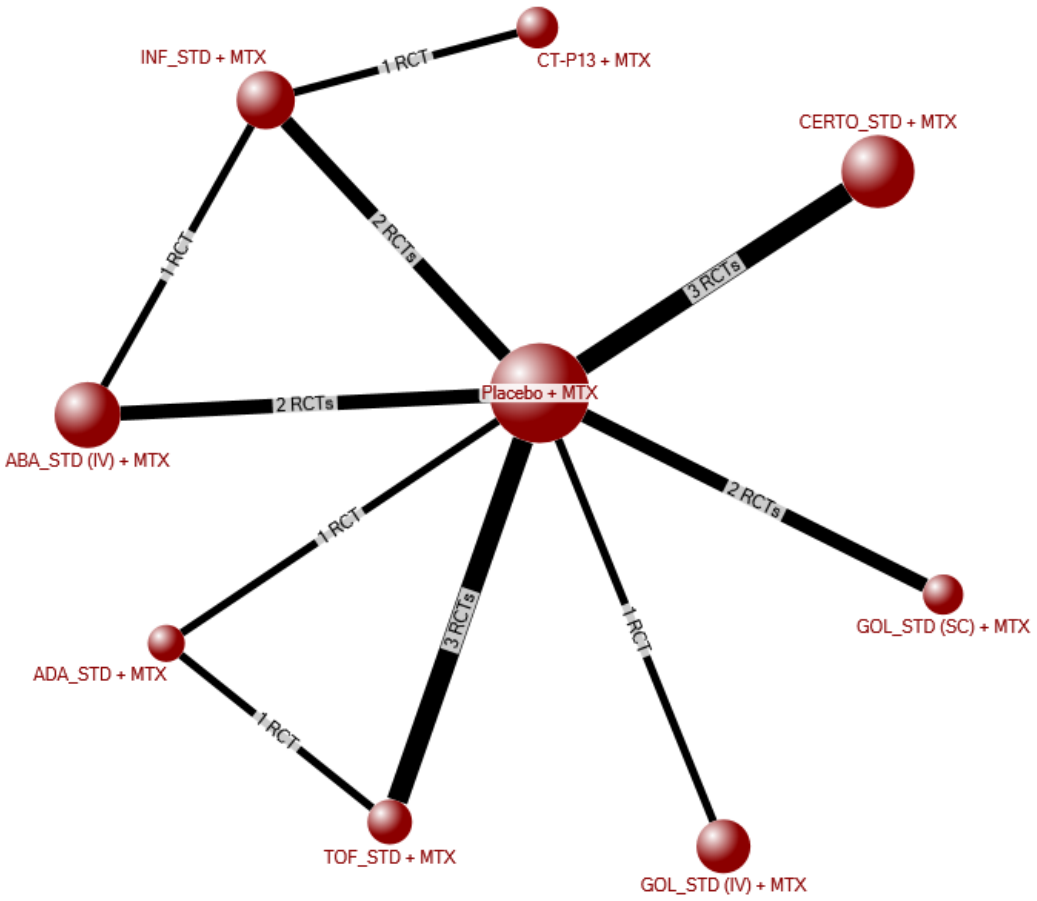
### Health-Related Quality of Life

#### *Methotrexate Monotherapy as a Comparator*

In terms of HRQoL as measured by the SF-36 Physical Component Score (PCS), 13 studies[95,134,161,181,186,193,212,220-222,230,248,251] were included in the evidence network with MTX monotherapy as the common comparator (placebo + MTX). There were 17 direct comparisons in the evidence network based on nine treatments with 11 two-arm studies and two three-arm studies. A total of 4,520 participants contributed to the evidence network (Figure 11).

Assessment for consistency demonstrated that the model was consistent. The mean differences for all treatment comparisons with placebo as the common comparator are available in Table 15. A staircase table of the results as mean differences is also presented in Appendix 10 (tables 93 and 94).

## Figure 11: Evidence Network: Health-Related Quality of Life, SF-36 Physical Component Score (Placebo + Methotrexate)




ABA = abatacept; ADA = adalimumab; CERTO = certolizumab pegol; CT-P13 = biosimilar infliximab; GOL = golimumab; INF = infliximab; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; SC = subcutaneous; STD = standard dose; TOF = tofacitinib.

A statistically significant improvement in physical HRQoL was observed for each of the treatments compared with MTX monotherapy. No significant results were found for any of the head-to-head comparisons of biologics, tsDMARD, and biosimilars.

## Table 15: Health-Related Quality of Life, SF-36 Physical Component Score (Placebo + MTX): Mean Differences for All Treatment Comparisons – Random-Effects Model

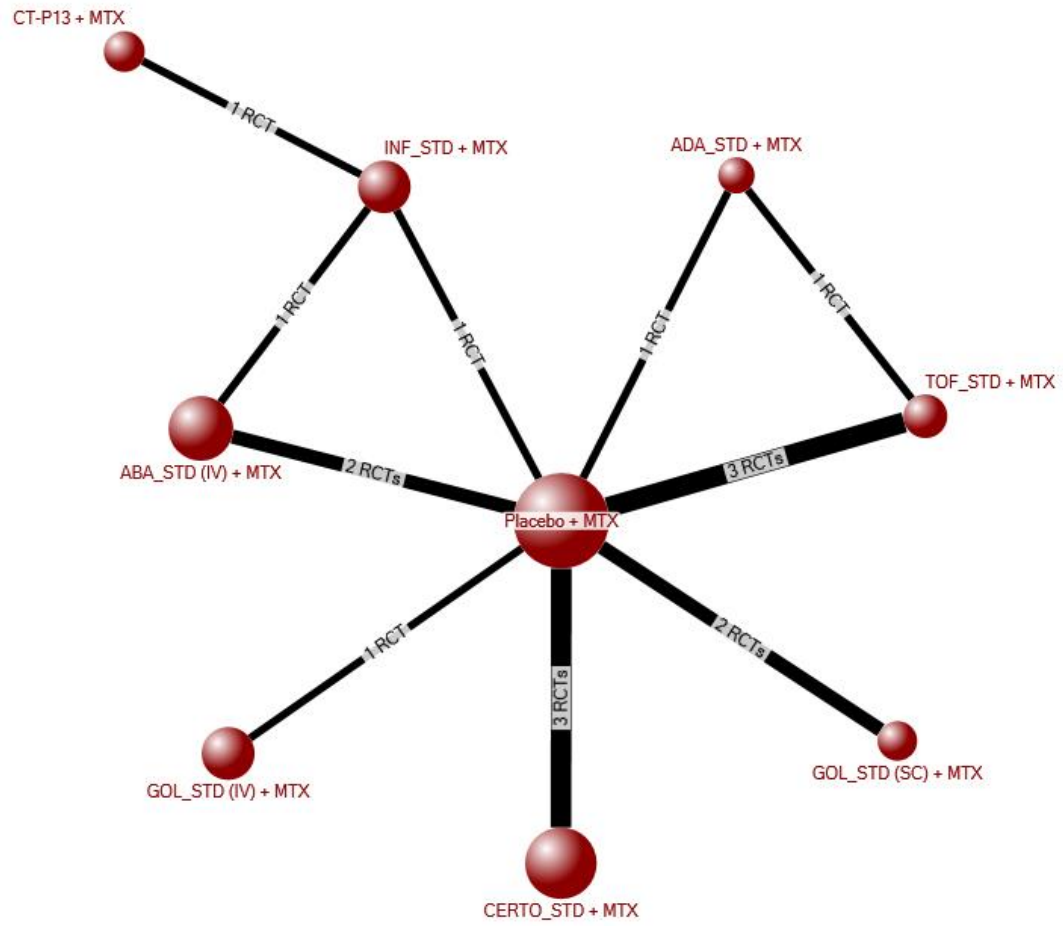
| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| ABA_STD (IV) + MTX | Placebo + MTX | 4.14 (2.51 to 5.81) |
| TOF_STD + MTX | | 3.78 (2.03 to 5.54) |
| ADA_STD + MTX | | 3.07 (0.73 to 5.45) |
| GOL_STD (SC) + MTX | | 4.83 (3.03 to 6.76) |
| GOL_STD (IV) + MTX | | 3.65 (1.28 to 6.00) |
| INF_STD + MTX | | 4.58 (2.73 to 6.01) |
| CERTO_STD + MTX | | 5.07 (3.67 to 6.49) |
| CT-P13 + MTX | | 5.37 (2.22 to 8.18) |
| TOF_STD + MTX | ABA_STD (IV) + MTX | –0.37 (–2.76 to 2.03) |
| ADA_STD + MTX | | –1.07 (–3.93 to 1.80) |
| GOL_STD (SC) + MTX | | 0.69 (–1.73 to 3.22) |
| GOL_STD (IV) + MTX | | –0.50 (–3.42 to 2.35) |
| INF_STD + MTX | | 0.44 (–1.85 to 2.27) |
| CERTO_STD + MTX | | 0.91 (–1.27 to 3.10) |
| CT-P13 + MTX | | 1.24 (–2.18 to 4.25) |
| ADA_STD + MTX | TOF_STD + MTX | –0.70 (–2.96 to 1.58) |
| GOL_STD (SC) + MTX | | 1.05 (–1.47 to 3.66) |
| GOL_STD (IV) + MTX | | –0.13 (–3.10 to 2.80) |
| INF_STD + MTX | | 0.79 (–1.77 to 2.99) |
| CERTO_STD + MTX | | 1.27 (–0.95 to 3.52) |
| CT-P13 + MTX | | 1.59 (–1.99 to 4.86) |
| GOL_STD (SC) + MTX | ADA_STD + MTX | 1.75 (–1.21 to 4.82) |
| GOL_STD (IV) + MTX | | 0.59 (–2.78 to 3.88) |
| INF_STD + MTX | | 1.50 (–1.59 to 4.15) |
| CERTO_STD + MTX | | 1.99 (–0.75 to 4.73) |
| CT-P13 + MTX | | 2.30 (–1.67 to 5.87) |
| GOL_STD (IV) + MTX | GOL_STD (SC) + MTX | –1.18 (–4.29 to 1.76) |
| INF_STD + MTX | | –0.27 (–2.99 to 1.95) |
| CERTO_STD + MTX | | 0.22 (–2.16 to 2.49) |
| CT-P13 + MTX | | 0.54 (–3.23 to 3.79) |
| INF_STD + MTX | GOL_STD (IV) + MTX | 0.92 (–2.14 to 3.57) |
| CERTO_STD + MTX | | 1.40 (–1.31 to 4.19) |
| CT-P13 + MTX | | 1.72 (–2.21 to 5.34) |
| CERTO_STD + MTX | INF_STD + MTX | 0.46 (–1.45 to 2.86) |
| CT-P13 + MTX | | 0.80 (–1.66 to 3.29) |

| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| CT-P13 + MTX | CERTO_STD + MTX | 0.32 (–3.16 to 3.41) |
| | | |
| Random-Effects Model | Residual Deviance | 29.07 vs. 28 data points |
| | Deviance Information Criteria | 64.546 |
| Fixed-Effect Model | Residual Deviance | 30.85 vs 28 data points |
| | Deviance Information Criteria | 63.398 |

ABA = abatacept; ADA = adalimumab; CERTO = certolizumab pegol; CrI = credible interval; CT-P13 = biosimilar infliximab; GOL = golimumab; INF = infliximab; IV = intravenous; MD = mean difference; MTX = methotrexate; SC = subcutaneous; SF36 = Short Form (36) Health Survey; STD = standard dose; TOF = tofacitinib; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator.

The Mental Component Score (MCS) of the SF-36 was also assessed for HRQoL. Twelve studies were included.[95,134,161,186,193,212,220-222,230,248,251] There were 16 direct comparisons in the evidence network based on nine treatments from 10 two-arm studies and two three-arm studies. A total of 4,376 participants contributed to the evidence network (Figure 12). Assessment for consistency demonstrated that the model was consistent. The mean differences for all treatment comparisons with placebo as the common comparator are available in Table 16. A staircase table of the results as mean differences is also presented in Appendix 10.

## Figure 12: Evidence Network: Health-Related Quality of Life, SF-36 Mental Component Score (Placebo + MTX)




ABA = abatacept; ADA = adalimumab; CERTO = certolizumab pegol; CT-P13 = biosimilar infliximab; GOL = golimumab; INF = infliximab; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; SC = subcutaneous; STD = standard dose; TOF = tofacitinib.

Compared with MTX monotherapy, abatacept (IV), tofacitinib, golimumab (SC), and golimumab (IV), all in combination with MTX, demonstrated a statistically significant improvement in mental HRQoL. No significant results were found for any of the head-to-head comparisons of biologics, tsDMARDs, or biosimilars.

## Table 16: Health-Related Quality of Life, SF-36 Mental Component Score (Placebo + MTX): Mean Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| ABA_STD (IV) + MTX | Placebo + MTX | 2.72 (0.41 to 5.89) |
| TOF_STD + MTX | | 2.79 (0.35 to 5.54) |
| ADA_STD + MTX | | 2.43 (–1.16 to 6.11) |
| GOL_STD (SC) + MTX | | 1.85 (–1.23 to 4.93) |
| GOL_STD (IV) + MTX | | 5.88 (2.18 to 9.71) |
| INF_STD + MTX | | 2.16 (–1.56 to 6.26) |
| CERTO_STD + MTX | | 3.60 (1.35 to 5.83) |
| CT-P13 + MTX | | 2.08 (–3.23 to 7.79) |
| TOF_STD + MTX | ABA_STD (IV) + MTX | 0.04 (–3.86 to 3.58) |
| ADA_STD + MTX | | –0.32 (–5.15 to 3.89) |
| GOL_STD (SC) + MTX | | –0.92 (–5.35 to 2.89) |
| GOL_STD (IV) + MTX | | 3.15 (–1.84 to 7.42) |
| INF_STD + MTX | | –0.61 (–4.62 to 3.15) |
| CERTO_STD + MTX | | 0.89 (–3.06 to 4.01) |
| CT-P13 + MTX | | –0.69 (–6.34 to 4.68) |
| ADA_STD + MTX | TOF_STD + MTX | –0.35 (–4.06 to 3.04) |
| GOL_STD (SC) + MTX | | –0.95 (–5.13 to 2.93) |
| GOL_STD (IV) + MTX | | 3.10 (–1.63 to 7.54) |
| INF_STD + MTX | | –0.64 (–5.29 to 4.07) |
| CERTO_STD + MTX | | 0.82 (–2.79 to 4.00) |
| CT-P13 + MTX | | –0.70 (–6.81 to 5.37) |
| GOL_STD (SC) + MTX | ADA_STD+MTX | –0.60 (–5.35 to 4.14) |
| GOL_STD (IV) + MTX | | 3.45 (–1.74 to 8.72) |
| INF_STD + MTX | | –0.29 (–5.44 to 5.23) |
| CERTO_STD + MTX | | 1.17 (–3.09 to 5.37) |
| CT-P13 + MTX | | –0.35 (–6.76 to 6.38) |
| GOL_STD (IV) + MTX | GOL_STD (SC) + MTX | 4.05 (–0.78 to 8.89) |
| INF_STD + MTX | | 0.32 (–4.53 to 5.44) |
| CERTO_STD + MTX | | 1.76 (–2.02 to 5.50) |
| CT-P13 + MTX | | 0.22 (–5.91 to 6.70) |
| INF_STD + MTX | GOL_STD (IV) + MTX | –3.72 (–9.00 to 1.88) |
| CERTO_STD + MTX | | –2.29 (–6.72 to 2.03) |
| CT-P13 + MTX | | –3.81 (–10.34 to 3.00) |
| CERTO_STD + MTX | INF_STD + MTX | 1.45 (–3.29 to 5.74) |
| CT-P13 + MTX | | –0.08 (–3.97 to 3.85) |

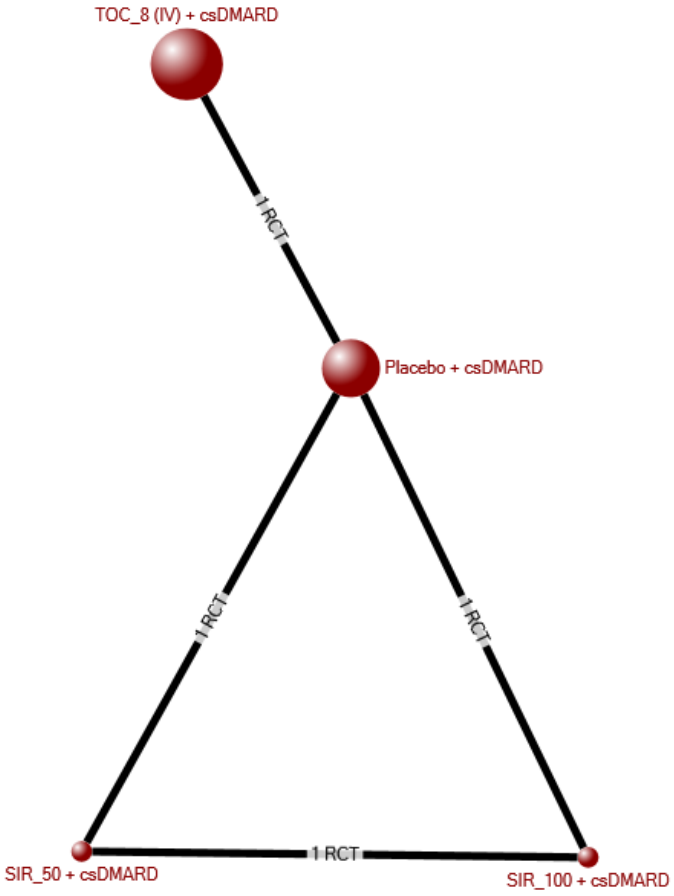
| Treatment | Reference | MD (95% CrI) |
|---|---|---|
| CT-P13 + MTX | CERTO_STD + MTX | –1.52 (–7.24 to 4.63) |
| | | |
| Random-Effects Model | Residual Deviance | 26.43 vs. 26 data points |
| | Deviance Information Criteria | 77.327 |
| Fixed-Effect Model | Residual Deviance | 30.2 vs 26 data points |
| | Deviance Information Criteria | 77.663 |

ABA = abatacept; ADA = adalimumab; CERTO = certolizumab pegol; CrI = credible interval; CT-P13 = biosimilar infliximab; GOL = golimumab; INF = infliximab; IV = intravenous; MD = mean difference; MTX = methotrexate; SC = subcutaneous; SF36 = Short Form (36) Health Survey; STD = standard dose; TOF = tofacitinib; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator.

### *Conventional Synthetic DMARD as a Comparator*

Only two studies with csDMARD as the common comparator had data on the SF-36 PCS and MCS based on a total of 633 participants.[217,249] The included studies were the same for the SF-36 PCS and MCS; thus, a single geometric illustration of the evidence network is presented for both outcomes in Figure 13. The mean changes from baseline values for the SF-36 PCS were reported in Table 17. The values for the SF-36 MCS are reported in Table 18.

## Figure 13: Evidence Network: Health-Related Quality of Life, SF-36 Physical and Mental Component Scores (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




csDMARD = conventional synthetic disease-modifying antirheumatic drug; IV = intravenous; SIR_50 = 50 mg sirukumab; SIR_100 = 100 mg sirukumab; RCT = randomized controlled trial; SF36 = Short Form (36) Health Survey; TOC_8 = 8 mg/kg tocilizumab.

Tocilizumab at 8 mg/kg in combination with csDMARD resulted in a greater mean improvement from baseline in terms of physical HRQoL compared with csDMARD monotherapy (mean difference: 4.72; 95% Confidence Interval [CI], 3.11 to 6.33); neither treatment resulted in a greater improvement than the other for mental HRQoL (mean difference: 1.03; 95% CI, –0.85 to 2.91).[249] Likewise, sirukumab at 100 mg in combination with a csDMARD resulted in a greater mean improvement from baseline versus csDMARD monotherapy in terms of physical HRQoL (mean difference: 3.80; 95% CI, 0.08 to 7.52); but in terms of mental HRQoL, there was no statistically significant difference (mean difference: –1.10; 95% CI,
–6.31 to 4.11).[217] When comparing 50 mg/kg of sirukumab in combination with a csDMARD versus csDMARD monotherapy, sirukumab also demonstrated a statistically significant improvement from baseline for physical HRQoL (mean difference: 3.80; 95% CI, 0.19 to 7.41), but not for mental HRQoL (mean difference: 2.80; 95% CI, –2.74 to 8.34).[217] It should

be noted that submissions for regulatory approval were withdrawn globally for sirukumab after the analysis was completed.[57]

## Table 17: Health-Related Quality of Life, SF-36 PCS Mean Change from Baseline Data, Concomitant csDMARD

| Author, Year | Treatment 1 | N | Mean (SE) | Treatment 2 | N | Mean (SE) | Treatment 3 | N | Mean (SE) |
|---|---|---|---|---|---|---|---|---|---|
| Yazici 2012 | Placebo + csDMARD | 185 | 2.4 (0.66) | TOC_8 (IV) +csDMARD | 358 | 7.12 (0.49) | | | |
| Smolen 2014 | Placebo + csDMARD | 30 | 2.6 (1.50) | SIR_100 + csDMARD | 30 | 6.4 (1.17) | SIR_50 + csDMARD | 30 | 6.4 (1.08) |

csDMARD = conventional synthetic disease-modifying antirheumatic drug; SF36 = Short Form (36) Health Survey; SIR_50 = 50 mg sirukumab; SIR_100 = 100 mg sirukumab; TOC_8 = 8 mg/kg tocilizumab.
Note: Results are presented as the mean change from baseline, with larger numbers indicating greater improvement in the mental component of health-related quality of life.

## Table 18: Health-Related Quality of Life, SF-36 MCS Mean Change from Baseline Data, Concomitant csDMARD

| Author, Year | Treatment 1 | N | Mean (SE) | Treatment 2 | N | Mean (SE) | Treatment 3 | N | Mean (SE) |
|---|---|---|---|---|---|---|---|---|---|
| Yazici 2012 | Placebo + csDMARD | 185 | 2.23 (0.77) | TOC_8 (IV) + csDMARD | 358 | 3.26 (0.57) | | | |
| Smolen 2014 | Placebo + csDMARD | 30 | 5.1 (1.94) | SIR_100 + csDMARD | 30 | 4.0 (1.83) | SIR_50 + csDMARD | 30 | 7.9 (2.06) |

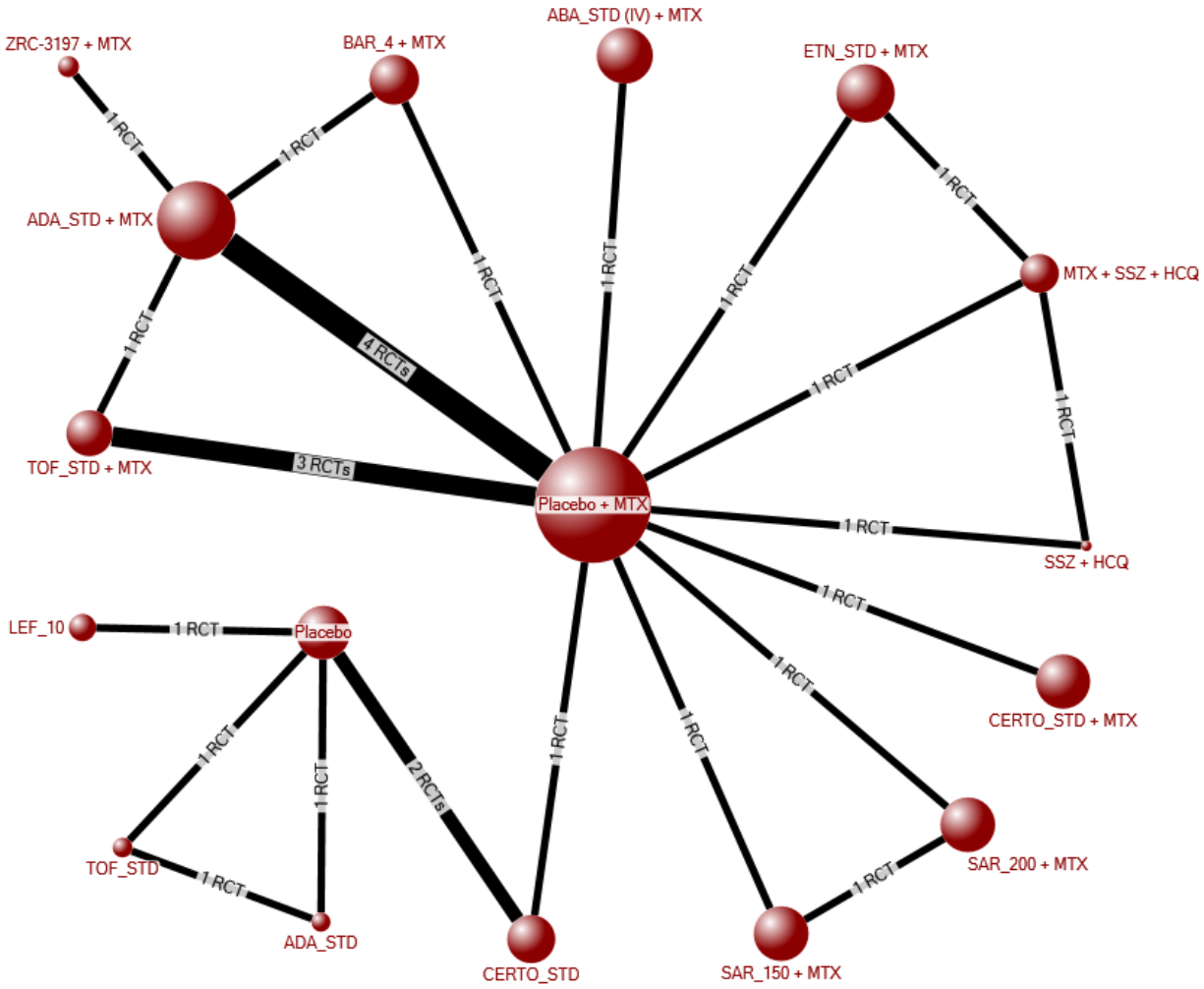
csDMARD = conventional synthetic disease-modifying antirheumatic drug; SF36 = Short Form (36) Health Survey; SIR_50 = 50 mg sirukumab; IV = intravenous; SIR_100 = 100 mg sirukumab; TOC_8 = 8 mg/kg tocilizumab.
Note: Results are presented as the mean change from baseline, with larger numbers indicating greater improvement in the mental component of health-related quality of life.

### Pain

#### *Methotrexate as a Common Comparator*

Eighteen studies[97,102,136,156,165,186,188,195,202,205,207,219,220,222,230,245,247,248] were included for pain in the evidence network with MTX monotherapy as the common comparator. The evidence network involved 6,458 participants and 17 treatments (13 two-arm studies and five three-arm studies), forming 28 direct comparisons. Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in Figure 14. Two different visual analogue scales were reported in the included studies, so the results are reported as SMDs in Table 19 for all treatment comparisons.

## Figure 14: Evidence Network: Pain (Placebo + Methotrexate)




ABA = abatacept; ADA = adalimumab; BAR_4 = 4 mg baricitinib 4 mg; CERTO = certolizumab pegol; CrI = credible interval; ETN = etanercept; HCQ = hydroxychloroquine; IV = intravenous; LEF_10 = 10 mg leflunomide; MTX = methotrexate; RCT = randomized controlled trial; SAR_150 = 150 mg sarilumab; SAR_200 = 200 mg sarilumab; SMD = standardized mean difference; SSZ = sulfasalazine; STD = standard dose; TOF = tofacitinib; ZRC-3197 = biosimilar of adalimumab; vs. = versus; ZRC-3197 = biosimilar of adalimumab.

Compared with MTX monotherapy, the following treatments demonstrated a statistically significant reduction in pain: etanercept, abatacept (IV), adalimumab, tofacitinib, certolizumab pegol, 150 mg and 200 mg sarilumab, and 4 mg baricitinib, all in combination with MTX. Compared with no treatment (placebo), the same treatments listed earlier — as well as 10 mg LEF and certolizumab pegol monotherapy — demonstrated a statistically significant reduction in pain. Most of these comparisons had large effect sizes. These are represented in bold in Table 19.

Certolizumab pegol and 200 mg sarilumab (both in combination with MTX) resulted in statistically significant reductions in pain compared with double-csDMARD therapy with SSZ and HCQ (SMD of –1.70 [95% CrI, –2.93 to –0.41] and SMD of –1.43 [95% CrI, -2.67 to –0.13], respectively), representing a large effect size. Certolizumab pegol in combination with MTX also resulted in greater reductions in pain compared with adalimumab monotherapy (SMD of –1.60; 95% CrI, –3.11 to –0.04). These results had large effect sizes. In addition, certolizumab in combination with MTX demonstrated a greater reduction in pain compared with tofacitinib monotherapy (–1.60; 95% CrI, –3.12 to –0.03), with a large effect size based on the point estimate, but minimal statistical significance.

There were no other statistically significant results for the comparisons of csDMARDs, biologics, biosimilars, and tsDMARDs with one another.

## Table 19: Pain (Placebo + Methotrexate): Standardized Mean Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| Placebo | Placebo + MTX | 0.61 (–0.42 to 1.60) |
| LEF_10 | | –0.65 (–1.99 to 0.63) |
| SSZ + HCQ | | 0.11 (–0.89 to 1.07) |
| MTX + SSZ + HCQ | | –0.58 (–1.39 to 0.13) |
| ETN_STD + MTX | | –0.72 (–1.43 to –0.06) |
| ABA_STD (IV) + MTX | | **–0.91 (–1.71 to –0.11)** |
| ADA_STD | | 0.02 (–1.32 to 1.31) |
| ADA_STD + MTX | | –0.66 (–1.15 to –0.30) |
| TOF_STD | | 0.02 (–1.33 to 1.31) |
| TOF_STD + MTX | | **–0.81 (–1.32 to –0.36)** |
| CERTO_STD | | –0.79 (–1.64 to 0.02) |
| CERTO_STD + MTX | | **–1.58 (–2.38 to –0.77)** |
| SAR_150 + MTX | | **–0.93 (–1.73 to –0.13)** |
| SAR_200 + MTX | | **–1.31 (–2.11 to –0.52)** |
| BAR_4 + MTX | | –0.68 (–1.44 to –0.01) |
| ZRC-3197 + MTX | | –0.71 (–1.73 to 0.17) |
| LEF_10 | Placebo | **–1.27 (–2.10 to –0.44)** |
| SSZ + HCQ | | –0.49 (–1.91 to 0.90) |
| MTX + SSZ + HCQ | | –1.19 (–2.49 to 0.04) |
| ETN_STD + MTX | | **–1.33 (–2.55 to –0.11)** |
| ABA_STD (IV) + MTX | | **–1.52 (–2.79 to –0.20)** |
| ADA_STD | | –0.59 (–1.45 to 0.27) |
| ADA_STD + MTX | | **–1.26 (–2.41 to –0.23)** |
| TOF_STD | | –0.59 (–1.46 to 0.27) |
| TOF_STD + MTX | | **–1.41 (–2.55 to –0.31)** |
| CERTO_STD | | **–1.40 (–1.98 to –0.81)** |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| CERTO_STD + MTX | | **–2.19 (–3.46 to –0.88)** |
| SAR_150 + MTX | | **–1.54 (–2.81 to –0.23)** |
| SAR_200 + MTX | | **–1.92 (–3.19 to –0.62)** |
| BAR_4 + MTX | | **–1.29 (–2.56 to –0.08)** |
| ZRC-3197 + MTX | | –1.32 (–2.76 to 0.01) |
| SSZ + HCQ | LEF_10 | 0.77 (–0.88 to 2.39) |
| MTX + SSZ + HCQ | | 0.08 (–1.46 to 1.56) |
| ETN_STD + MTX | | –0.06 (–1.55 to 1.41) |
| ABA_STD (IV) + MTX | | –0.26 (–1.76 to 1.31) |
| ADA_STD | | 0.68 (–0.53 to 1.87) |
| ADA_STD + MTX | | 0.003 (–1.43 to 1.33) |
| TOF_STD | | 0.68 (–0.52 to 1.87) |
| TOF_STD + MTX | | –0.15 (–1.56 to 1.24) |
| CERTO_STD | | –0.14 (–1.15 to 0.89) |
| CERTO_STD + MTX | | –0.93 (–2.44 to 0.64) |
| SAR_150 + MTX | | –0.27 (–1.78 to 1.29) |
| SAR_200 + MTX | | –0.66 (–2.17 to 0.90) |
| BAR_4 + MTX | | –0.03 (–1.55 to 1.44) |
| ZRC-3197 + MTX | | –0.06 (–1.73 to 1.51) |
| MTX + SSZ + HCQ | SSZ + HCQ | –0.70 (–1.65 to 0.23) |
| ETN_STD + MTX | | –0.84 (–1.88 to 0.22) |
| ABA_STD (IV) + MTX | | –1.03 (–2.26 to 0.27) |
| ADA_STD | | –0.09 (–1.73 to 1.55) |
| ADA_STD + MTX | | –0.77 (–1.87 to 0.27) |
| TOF_STD | | –0.09 (–1.73 to 1.55) |
| TOF_STD + MTX | | –0.92 (–2.01 to 0.17) |
| CERTO_STD | | –0.91 (–2.17 to 0.39) |
| CERTO_STD + MTX | | **–1.70 (–2.93 to –0.41)** |
| SAR_150 + MTX | | –1.05 (–2.29 to 0.25) |
| SAR_200 + MTX | | **–1.43 (–2.67 to –0.13)** |
| BAR_4 + MTX | | –0.80 (–2.02 to 0.40) |
| ZRC-3197 + MTX | | –0.83 (–2.22 to 0.50) |
| ETN_STD + MTX | MTX + SSZ + HCQ | –0.14 (–0.80 to 0.57) |
| ABA_STD (IV) + MTX | | –0.33 (–1.38 to 0.82) |
| ADA_STD | | 0.60 (–0.90 to 2.14) |
| ADA_STD + MTX | | –0.08 (–0.96 to 0.77) |
| TOF_STD | | 0.60 (–0.90 to 2.15) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| TOF_STD + MTX | | –0.22 (–1.10 to 0.69) |
| CERTO_STD | | –0.21 (–1.30 to 0.95) |
| CERTO_STD + MTX | | –1.00 (–2.06 to 0.16) |
| SAR_150 + MTX | | –0.35 (–1.39 to 0.80) |
| SAR_200 + MTX | | –0.74 (–1.77 to 0.42) |
| BAR_4 + MTX | | –0.11 (–1.14 to 0.94) |
| ZRC-3197 + MTX | | –0.13 (–1.36 to 1.06) |
| ABA_STD (IV) + MTX | ETN_STD + MTX | –0.19 (–1.22 to 0.90) |
| ADA_STD | | 0.74 (–0.75 to 2.22) |
| ADA_STD + MTX | | 0.07 (–0.79 to 0.83) |
| TOF_STD | | 0.74 (–0.75 to 2.23) |
| TOF_STD + MTX | | –0.09 (–0.93 to 0.73) |
| CERTO_STD | | –0.07 (–1.14 to 1.01) |
| CERTO_STD + MTX | | –0.86 (–1.89 to 0.22) |
| SAR_150 + MTX | | –0.21 (–1.23 to 0.88) |
| SAR_200 + MTX | | –0.60 (–1.61 to 0.49) |
| BAR_4 + MTX | | 0.03 (–0.97 to 1.01) |
| ZRC-3197 + MTX | | 0.01 (–1.20 to 1.14) |
| ADA_STD | ABA_STD (IV) + MTX | 0.94 (–0.65 to 2.44) |
| ADA_STD + MTX | | 0.26 (–0.73 to 1.09) |
| TOF_STD | | 0.93 (–0.65 to 2.46) |
| TOF_STD + MTX | | 0.11 (–0.86 to 1.00) |
| CERTO_STD | | 0.12 (–1.06 to 1.27) |
| CERTO_STD + MTX | | –0.67 (–1.81 to 0.46) |
| SAR_150 + MTX | | –0.02 (–1.14 to 1.12) |
| SAR_200 + MTX | | –0.40 (–1.53 to 0.73) |
| BAR_4 + MTX | | 0.23 (–0.89 to 1.27) |
| ZRC-3197 + MTX | | 0.20 (–1.11 to 1.37) |
| ADA_STD + MTX | ADA_STD | –0.67 (–2.11 to 0.67) |
| TOF_STD | | –0.004 (–0.88 to 0.86) |
| TOF_STD + MTX | | –0.83 (–2.24 to 0.57) |
| CERTO_STD | | –0.81 (–1.84 to 0.23) |
| CERTO_STD + MTX | | **–1.60 (–3.11 to –0.04)** |
| SAR_150 + MTX | | –0.95 (–2.46 to 0.62) |
| SAR_200 + MTX | | –1.34 (–2.85 to 0.23) |
| BAR_4 + MTX | | –0.71 (–2.21 to 0.78) |
| ZRC-3197 + MTX | | –0.73 (–2.40 to 0.83) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| TOF_STD | ADA_STD + MTX | 0.67 (–0.67 to 2.09) |
| TOF_STD + MTX | | –0.15 (–0.68 to 0.45) |
| CERTO_STD | | –0.14 (–1.00 to 0.86) |
| CERTO_STD + MTX | | –0.93 (–1.76 to 0.06) |
| SAR_150 + MTX | | –0.28 (–1.10 to 0.71) |
| SAR_200 + MTX | | –0.66 (–1.48 to 0.31) |
| BAR_4 + MTX | | –0.04 (–0.71 to 0.73) |
| ZRC-3197 + MTX | | –0.06 (–0.91 to 0.80) |
| TOF_STD + MTX | TOF_STD | –0.83 (–2.24 to 0.57) |
| CERTO_STD | | –0.81 (–1.84 to 0.24) |
| CERTO_STD + MTX | | **–1.60 (–3.12 to –0.03)** |
| SAR_150 + MTX | | –0.95 (–2.47 to 0.62) |
| SAR_200 + MTX | | –1.34 (–2.86 to 0.24) |
| BAR_4 + MTX | | –0.71 (–2.22 to 0.78) |
| ZRC-3197 + MTX | | –0.73 (–2.39 to 0.85) |
| CERTO_STD | TOF_STD + MTX | 0.01 (–0.93 to 0.99) |
| CERTO_STD + MTX | | –0.78 (–1.68 to 0.20) |
| SAR_150 + MTX | | –0.13 (–1.01 to 0.85) |
| SAR_200 + MTX | | –0.51 (–1.40 to 0.46) |
| BAR_4 + MTX | | 0.12 (–0.72 to 0.95) |
| ZRC-3197 + MTX | | 0.09 (–0.96 to 1.08) |
| CERTO_STD + MTX | CERTO_STD | –0.79 (–1.93 to 0.39) |
| SAR_150 + MTX | | –0.14 (–1.27 to 1.04) |
| SAR_200 + MTX | | –0.52 (–1.66 to 0.65) |
| BAR_4 + MTX | | 0.11 (–1.02 to 1.18) |
| ZRC-3197 + MTX | | 0.08 (–1.24 to 1.28) |
| SAR_150 + MTX | CERTO_STD + MTX | 0.65 (–0.48 to 1.79) |
| SAR_200 + MTX | | 0.27 (–0.86 to 1.41) |
| BAR_4 + MTX | | 0.90 (–0.22 to 1.93) |
| ZRC-3197 + MTX | | 0.87 (–0.44 to 2.05) |
| SAR_200 + MTX | SAR_150 + MTX | –0.38 (–1.18 to 0.41) |
| BAR_4 + MTX | | 0.25 (–0.88 to 1.27) |
| ZRC-3197 + MTX | | 0.22 (–1.08 to 1.38) |
| BAR_4 + MTX | SAR_200 + MTX | 0.63 (–0.48 to 1.66) |
| ZRC-3197 + MTX | | 0.60 (–0.71 to 1.76) |
| ZRC-3197 + MTX | BAR_4 + MTX | –0.03 (–1.16 to 1.05) |
| | | |

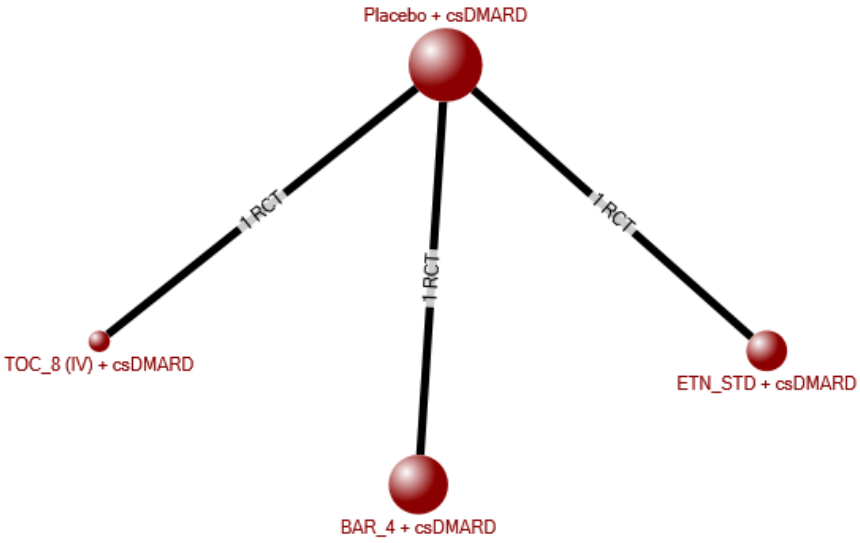
| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| Random-Effects Model | Residual Deviance | 24.66 vs. 41 data points |
| | Deviance Information Criteria | –1.072 |
| Fixed-Effect Model | Residual Deviance | 38.93 vs 41 data points |
| | Deviance Information Criteria | 7.678 |

ABA = abatacept; ADA = adalimumab; BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; CrI = credible interval; ETN = etanercept; HCQ = hydroxychloroquine; IV = intravenous; LEF_10 = 10 mg leflunomide; MTX = methotrexate; SAR_150 = 150 mg sarilumab; SAR_200 = 200 mg sarilumab; SMD = standardized mean difference; SSZ = sulfasalazine; STD = standard dose; TOF = tofacitinib; ZRC-3197 = biosimilar adalimumab; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator. Bold results represent large effect sizes.

*Conventional Synthetic DMARD as a Common Comparator*

There were three studies that reported on pain outcomes with a total of 712 participants contributing data.[151,163,211] It was not possible to conduct an NMA due to the limited number of trials. No two studies investigated the same treatment comparison, so a descriptive analysis is presented. The comparator in all cases was csDMARD monotherapy; the treatments of interest were etanercept, 8 mg/kg tocilizumab, and 4 mg baricitinib, all in combination with a csDMARD (Figure 15). In all three studies, the treatments of interest had a statistically significant reduction in pain from baseline compared with csDMARD monotherapy (Table 20).

## Figure 15: Evidence Network: Pain (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




BAR_4 = 4 mg baricitinib; ETN = etanercept; csDMARD = conventional synthetic disease-modifying antirheumatic drug; RCT = randomized controlled trial; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab.

## Table 20: Pain, Standardized Mean Change from Baseline Data, Concomitant csDMARD

| Author, Year | Treatment 1 | Treatment 2 | SMD (95% CI) | SE |
|---|---|---|---|---|
| Hobbs 2015 | Placebo + csDMARD | ETN_STD + csDMARD | –0.65 (–0.93 to –0.38) | 0.14 |
| Hoffmann–La Roche 2015 | Placebo + csDMARD | TOC_8 (IV) + csDMARD | –0.76 (–1.36 to –0.15) | 0.31 |
| Dougados 2017 | Placebo + csDMARD | BAR_4 + csDMARD | –0.60 (–0.79 to –0.41) | 0.096 |

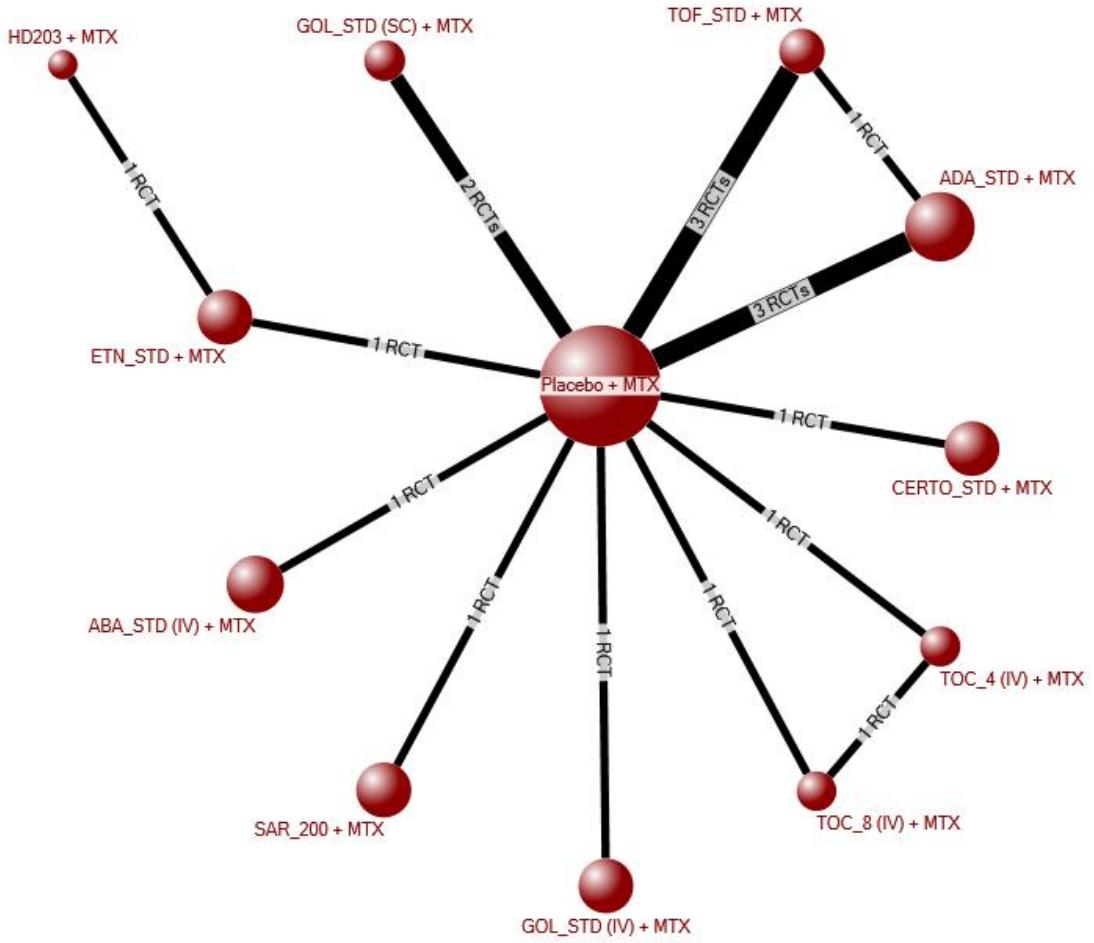
BAR_4 = 4 mg baricitinib; CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; IV = intravenous; SE = standard error; SMD = standardized mean difference; TOC_8 = 8 mg/kg tocilizumab.
Note: Results are presented as the SMD, with negative numbers indicating greater reduction in pain.

### Fatigue

#### *Methotrexate as a Common Comparator*

Fourteen RCTs published in 13 articles[132,134,161,186,193,195,212,215,219,220,222,230,252] were included for the reference case NMA of fatigue in the evidence network with MTX monotherapy as the common comparator. The evidence network involved 6,082 participants and 13 treatments (11 two-arm studies and three three-arm studies) forming 20 direct comparisons. More than one scale was used to measure fatigue; thus, SMDs were calculated. Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in Figure 16; SMDs for all treatment comparisons with MTX monotherapy as the common comparator are available in Table 21. A staircase table of the results as SMDs is also presented in Appendix 10 (Table 95).

## Figure 16: Evidence Network: Fatigue (Placebo + Methotrexate)




ABA = abatacept; ADA = adalimumab; CERTO = certolizumab pegol; ETN = etanercept; GOL = golimumab; HD203 = biosimilar etanercept; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; SAR_150 = 150 mg sarilumab; SAR_200 = 200 mg sarilumab; SC = subcutaneous; STD = standard dose; TOF = tofacitinib; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab.

Only the standard dose of tofacitinib in combination with MTX and certolizumab pegol in combination with MTX demonstrated a statistically significantly greater reduction in fatigue compared with MTX monotherapy (SMD = 0.58; 95% CrI, 0.01 to 1.30 and SMD = 1.25, 0.17 to 2.36, respectively). Of these two biologics, certolizumab pegol had a large effect size, whereas tofacitinib demonstrated a moderate effect size for the SMD compared with MTX monotherapy. There were no statistically significant results when comparing the biologics, tsDMARDs, and biosimilars with one another.

## Table 21: Fatigue (Placebo + Methotrexate): Standardized Mean Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| ETN_STD + MTX | Placebo + MTX | 0.47 (–0.64 to 1.58) |
| ABA_STD (IV) + MTX | | 0.43 (–0.67 to 1.53) |
| TOF_STD + MTX | | 0.58 (0.01 to 1.30) |
| ADA_STD + MTX | | 0.39 (–0.21 to 1.05) |
| TOC_4 (IV) + MTX | | 0.28 (–0.83 to 1.38) |
| TOC_8 (IV) + MTX | | 0.37 (–0.75 to 1.47) |
| GOL_STD (SC) + MTX | | 0.54 (–0.25 to 1.33) |
| GOL_STD (IV) + MTX | | 0.52 (–0.59 to 1.63) |
| CERTO_STD + MTX | | **1.25 (0.17 to 2.36)** |
| SAR_150 + MTX | | 0.45 (–0.65 to 1.55) |
| SAR_200 + MTX | | 0.54 (–0.56 to 1.65) |
| HD203 + MTX | | 0.56 (–1.02 to 2.14) |
| ABA_STD (IV) + MTX | ETN_STD + MTX | –0.04 (–1.61 to 1.52) |
| TOF_STD + MTX | | 0.11 (–1.09 to 1.46) |
| ADA_STD + MTX | | –0.09 (–1.33 to 1.22) |
| TOC_4 (IV) + MTX | | –0.19 (–1.76 to 1.36) |
| TOC_8 (IV) + MTX | | –0.11 (–1.69 to 1.45) |
| GOL_STD (SC) + MTX | | 0.07 (–1.29 to 1.41) |
| GOL_STD (IV) + MTX | | 0.05 (–1.52 to 1.63) |
| CERTO_STD + MTX | | 0.78 (–0.78 to 2.34) |
| SAR_150 + MTX | | –0.03 (–1.59 to 1.54) |
| SAR_200 + MTX | | 0.07 (–1.49 to 1.62) |
| HD203 + MTX | | 0.08 (–1.04 to 1.22) |
| TOF_STD + MTX | ABA_STD (IV) + MTX | 0.14 (–1.05 to 1.51) |
| ADA_STD + MTX | | –0.05 (–1.29 to 1.26) |
| TOC_4 (IV) + MTX | | –0.15 (–1.72 to 1.39) |
| TOC_8 (IV) + MTX | | –0.07 (–1.63 to 1.49) |
| GOL_STD (SC) + MTX | | 0.11 (–1.25 to 1.46) |
| GOL_STD (IV) + MTX | | 0.08 (–1.48 to 1.64) |
| CERTO_STD + MTX | | 0.82 (–0.73 to 2.38) |
| SAR_150 + MTX | | 0.01 (–1.54 to 1.58) |
| SAR_200 + MTX | | 0.11 (–1.45 to 1.66) |
| HD203 + MTX | | 0.12 (–1.81 to 2.06) |
| ADA_STD + MTX | TOF_STD + MTX | –0.19 (–1.03 to 0.56) |
| TOC_4 (IV) + MTX | | –0.30 (–1.66 to 0.89) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| TOC_8 (IV) + MTX | | –0.21 (–1.58 to 0.98) |
| GOL_STD (SC) + MTX | | –0.04 (–1.14 to 0.92) |
| GOL_STD (IV) + MTX | | –0.06 (–1.42 to 1.15) |
| CERTO_STD + MTX | | 0.67 (–0.67 to 1.88) |
| SAR_150 + MTX | | –0.13 (–1.48 to 1.08) |
| SAR_200 + MTX | | –0.03 (–1.39 to 1.17) |
| HD203 + MTX | | –0.02 (–1.80 to 1.62) |
| TOC_4 (IV) + MTX | ADA_STD + MTX | –0.10 (–1.41 to 1.12) |
| TOC_8 (IV) + MTX | | –0.02 (–1.33 to 1.21) |
| GOL_STD (SC) + MTX | | 0.15 (–0.89 to 1.14) |
| GOL_STD (IV) + MTX | | 0.13 (–1.17 to 1.38) |
| CERTO_STD + MTX | | 0.87 (–0.43 to 2.11) |
| SAR_150 + MTX | | 0.06 (–1.23 to 1.30) |
| SAR_200 + MTX | | 0.16 (–1.15 to 1.40) |
| HD203 + MTX | | 0.17 (–1.56 to 1.85) |
| TOC_8 (IV) + MTX | TOC_4 (IV) + MTX | 0.09 (–1.02 to 1.20) |
| GOL_STD (SC) + MTX | | 0.26 (–1.09 to 1.63) |
| GOL_STD (IV) + MTX | | 0.24 (–1.32 to 1.82) |
| CERTO_STD + MTX | | 0.97 (–0.57 to 2.52) |
| SAR_150 + MTX | | 0.17 (–1.39 to 1.74) |
| SAR_200 + MTX | | 0.26 (–1.28 to 1.83) |
| HD203 + MTX | | 0.28 (–1.64 to 2.22) |
| GOL_STD (SC) + MTX | TOC_8 (IV) + MTX | 0.17 (–1.17 to 1.54) |
| GOL_STD (IV) + MTX | | 0.15 (–1.40 to 1.71) |
| CERTO_STD + MTX | | 0.88 (–0.64 to 2.46) |
| SAR_150 + MTX | | 0.08 (–1.47 to 1.66) |
| SAR_200 + MTX | | 0.17 (–1.37 to 1.75) |
| HD203 + MTX | | 0.19 (–1.73 to 2.13) |
| GOL_STD (IV) + MTX | GOL_STD (SC) + MTX | –0.02 (–1.37 to 1.33) |
| CERTO_STD + MTX | | 0.71 (–0.64 to 2.08) |
| SAR_150 + MTX | | –0.09 (–1.44 to 1.27) |
| SAR_200 + MTX | | 0.004 (–1.36 to 1.35) |
| HD203 + MTX | | 0.02 (–1.75 to 1.78) |
| CERTO_STD + MTX | GOL_STD (IV) + MTX | 0.73 (–0.81 to 2.31) |
| SAR_150 + MTX | | –0.07 (–1.63 to 1.48) |
| SAR_200 + MTX | | 0.03 (–1.55 to 1.59) |
| HD203 + MTX | | 0.04 (–1.89 to 1.96) |

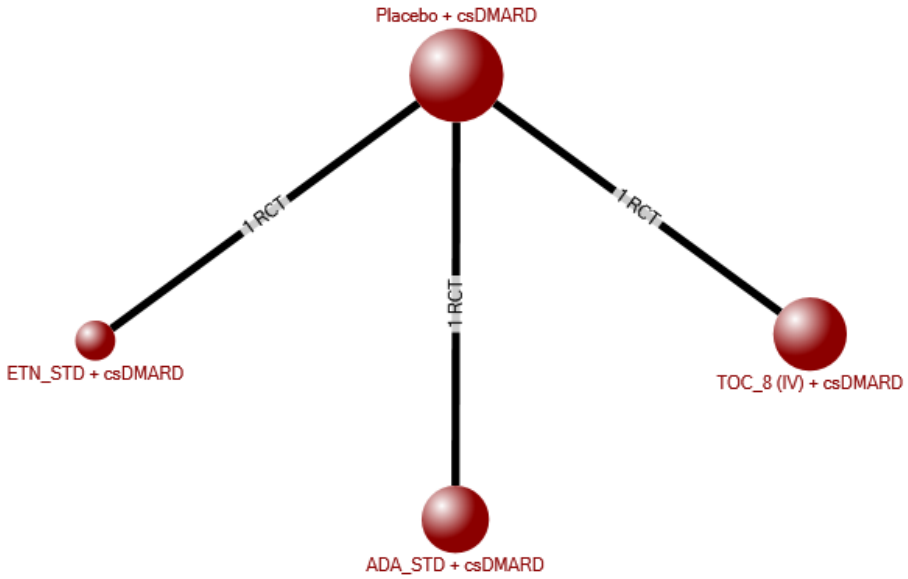
| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| SAR_150 + MTX | CERTO_STD + MTX | –0.80 (–2.37 to 0.74) |
| SAR_200 + MTX | | –0.71 (–2.27 to 0.83) |
| HD203 + MTX | | –0.69 (–2.61 to 1.20) |
| SAR_200 + MTX | SAR_150 + MTX | 0.10 (–1.00 to 1.20) |
| HD203 + MTX | | 0.11 (–1.80 to 2.03) |
| HD203 + MTX | SAR_200 + MTX | 0.01 (–1.91 to 1.95) |
| | | |
| Random-Effects Model | Residual Deviance | 18.49 vs. 31 data points |
| | Deviance Information Criteria | –7.7 |
| Fixed-Effect Model | Residual Deviance | 31.09 vs 31 data points |
| | Deviance Information Criteria | 0.194 |

ABA = abatacept; ADA = adalimumab; CERTO = certolizumab pegol; CrI = credible interval; ETN = etanercept; GOL = golimumab; HD203 = biosimilar etanercept; IV = intravenous; MTX = methotrexate; SAR_150 = 150 mg sarilumab; SAR_200 = 200 mg sarilumab; SC = subcutaneous; SMD = standardized mean difference; STD = standard dose; TOF = tofacitinib; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator.

### *Conventional Synthetic DMARD as a Common Comparator*

A total of three RCTs reported on fatigue outcomes, with 1,817 participants contributing data.[163,249,252] No NMA was conducted because there were not enough studies for the model to run. In addition, none of the three studies compared the same two treatments for a pairwise MA; thus, a descriptive analysis is presented here. The common comparator in all studies was csDMARD monotherapy; active treatments were 8 mg/kg tocilizumab, etanercept, and adalimumab (Figure 17).

## Figure 17: Evidence Network: Fatigue (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




ADA = adalimumab; ETN = etanercept; IV = intravenous; RCT = randomized controlled trial; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab.

The SMD was calculated because not all studies presented the same fatigue scale. All three biologics in combination with a csDMARD (8 mg/kg tocilizumab, etanercept, and adalimumab) demonstrated a statistically significant improvement in fatigue (i.e., less fatigue) compared with csDMARD monotherapy (Table 22).

## Table 22: Fatigue, Standardized Mean Difference Data, Concomitant Conventional Synthetic Disease-Modifying Antirheumatic Drug

| Author | Treatment 1 | Treatment 2 | Mean (95% CI) | SE |
|---|---|---|---|---|
| Yazici 2012 | Placebo + csDMARD | TOC_8 (IV) + csDMARD | 0.27 (0.09 to 0.45) | 0.091 |
| Hobbs 2015 | Placebo + csDMARD | ETN_STD + csDMARD | 0.28 (0.007 to 0.55) | 0.14 |
| Yount 2007 | Placebo + csDMARD | ADA_STD + csDMARD | 0.45 (0.29 to 0.61) | 0.083 |

ADA = adalimumab; CI = confidence interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; IV = intravenous; SE = standard error; TOC_8 = 8 mg/kg tocilizumab.
Note: Results are presented as the standardized mean difference, with positive numbers indicating greater improvement in fatigue.

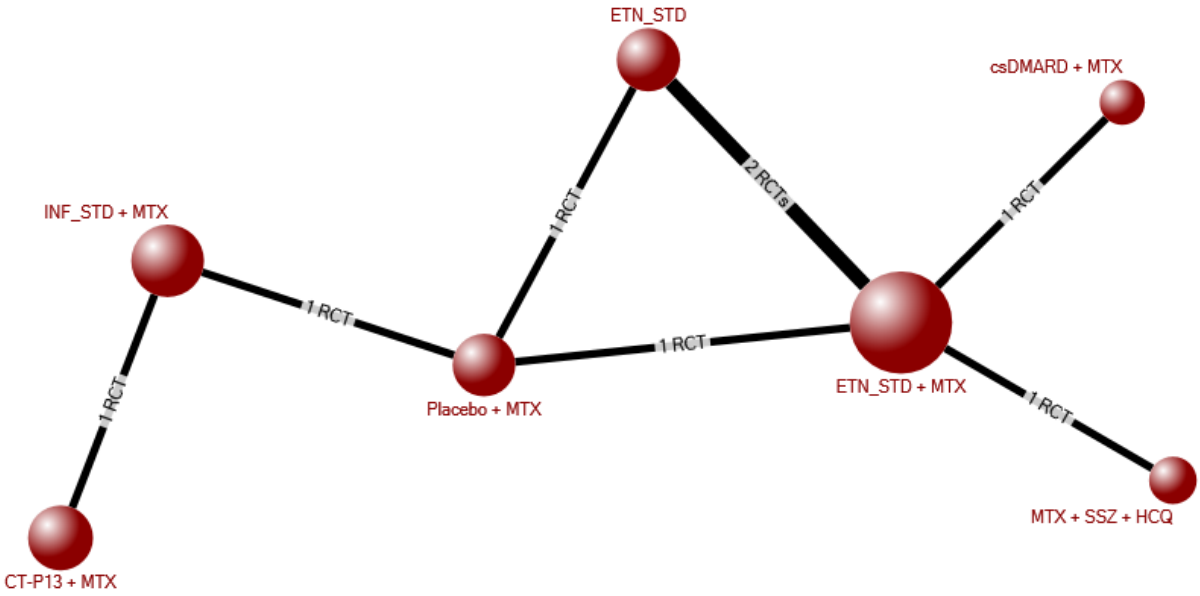
### Radiographic Progression

#### *Methotrexate as a Common Comparator*

There were six studies[167,194,195,207,232,251] included in the reference case NMA for radiographic progression in which MTX monotherapy is the common comparator. The evidence network involved 2,244 participants and seven treatments (within five two-arm studies and one three-arm study) forming eight direct comparisons. Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in

Figure 18; the SMDs for all treatment comparisons are available in Table 23. A staircase table of the results as SMDs is also presented in Appendix 10 (Table 96).

## Figure 18: Evidence Network: Radiographic Progression (Placebo + MTX)




csDMARDs = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; HCQ = hydroxychloroquine; INF = infliximab; MTX = methotrexate; RCT = randomized controlled trial; SSZ = sulfasalazine; STD = standard dose.

There were no statistically significant differences in radiographic progression for the treatments compared with placebo or for any head-to-head comparisons of double- or triple-csDMARD therapies, biologics, or biosimilars. Results are based only on studies with end-of-treatment data that did not employ an adaptive design because the adaptive design trials did not report radiographic progression before the time of adaptation. Therefore, there is limited long-term evidence available for this outcome.

## Table 23: Radiographic Progression (Placebo + Methotrexate): Standardized Mean Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| csDMARD + MTX | Placebo + MTX | –0.25 (–6.03 to 5.52) |
| MTX + SSZ + HCQ | | –0.27 (–6.02 to 5.48) |
| ETN_STD | | –0.23 (–4.15 to 3.67) |
| ETN_STD + MTX | | –0.41 (–4.33 to 3.53) |
| INF_STD + MTX | | –0.68 (–4.85 to 3.46) |
| CT-P13 + MTX | | –0.61 (–6.56 to 5.26) |
| MTX + SSZ + HCQ | csDMARD + MTX | –0.01 (–5.85 to 5.90) |
| ETN_STD | | 0.03 (–5.15 to 5.18) |
| ETN_STD + MTX | | –0.16 (–4.36 to 4.09) |

| Treatment | Reference | SMD (95% CrI) |
|---|---|---|
| INF_STD + MTX | | –0.43 (–7.56 to 6.71) |
| CT-P13 + MTX | | –0.36 (–8.54 to 7.88) |
| ETN_STD | MTX + SSZ + HCQ | 0.04 (–5.11 to 5.22) |
| ETN_STD + MTX | | –0.14 (–4.32 to 4.00) |
| INF_STD + MTX | | –0.41 (–7.48 to 6.62) |
| CT-P13 + MTX | | –0.35 (–8.57 to 7.88) |
| ETN_STD + MTX | ETN_STD | –0.18 (–3.15 to 2.81) |
| INF_STD + MTX | | –0.45 (–6.13 to 5.23) |
| CT-P13 + MTX | | –0.39 (–7.42 to 6.64) |
| INF_STD + MTX | ETN_STD + MTX | –0.27 (–5.99 to 5.46) |
| CT-P13 + MTX | | –0.20 (–7.25 to 6.85) |
| CT-P13 + MTX | INF_STD + MTX | 0.07 (–4.14 to 4.26) |
| | | |
| Random-Effects Model | Residual Deviance | 6.923 vs. 13 data points |
| | Deviance Information Criteria | –3.873 |
| Fixed-Effect Model | Residual Deviance | 6.847 vs 13 data points |
| | Deviance Information Criteria | -4.826 |

CrI = credible interval; CT-P13 = biosimilar infliximab; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; HCQ = hydroxychloroquine; INF = infliximab; MTX = methotrexate; SMD = standardized mean difference; SSZ = sulfasalazine; STD = standard dose; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator. Bold results represent large effect sizes.

### *Conventional Synthetic DMARD as a Common Comparator*

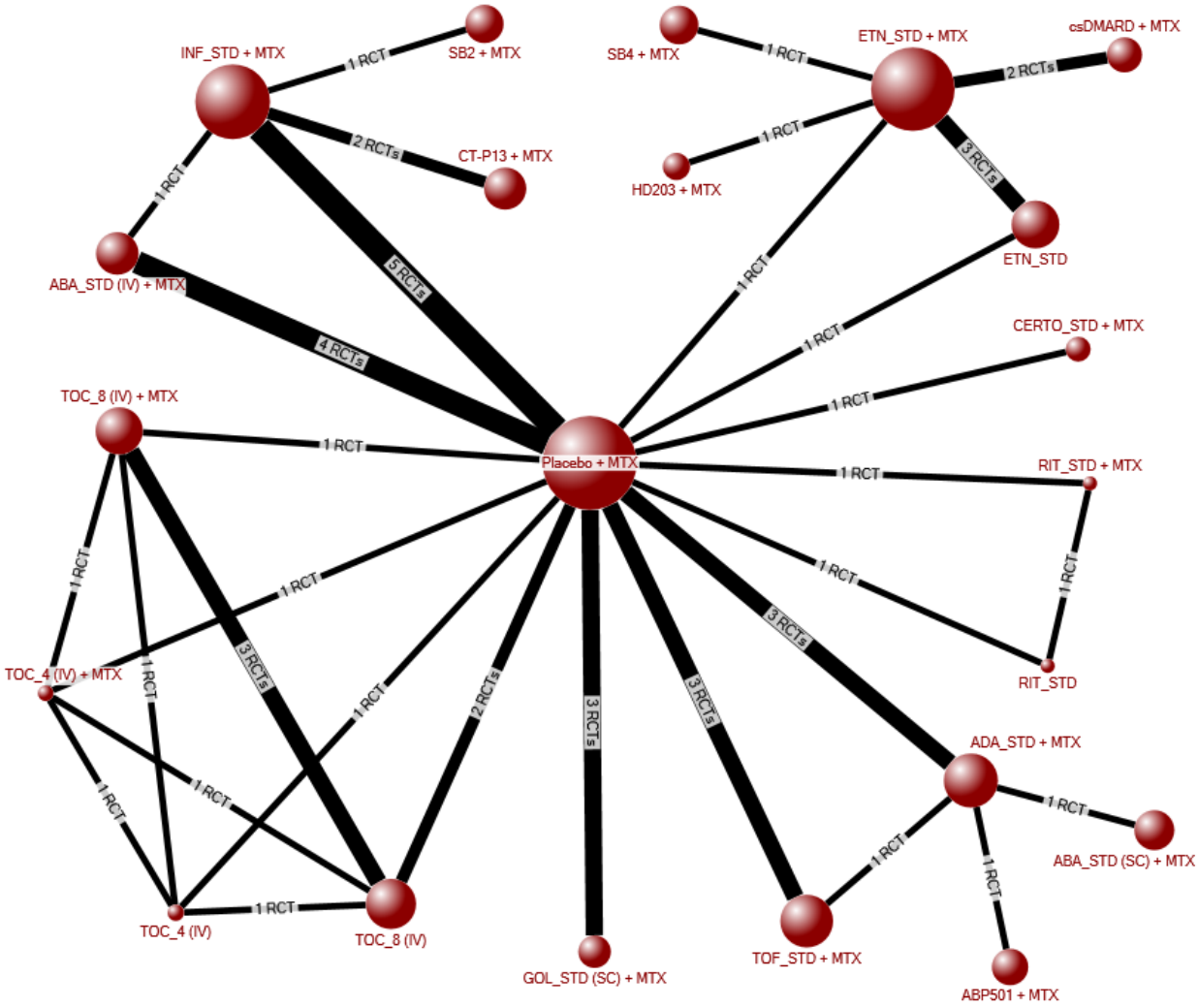
There were no studies reporting on radiographic progression outcomes that involved a csDMARD (other than MTX) as the common comparator.

## Serious Adverse Events

### *Methotrexate as a Common Comparator*

A total of 34 studies[95,99,100,128,130,132,136,138,139,145,150,152,155,167,169,171,175,179,181,182,190,194,195,199,204,224,226,229,230,232,234,236,251,253] (29 two-arm studies, four three-arm studies and one five-arm study) with MTX monotherapy as the common comparator were included for the number of participants with a serious adverse event (SAE). The evidence network involved 9,245 participants and 22 treatments, forming 51 direct comparisons. Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in Figure 19. The odds ratios for all treatment comparisons with MTX monotherapy as the common comparator are available in Table 24.

## Figure 19: Evidence Network: Serious Adverse Events (Placebo + Methotrexate)




ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; GOL = golimumab; HD203 = etanercept biosimilar; INF = infliximab; IV = intravenous; MTX = methotrexate; RIT = rituximab; RCT = randomized controlled trial; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib.

For all treatments (except abatacept [IV] in combination with MTX), there was insufficient evidence to detect a difference in the odds of SAEs. Participants receiving a combination of abatacept (IV) and MTX had statistically significantly lower odds of developing an SAE compared with participants receiving MTX monotherapy (odds ratio = 0.34; CrI, 0.18 to 0.65), etanercept monotherapy (odds ratio = 0.31; CrI, 0.14 to 0.74), or etanercept in combination with MTX (odds ratio = 0.28; CrI, 0.12 to 0.64). When abatacept (IV) in combination with MTX was the common comparator, the following treatments resulted in higher odds of SAEs in comparison: combination therapy of MTX and tofacitinib, adalimumab, 8 mg/kg tocilizumab, golimumab (SC), certolizumab pegol, HD203 (biosimilar

etanercept), and SB4 (biosimilar etanercept), as well as 4 mg/kg and 8 mg/kg tocilizumab monotherapy (Table 24).

Compared with tofacitinib in combination with MTX, participants who received infliximab in combination with MTX, or SB2 (biosimilar infliximab) in combination with MTX, had statistically significantly lower odds of developing an SAE (odds ratio = 0.28; 95% CrI, 0.11 to 0.77 and odds ratio = 0.29; 95% CrI, 0.08 to 0.95, respectively). In the comparison of 8 mg/kg tocilizumab with 4 mg/kg tocilizumab (both in combination with MTX), the 8 mg/kg dose had higher odds of SAEs, though the 95% CrI was very wide (Table 24). The odds of SAEs were found to be lower for infliximab in combination with MTX compared with 8 mg/kg tocilizumab in combination with MTX (odds ratio = 0.26; 95% CrI, 0.07 to 0.78) and compared with golimumab (SC) in combination with MTX (odds ratio = 0.30; 95% CrI, 0.09 to 0.93). SB2, a biosimilar infliximab, in combination with MTX also had statistically significant lower odds of SAEs compared with 8 mg/kg tocilizumab in combination with MTX (odds ratio = 0.26; 95% CrI, 0.06 to 0.96). There were no other statistically significant comparisons of biologics, biosimilars, or tsDMARDs with one another for SAE outcomes (Table 24).

## Table 24: Serious Adverse Events: Odds Ratios, Relative Risks, and Risk Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| csDMARD + MTX | Placebo + MTX | 0.70 (0.19 to 2.22) | 0.71 (0.20 to 2.08) | –0.01 (–0.04 to 0.06) |
| ETN_STD | | 1.10 (0.63 to 1.85) | 1.09 (0.65 to 1.77) | 0.005 (–0.02 to 0.04) |
| ETN_STD + MTX | | 1.24 (0.73 to 2.13) | 1.22 (0.74 to 2.02) | 0.01 (–0.01 to 0.05) |
| ABA_STD (IV) + MTX | | 0.34 (0.18 to 0.65) | 0.35 (0.19 to 0.67) | –0.03 (–0.05 to –0.02) |
| ABA_STD (SC) + MTX | | 0.87 (0.32 to 2.71) | 0.88 (0.34 to 2.51) | –0.01 (–0.04 to 0.07) |
| TOF_STD + MTX | | 2.18 (0.99 to 5.47) | 2.05 (0.99 to 4.53) | 0.05 (–0.001 to 0.17) |
| ADA_STD + MTX | | 1.08 (0.46 to 2.92) | 1.08 (0.47 to 2.68) | 0.004 (–0.03 to 0.08) |
| TOC_4 (IV) | | 1.88 (0.44 to 8.43) | 1.80 (0.46 to 6.20) | 0.04 (–0.03 to 0.26) |
| TOC_8 (IV) | | 1.65 (0.59 to 5.19) | 1.59 (0.60 to 4.32) | 0.03 (–0.02 to 0.16) |
| TOC_4 (IV) + MTX | | 0.23 (0.01 to 2.16) | 0.24 (0.01 to 2.04) | –0.04 (–0.06 to 0.05) |
| TOC_8 (IV) + MTX | | 2.43 (0.87 to 8.43) | 2.26 (0.88 to 6.21) | 0.07 (–0.01 to 0.25) |
| GOL_STD (SC) + MTX | | 2.10 (0.73 to 6.43) | 1.99 (0.74 to 5.13) | 0.05 (–0.01 to 0.19) |
| INF_STD + MTX | | 0.62 (0.39 to 1.03) | 0.64 (0.40 to 1.03) | –0.02 (–0.03 to 0.001) |
| CERTO_STD + MTX | | 1.30 (0.55 to 3.41) | 1.28 (0.56 to 3.03) | 0.01 (–0.02 to 0.10) |
| RIT_STD | | 0.66 (0.07 to 5.82) | 0.67 (0.07 to 4.71) | –0.02 (–0.05 to 0.18) |
| RIT_STD + MTX | | 1.12 (0.18 to 7.89) | 1.11 (0.19 to 5.89) | 0.01 (–0.04 to 0.24) |
| HD203 + MTX | | 1.30 (0.51 to 3.42) | 1.28 (0.53 to 3.03) | 0.01 (–0.03 to 0.11) |
| SB4 + MTX | | 1.21 (0.44 to 3.41) | 1.20 (0.45 to 3.03) | 0.01 (–0.03 to 0.11) |
| CT-P13 + MTX | | 0.81 (0.39 to 1.69) | 0.82 (0.41 to 1.63) | –0.01 (–0.03 to 0.03) |
| SB2 + MTX | | 0.63 (0.28 to 1.44) | 0.64 (0.29 to 1.41) | –0.02 (–0.04 to 0.02) |
| ABP501 + MTX | | 0.81 (0.23 to 3.20) | 0.82 (0.24 to 2.89) | –0.01 (–0.04 to 0.09) |
| ETN_STD | csDMARD + MTX | 1.56 (0.51 to 5.61) | 1.52 (0.54 to 5.32) | 0.02 (–0.05 to 0.06) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ETN_STD + MTX | | 1.76 (0.65 to 5.75) | 1.71 (0.67 to 5.42) | 0.02 (–0.03 to 0.06) |
| ABA_STD (IV) + MTX | | 0.49 (0.13 to 2.12) | 0.50 (0.14 to 2.09) | –0.02 (–0.09 to 0.01) |
| ABA_STD (SC) + MTX | | 1.25 (0.27 to 7.54) | 1.24 (0.29 to 6.88) | 0.01 (–0.07 to 0.09) |
| TOF_STD + MTX | | 3.13 (0.79 to 13.99) | 2.89 (0.81 to 12.01) | 0.07 (–0.02 to 0.18) |
| ADA_STD + MTX | | 1.53 (0.36 to 8.29) | 1.50 (0.39 to 7.53) | 0.02 (–0.06 to 0.10) |
| TOC_4 (IV) | | 2.72 (0.43 to 19.20) | 2.55 (0.46 to 14.73) | 0.05 (–0.05 to 0.27) |
| TOC_8 (IV) | | 2.39 (0.51 to 12.56) | 2.27 (0.53 to 10.61) | 0.04 (–0.04 to 0.18) |
| TOC_4 (IV) + MTX | | 0.32 (0.02 to 4.16) | 0.33 (0.02 to 3.89) | –0.02 (–0.09 to 0.06) |
| TOC_8 (IV) + MTX | | 3.57 (0.76 to 20.01) | 3.24 (0.78 to 15.31) | 0.08 (–0.02 to 0.27) |
| GOL_STD (SC) + MTX | | 2.98 (0.61 to 17.50) | 2.76 (0.63 to 14.42) | 0.06 (–0.03 to 0.21) |
| INF_STD + MTX | | 0.89 (0.25 to 3.62) | 0.89 (0.27 to 3.50) | –0.004 (–0.08 to 0.03) |
| CERTO_STD + MTX | | 1.90 (0.42 to 9.92) | 1.83 (0.44 to 8.78) | 0.03 (–0.05 to 0.13) |
| RIT_STD | | 0.94 (0.07 to 11.30) | 0.94 (0.08 to 9.20) | –0.002 (–0.08 to 0.19) |
| RIT_STD + MTX | | 1.64 (0.19 to 15.15) | 1.60 (0.20 to 11.96) | 0.02 (–0.07 to 0.25) |
| HD203 + MTX | | 1.86 (0.54 to 8.02) | 1.80 (0.56 to 7.29) | 0.03 (–0.04 to 0.12) |
| SB4 + MTX | | 1.73 (0.46 to 7.61) | 1.68 (0.48 to 6.84) | 0.02 (–0.04 to 0.11) |
| CT-P13 + MTX | | 1.17 (0.29 to 5.32) | 1.16 (0.31 to 5.02) | 0.01 (–0.07 to 0.06) |
| SB2 + MTX | | 0.90 (0.22 to 4.24) | 0.90 (0.23 to 4.06) | –0.003 (–0.08 to 0.04) |
| ABP501 + MTX | | 1.16 (0.20 to 7.72) | 1.16 (0.22 to 7.00) | 0.01 (–0.07 to 0.11) |
| ETN_STD + MTX | ETN_STD | 1.13 (0.72 to 1.83) | 1.12 (0.74 to 1.76) | 0.01 (–0.02 to 0.04) |
| ABA_STD (IV) + MTX | | 0.31 (0.14 to 0.74) | 0.33 (0.15 to 0.74) | –0.04 (–0.08 to –0.01) |
| ABA_STD (SC) + MTX | | 0.79 (0.27 to 2.92) | 0.80 (0.28 to 2.71) | –0.01 (–0.06 to 0.07) |
| TOF_STD + MTX | | 2.01 (0.75 to 5.73) | 1.90 (0.77 to 4.80) | 0.05 (–0.02 to 0.16) |
| ADA_STD + MTX | | 0.98 (0.37 to 3.13) | 0.98 (0.39 to 2.88) | –0.001 (–0.05 to 0.08) |
| TOC_4 (IV) | | 1.71 (0.37 to 8.72) | 1.64 (0.39 to 6.48) | 0.04 (–0.04 to 0.25) |
| TOC_8 (IV) | | 1.50 (0.48 to 5.48) | 1.46 (0.50 to 4.58) | 0.03 (–0.04 to 0.16) |
| TOC_4 (IV) + MTX | | 0.21 (0.01 to 2.17) | 0.22 (0.01 to 2.04) | –0.04 (–0.08 to 0.05) |
| TOC_8 (IV) + MTX | | 2.22 (0.70 to 8.76) | 2.07 (0.72 to 6.59) | 0.06 (–0.02 to 0.25) |
| GOL_STD (SC) + MTX | | 1.91 (0.58 to 6.67) | 1.82 (0.60 to 5.37) | 0.05 (–0.03 to 0.19) |
| INF_STD + MTX | | 0.57 (0.28 to 1.21) | 0.58 (0.30 to 1.20) | –0.02 (–0.06 to 0.01) |
| CERTO_STD + MTX | | 1.19 (0.43 to 3.63) | 1.18 (0.45 to 3.26) | 0.01 (–0.04 to 0.10) |
| RIT_STD | | 0.60 (0.06 to 5.72) | 0.62 (0.06 to 4.61) | –0.02 (–0.07 to 0.18) |
| RIT_STD + MTX | | 1.02 (0.16 to 7.55) | 1.02 (0.17 to 5.75) | 0.001 (–0.06 to 0.23) |
| HD203 + MTX | | 1.18 (0.48 to 3.05) | 1.17 (0.50 to 2.75) | 0.01 (–0.03 to 0.09) |
| SB4 + MTX | | 1.10 (0.41 to 3.02) | 1.09 (0.43 to 2.73) | 0.01 (–0.04 to 0.09) |
| CT-P13 + MTX | | 0.74 (0.30 to 1.86) | 0.76 (0.32 to 1.80) | –0.01 (–0.06 to 0.03) |
| SB2 + MTX | | 0.57 (0.22 to 1.57) | 0.59 (0.23 to 1.53) | –0.02 (–0.07 to 0.02) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ABP501 + MTX | | 0.74 (0.19 to 3.26) | 0.75 (0.20 to 2.97) | –0.01 (–0.06 to 0.09) |
| ABA_STD (IV) + MTX | ETN_STD + MTX | 0.28 (0.12 to 0.64) | 0.29 (0.13 to 0.65) | –0.04 (–0.09 to –0.01) |
| ABA_STD (SC) + MTX | | 0.70 (0.23 to 2.60) | 0.72 (0.24 to 2.42) | –0.02 (–0.07 to 0.07) |
| TOF_STD + MTX | | 1.78 (0.66 to 5.06) | 1.69 (0.69 to 4.27) | 0.04 (–0.03 to 0.16) |
| ADA_STD + MTX | | 0.86 (0.32 to 2.82) | 0.87 (0.34 to 2.61) | –0.01 (–0.06 to 0.07) |
| TOC_4 (IV) | | 1.51 (0.33 to 7.52) | 1.46 (0.35 to 5.65) | 0.03 (–0.05 to 0.25) |
| TOC_8 (IV) | | 1.33 (0.43 to 4.90) | 1.30 (0.45 to 4.13) | 0.02 (–0.05 to 0.15) |
| TOC_4 (IV) + MTX | | 0.19 (0.01 to 1.82) | 0.20 (0.01 to 1.74) | –0.05 (–0.10 to 0.04) |
| TOC_8 (IV) + MTX | | 1.96 (0.62 to 7.71) | 1.84 (0.64 to 5.82) | 0.05 (–0.03 to 0.24) |
| GOL_STD (SC) + MTX | | 1.70 (0.52 to 5.71) | 1.63 (0.54 to 4.64) | 0.04 (–0.04 to 0.18) |
| INF_STD + MTX | | 0.51 (0.24 to 1.05) | 0.52 (0.26 to 1.05) | –0.03 (–0.08 to 0.002) |
| CERTO_STD + MTX | | 1.06 (0.38 to 3.14) | 1.06 (0.40 to 2.83) | 0.003 (–0.05 to 0.10) |
| RIT_STD | | 0.53 (0.05 to 5.04) | 0.55 (0.06 to 4.12) | –0.03 (–0.09 to 0.17) |
| RIT_STD + MTX | | 0.91 (0.14 to 6.83) | 0.92 (0.15 to 5.21) | –0.01 (–0.07 to 0.23) |
| HD203 + MTX | | 1.05 (0.48 to 2.38) | 1.04 (0.50 to 2.18) | 0.003 (–0.04 to 0.08) |
| SB4 + MTX | | 0.98 (0.40 to 2.36) | 0.98 (0.42 to 2.17) | –0.001 (–0.04 to 0.08) |
| CT-P13 + MTX | | 0.66 (0.26 to 1.63) | 0.67 (0.28 to 1.59) | –0.02 (–0.07 to 0.03) |
| SB2 + MTX | | 0.51 (0.19 to 1.37) | 0.53 (0.20 to 1.35) | –0.03 (–0.08 to 0.02) |
| ABP501 + MTX | | 0.65 (0.16 to 2.91) | 0.67 (0.17 to 2.66) | –0.02 (–0.08 to 0.08) |
| ABA_STD (SC) + MTX | ABA_STD (IV) + MTX | 2.58 (0.78 to 9.64) | 2.50 (0.79 to 8.68) | 0.03 (–0.01 to 0.10) |
| TOF_STD + MTX | | 6.35 (2.28 to 18.57) | 5.77 (2.21 to 15.34) | 0.09 (0.03 to 0.20) |
| ADA_STD + MTX | | 3.21 (1.08 to 10.12) | 3.07 (1.08 to 9.11) | 0.04 (0.002 to 0.11) |
| TOC_4 (IV) | | 5.54 (1.02 to 28.30) | 5.10 (1.02 to 20.34) | 0.07 (0.0005 to 0.29) |
| TOC_8 (IV) | | 4.83 (1.37 to 17.17) | 4.50 (1.36 to 13.97) | 0.06 (0.01 to 0.20) |
| TOC_4 (IV) + MTX | | 0.67 (0.03 to 6.84) | 0.68 (0.03 to 6.25) | –0.01 (–0.03 to 0.09) |
| TOC_8 (IV) + MTX | | 7.20 (2.06 to 26.59) | 6.46 (2.00 to 19.67) | 0.10 (0.02 to 0.28) |
| GOL_STD (SC) + MTX | | 6.08 (1.80 to 21.46) | 5.54 (1.76 to 16.87) | 0.08 (0.02 to 0.23) |
| INF_STD + MTX | | 1.81 (0.89 to 3.82) | 1.78 (0.89 to 3.70) | 0.01 (–0.003 to 0.03) |
| CERTO_STD + MTX | | 3.84 (1.26 to 11.63) | 3.64 (1.25 to 10.18) | 0.05 (0.01 to 0.14) |
| RIT_STD | | 1.90 (0.19 to 20.33) | 1.87 (0.19 to 15.86) | 0.02 (–0.02 to 0.22) |
| RIT_STD + MTX | | 3.21 (0.46 to 26.00) | 3.08 (0.47 to 18.84) | 0.04 (–0.01 to 0.27) |
| HD203 + MTX | | 3.81 (1.21 to 11.95) | 3.62 (1.21 to 10.34) | 0.05 (0.005 to 0.14) |
| SB4 + MTX | | 3.53 (1.05 to 12.17) | 3.36 (1.05 to 10.55) | 0.04 (0.001 to 0.14) |
| CT-P13 + MTX | | 2.40 (0.96 to 5.84) | 2.34 (0.96 to 5.48) | 0.02 (–0.001 to 0.07) |
| SB2 + MTX | | 1.84 (0.68 to 4.87) | 1.81 (0.68 to 4.63) | 0.01 (–0.01 to 0.05) |
| ABP501 + MTX | | 2.36 (0.58 to 10.81) | 2.30 (0.58 to 9.49) | 0.02 (–0.01 to 0.12) |
| TOF_STD + MTX | ABA_STD (SC) + MTX | 2.46 (0.81 to 7.52) | 2.30 (0.83 to 6.49) | 0.06 (–0.02 to 0.16) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ADA_STD + MTX | | 1.23 (0.70 to 2.19) | 1.22 (0.72 to 2.12) | 0.01 (–0.02 to 0.04) |
| TOC_4 (IV) | | 2.12 (0.31 to 13.79) | 2.00 (0.33 to 10.36) | 0.04 (–0.06 to 0.27) |
| TOC_8 (IV) | | 1.88 (0.38 to 9.09) | 1.81 (0.40 to 7.64) | 0.04 (–0.06 to 0.17) |
| TOC_4 (IV) + MTX | | 0.25 (0.01 to 3.22) | 0.26 (0.01 to 3.01) | –0.03 (–0.11 to 0.06) |
| TOC_8 (IV) + MTX | | 2.82 (0.54 to 14.38) | 2.59 (0.57 to 10.83) | 0.07 (–0.04 to 0.26) |
| GOL_STD (SC) + MTX | | 2.35 (0.54 to 10.32) | 2.21 (0.57 to 8.43) | 0.05 (–0.04 to 0.20) |
| INF_STD + MTX | | 0.71 (0.21 to 2.17) | 0.72 (0.23 to 2.12) | –0.01 (–0.09 to 0.02) |
| CERTO_STD + MTX | | 1.49 (0.36 to 6.16) | 1.45 (0.39 to 5.46) | 0.02 (–0.06 to 0.12) |
| RIT_STD | | 0.75 (0.06 to 8.70) | 0.76 (0.06 to 7.01) | –0.01 (–0.10 to 0.19) |
| RIT_STD + MTX | | 1.27 (0.14 to 11.99) | 1.25 (0.15 to 8.97) | 0.01 (–0.08 to 0.25) |
| HD203 + MTX | | 1.50 (0.33 to 5.78) | 1.47 (0.35 to 5.15) | 0.02 (–0.07 to 0.12) |
| SB4 + MTX | | 1.39 (0.30 to 5.74) | 1.36 (0.32 to 5.13) | 0.02 (–0.07 to 0.12) |
| CT-P13 + MTX | | 0.94 (0.24 to 3.15) | 0.94 (0.26 to 3.00) | –0.002 (–0.08 to 0.05) |
| SB2 + MTX | | 0.72 (0.17 to 2.61) | 0.73 (0.18 to 2.51) | –0.01 (–0.09 to 0.04) |
| ABP501 + MTX | | 0.93 (0.30 to 2.70) | 0.93 (0.32 to 2.53) | –0.003 (–0.06 to 0.06) |
| ADA_STD + MTX | TOF_STD + MTX | 0.50 (0.19 to 1.28) | 0.53 (0.21 to 1.25) | –0.05 (–0.15 to 0.02) |
| TOC_4 (IV) | | 0.85 (0.15 to 4.75) | 0.87 (0.17 to 3.70) | –0.01 (–0.15 to 0.21) |
| TOC_8 (IV) | | 0.75 (0.19 to 3.12) | 0.78 (0.22 to 2.73) | –0.02 (–0.15 to 0.12) |
| TOC_4 (IV) + MTX | | 0.11 (0.005 to 1.14) | 0.12 (0.01 to 1.13) | –0.09 (–0.20 to 0.01) |
| TOC_8 (IV) + MTX | | 1.12 (0.27 to 4.97) | 1.11 (0.32 to 3.89) | 0.01 (–0.13 to 0.21) |
| GOL_STD (SC) + MTX | | 0.94 (0.24 to 3.71) | 0.95 (0.28 to 3.15) | –0.01 (–0.14 to 0.15) |
| INF_STD + MTX | | 0.28 (0.10 to 0.77) | 0.31 (0.12 to 0.78) | –0.07 (–0.18 to –0.01) |
| CERTO_STD + MTX | | 0.60 (0.17 to 2.14) | 0.63 (0.20 to 1.98) | –0.04 (–0.15 to 0.07) |
| RIT_STD | | 0.30 (0.03 to 3.30) | 0.33 (0.03 to 2.78) | –0.07 (–0.18 to 0.14) |
| RIT_STD + MTX | | 0.51 (0.07 to 4.58) | 0.54 (0.08 to 3.55) | –0.05 (–0.17 to 0.20) |
| HD203 + MTX | | 0.59 (0.16 to 2.16) | 0.62 (0.19 to 2.00) | –0.04 (–0.15 to 0.07) |
| SB4 + MTX | | 0.55 (0.14 to 2.13) | 0.58 (0.17 to 1.97) | –0.04 (–0.16 to 0.07) |
| CT-P13 + MTX | | 0.37 (0.12 to 1.16) | 0.40 (0.14 to 1.15) | –0.06 (–0.18 to 0.01) |
| SB2 + MTX | | 0.29 (0.08 to 0.95) | 0.31 (0.10 to 0.96) | –0.07 (–0.18 to –0.003) |
| ABP501 + MTX | | 0.38 (0.09 to 1.41) | 0.41 (0.11 to 1.36) | –0.06 (–0.16 to 0.03) |
| TOC_4 (IV) | ADA_STD + MTX | 1.73 (0.27 to 10.02) | 1.65 (0.29 to 7.52) | 0.04 (–0.07 to 0.26) |
| TOC_8 (IV) | | 1.52 (0.33 to 6.59) | 1.48 (0.36 to 5.53) | 0.03 (–0.07 to 0.16) |
| TOC_4 (IV) + MTX | | 0.20 (0.01 to 2.36) | 0.22 (0.01 to 2.23) | –0.04 (–0.11 to 0.05) |
| TOC_8 (IV) + MTX | | 2.26 (0.50 to 10.55) | 2.10 (0.53 to 7.98) | 0.06 (–0.05 to 0.25) |
| GOL_STD (SC) + MTX | | 1.90 (0.49 to 7.69) | 1.80 (0.51 to 6.27) | 0.04 (–0.05 to 0.19) |
| INF_STD + MTX | | 0.58 (0.19 to 1.58) | 0.59 (0.21 to 1.56) | –0.02 (–0.10 to 0.02) |
| CERTO_STD + MTX | | 1.21 (0.33 to 4.47) | 1.19 (0.35 to 4.00) | 0.01 (–0.07 to 0.11) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| RIT_STD | | 0.60 (0.05 to 6.82) | 0.62 (0.05 to 5.48) | –0.02 (–0.10 to 0.19) |
| RIT_STD + MTX | | 1.03 (0.12 to 9.01) | 1.03 (0.14 to 6.70) | 0.001 (–0.09 to 0.24) |
| HD203 + MTX | | 1.21 (0.30 to 4.25) | 1.19 (0.32 to 3.81) | 0.01 (–0.08 to 0.11) |
| SB4 + MTX | | 1.13 (0.27 to 4.26) | 1.12 (0.29 to 3.78) | 0.01 (–0.08 to 0.11) |
| CT-P13 + MTX | | 0.76 (0.22 to 2.30) | 0.77 (0.24 to 2.21) | –0.01 (–0.09 to 0.04) |
| SB2 + MTX | | 0.58 (0.15 to 1.90) | 0.60 (0.17 to 1.85) | –0.02 (–0.10 to 0.03) |
| ABP501 + MTX | | 0.75 (0.29 to 1.83) | 0.77 (0.30 to 1.74) | –0.01 (–0.06 to 0.05) |
| TOC_8 (IV) | TOC_4 (IV) | 0.87 (0.25 to 3.11) | 0.88 (0.30 to 2.88) | –0.01 (–0.18 to 0.08) |
| TOC_4 (IV) + MTX | | 0.13 (0.005 to 1.20) | 0.14 (0.01 to 1.19) | –0.07 (–0.28 to 0.01) |
| TOC_8 (IV) + MTX | | 1.30 (0.39 to 4.82) | 1.26 (0.46 to 4.23) | 0.02 (–0.13 to 0.15) |
| GOL_STD (SC) + MTX | | 1.11 (0.17 to 7.31) | 1.10 (0.22 to 6.16) | 0.01 (–0.22 to 0.17) |
| INF_STD + MTX | | 0.33 (0.07 to 1.55) | 0.35 (0.09 to 1.52) | –0.06 (–0.28 to 0.01) |
| CERTO_STD + MTX | | 0.70 (0.12 to 3.89) | 0.72 (0.16 to 3.57) | –0.03 (–0.24 to 0.09) |
| RIT_STD | | 0.33 (0.03 to 4.58) | 0.36 (0.03 to 3.96) | –0.05 (–0.27 to 0.13) |
| RIT_STD + MTX | | 0.62 (0.06 to 6.43) | 0.65 (0.07 to 5.20) | –0.03 (–0.25 to 0.20) |
| HD203 + MTX | | 0.69 (0.12 to 3.90) | 0.72 (0.15 to 3.56) | –0.02 (–0.25 to 0.09) |
| SB4 + MTX | | 0.64 (0.11 to 3.69) | 0.67 (0.14 to 3.37) | –0.03 (–0.24 to 0.09) |
| CT-P13 + MTX | | 0.43 (0.08 to 2.28) | 0.46 (0.11 to 2.20) | –0.05 (–0.27 to 0.03) |
| SB2 + MTX | | 0.34 (0.06 to 1.79) | 0.36 (0.08 to 1.75) | –0.06 (–0.28 to 0.02) |
| ABP501 + MTX | | 0.44 (0.06 to 3.43) | 0.47 (0.08 to 3.17) | –0.05 (–0.27 to 0.07) |
| TOC_4 (IV) + MTX | TOC_8 (IV) | 0.15 (0.01 to 1.10) | 0.16 (0.01 to 1.09) | –0.06 (–0.19 to 0.01) |
| TOC_8 (IV) + MTX | | 1.50 (0.87 to 2.63) | 1.43 (0.88 to 2.36) | 0.03 (–0.01 to 0.13) |
| GOL_STD (SC) + MTX | | 1.27 (0.25 to 6.47) | 1.24 (0.30 to 5.35) | 0.02 (–0.14 to 0.18) |
| INF_STD + MTX | | 0.38 (0.11 to 1.15) | 0.40 (0.14 to 1.14) | –0.05 (–0.18 to 0.01) |
| CERTO_STD + MTX | | 0.80 (0.19 to 3.34) | 0.81 (0.22 to 3.02) | –0.02 (–0.15 to 0.09) |
| RIT_STD | | 0.39 (0.04 to 3.98) | 0.41 (0.04 to 3.38) | –0.04 (–0.18 to 0.15) |
| RIT_STD + MTX | | 0.69 (0.08 to 5.55) | 0.71 (0.09 to 4.43) | –0.02 (–0.17 to 0.21) |
| HD203 + MTX | | 0.78 (0.17 to 3.30) | 0.80 (0.21 to 2.99) | –0.02 (–0.16 to 0.09) |
| SB4 + MTX | | 0.74 (0.15 to 3.15) | 0.76 (0.18 to 2.86) | –0.02 (–0.16 to 0.09) |
| CT-P13 + MTX | | 0.49 (0.13 to 1.72) | 0.52 (0.16 to 1.67) | –0.04 (–0.17 to 0.03) |
| SB2 + MTX | | 0.39 (0.09 to 1.41) | 0.41 (0.11 to 1.39) | –0.05 (–0.18 to 0.02) |
| ABP501 + MTX | | 0.49 (0.08 to 2.81) | 0.52 (0.10 to 2.61) | –0.04 (–0.18 to 0.07) |
| TOC_8 (IV) + MTX | TOC_4 (IV) + MTX | *10.45 (1.34 to 247.30)* | *9.14 (1.30 to 211.80)* | *0.10 (0.02 to 0.27)* |
| GOL_STD (SC) + MTX | | *9.58 (0.72 to 206.80)* | *8.61 (0.74 to 177.90)* | *0.08 (–0.02 to 0.23)* |
| INF_STD + MTX | | 2.71 (0.28 to 61.91) | 2.66 (0.30 to 59.72) | 0.02 (–0.07 to 0.05) |
| CERTO_STD + MTX | | *5.82 (0.54 to 137.70)* | *5.45 (0.56 to 125.10)* | *0.05 (–0.04 to 0.14)* |
| RIT_STD | | 3.09 (0.11 to 88.47) | 2.99 (0.12 to 76.96) | 0.02 (–0.07 to 0.21) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| RIT_STD + MTX | | *5.37 (0.24 to 158.60)* | *5.03 (0.26 to 135.20)* | *0.04 (–0.06 to 0.27)* |
| HD203 + MTX | | *5.83 (0.48 to 134.00)* | *5.46 (0.51 to 122.00)* | *0.05 (–0.04 to 0.15)* |
| SB4 + MTX | | *5.45 (0.43 to 119.50)* | *5.11 (0.46 to 109.60)* | *0.05 (–0.05 to 0.15)* |
| CT-P13 + MTX | | 3.54 (0.34 to 84.59) | 3.42 (0.37 to 80.10) | 0.03 (–0.06 to 0.07) |
| SB2 + MTX | | 2.76 (0.25 to 65.02) | 2.69 (0.27 to 62.26) | 0.02 (–0.07 to 0.06) |
| ABP501 + MTX | | 3.67 (0.26 to 91.99) | 3.53 (0.28 to 84.80) | 0.03 (–0.06 to 0.12) |
| GOL_STD (SC) + MTX | TOC_8 (IV) + MTX | 0.84 (0.16 to 4.32) | 0.86 (0.21 to 3.64) | –0.02 (–0.22 to 0.16) |
| INF_STD + MTX | | 0.26 (0.07 to 0.78) | 0.28 (0.10 to 0.79) | –0.08 (–0.27 to –0.01) |
| CERTO_STD + MTX | | 0.53 (0.12 to 2.29) | 0.56 (0.16 to 2.12) | –0.05 (–0.24 to 0.07) |
| RIT_STD | | 0.26 (0.02 to 2.73) | 0.29 (0.03 to 2.38) | –0.08 (–0.26 to 0.12) |
| RIT_STD + MTX | | 0.47 (0.05 to 3.86) | 0.50 (0.06 to 3.14) | –0.05 (–0.25 to 0.18) |
| HD203 + MTX | | 0.53 (0.11 to 2.32) | 0.57 (0.15 to 2.13) | –0.05 (–0.24 to 0.07) |
| SB4 + MTX | | 0.50 (0.10 to 2.17) | 0.53 (0.12 to 2.02) | –0.05 (–0.25 to 0.07) |
| CT-P13 + MTX | | 0.33 (0.08 to 1.17) | 0.36 (0.11 to 1.16) | –0.07 (–0.26 to 0.01) |
| SB2 + MTX | | 0.26 (0.06 to 0.96) | 0.28 (0.08 to 0.96) | –0.08 (–0.27 to –0.002) |
| ABP501 + MTX | | 0.33 (0.05 to 1.88) | 0.36 (0.07 to 1.77) | –0.07 (–0.27 to 0.05) |
| INF_STD + MTX | GOL_STD (SC) + MTX | 0.30 (0.09 to 0.93) | 0.32 (0.12 to 0.94) | –0.07 (–0.21 to –0.003) |
| CERTO_STD + MTX | | 0.64 (0.15 to 2.56) | 0.66 (0.18 to 2.37) | –0.03 (–0.18 to 0.07) |
| RIT_STD | | 0.32 (0.03 to 3.44) | 0.35 (0.03 to 2.92) | –0.06 (–0.21 to 0.14) |
| RIT_STD + MTX | | 0.52 (0.07 to 4.64) | 0.55 (0.08 to 3.73) | –0.04 (–0.19 to 0.19) |
| HD203 + MTX | | 0.62 (0.15 to 2.64) | 0.65 (0.18 to 2.42) | –0.03 (–0.18 to 0.08) |
| SB4 + MTX | | 0.59 (0.13 to 2.58) | 0.61 (0.16 to 2.36) | –0.04 (–0.19 to 0.08) |
| CT-P13 + MTX | | 0.39 (0.11 to 1.37) | 0.42 (0.14 to 1.34) | –0.06 (–0.20 to 0.02) |
| SB2 + MTX | | 0.30 (0.08 to 1.11) | 0.33 (0.10 to 1.10) | –0.07 (–0.21 to 0.01) |
| ABP501 + MTX | | 0.39 (0.07 to 2.12) | 0.42 (0.09 to 2.00) | –0.06 (–0.20 to 0.06) |
| CERTO_STD + MTX | INF_STD + MTX | 2.09 (0.76 to 6.23) | 2.02 (0.77 to 5.44) | 0.03 (–0.01 to 0.13) |
| RIT_STD | | 1.06 (0.10 to 9.98) | 1.05 (0.11 to 7.92) | 0.002 (–0.04 to 0.20) |
| RIT_STD + MTX | | 1.79 (0.27 to 13.38) | 1.74 (0.28 to 9.89) | 0.02 (–0.03 to 0.26) |
| HD203 + MTX | | 2.09 (0.72 to 6.22) | 2.02 (0.73 to 5.45) | 0.03 (–0.01 to 0.13) |
| SB4 + MTX | | 1.94 (0.60 to 6.18) | 1.88 (0.61 to 5.40) | 0.03 (–0.02 to 0.13) |
| CT-P13 + MTX | | 1.31 (0.76 to 2.26) | 1.30 (0.76 to 2.16) | 0.01 (–0.01 to 0.04) |
| SB2 + MTX | | 1.01 (0.51 to 1.98) | 1.01 (0.52 to 1.91) | 0.0003 (–0.02 to 0.03) |
| ABP501 + MTX | | 1.28 (0.33 to 5.50) | 1.27 (0.34 to 4.91) | 0.01 (–0.03 to 0.11) |
| RIT_STD | CERTO_STD + MTX | 0.50 (0.05 to 5.53) | 0.52 (0.05 to 4.50) | –0.03 (–0.13 to 0.17) |
| RIT_STD + MTX | | 0.85 (0.11 to 7.22) | 0.86 (0.12 to 5.61) | –0.01 (–0.11 to 0.22) |
| HD203 + MTX | | 0.99 (0.26 to 3.70) | 0.99 (0.29 to 3.33) | –0.001 (–0.10 to 0.10) |
| SB4 + MTX | | 0.91 (0.24 to 3.65) | 0.92 (0.26 to 3.27) | –0.01 (–0.10 to 0.10) |

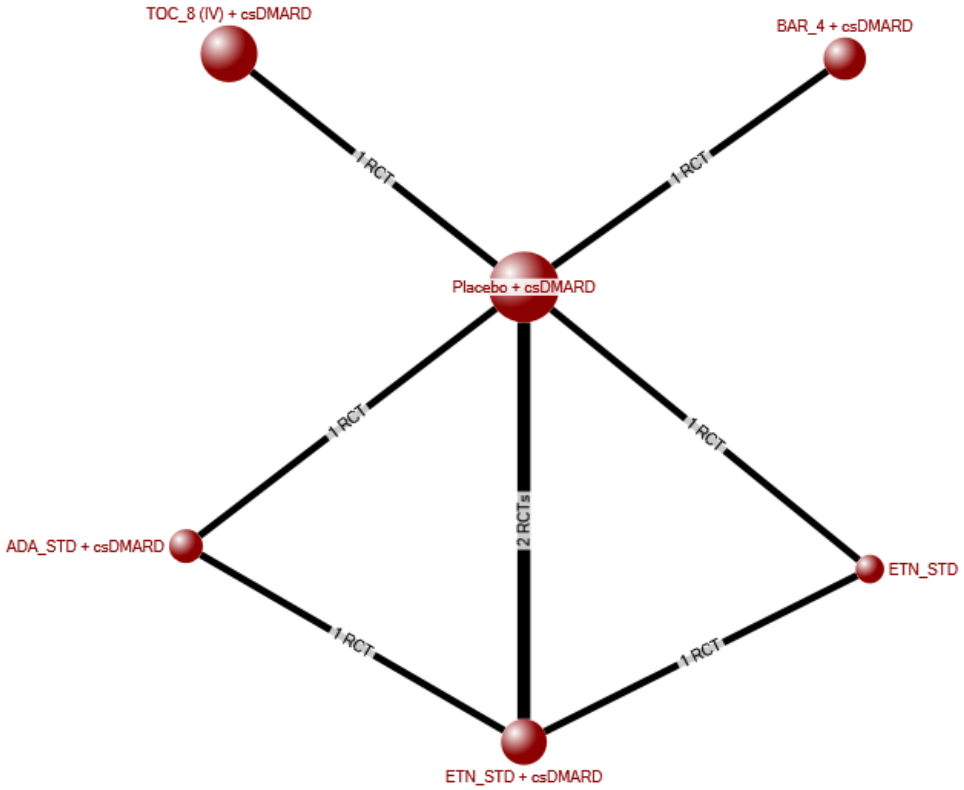
| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| CT-P13 + MTX | | 0.63 (0.19 to 1.97) | 0.64 (0.21 to 1.90) | –0.02 (–0.12 to 0.03) |
| SB2 + MTX | | 0.48 (0.14 to 1.60) | 0.50 (0.15 to 1.56) | –0.03 (–0.13 to 0.02) |
| ABP501 + MTX | | 0.62 (0.12 to 3.14) | 0.64 (0.14 to 2.86) | –0.02 (–0.12 to 0.08) |
| RIT_STD + MTX | RIT_STD | 1.72 (0.24 to 16.85) | 1.66 (0.27 to 15.07) | 0.02 (–0.10 to 0.18) |
| HD203 + MTX | | 2.00 (0.19 to 21.80) | 1.93 (0.23 to 19.64) | 0.03 (–0.17 to 0.13) |
| SB4 + MTX | | 1.87 (0.17 to 20.70) | 1.81 (0.21 to 18.77) | 0.02 (–0.18 to 0.13) |
| CT-P13 + MTX | | 1.25 (0.12 to 13.60) | 1.24 (0.15 to 12.84) | 0.01 (–0.19 to 0.06) |
| SB2 + MTX | | 0.94 (0.09 to 11.46) | 0.94 (0.12 to 11.00) | –0.002 (–0.20 to 0.05) |
| ABP501 + MTX | | 1.25 (0.09 to 18.43) | 1.24 (0.11 to 16.81) | 0.01 (–0.19 to 0.11) |
| HD203 + MTX | RIT_STD + MTX | 1.16 (0.14 to 8.71) | 1.15 (0.18 to 7.85) | 0.01 (–0.22 to 0.11) |
| SB4 + MTX | | 1.07 (0.12 to 9.16) | 1.06 (0.16 to 8.14) | 0.003 (–0.23 to 0.12) |
| CT-P13 + MTX | | 0.73 (0.09 to 5.10) | 0.74 (0.12 to 4.86) | –0.01 (–0.25 to 0.05) |
| SB2 + MTX | | 0.56 (0.07 to 4.29) | 0.58 (0.09 to 4.14) | –0.02 (–0.26 to 0.04) |
| ABP501 + MTX | | 0.73 (0.07 to 7.22) | 0.74 (0.09 to 6.62) | –0.01 (–0.25 to 0.10) |
| SB4 + MTX | HD203 + MTX | 0.93 (0.29 to 3.08) | 0.94 (0.31 to 2.83) | –0.004 (–0.09 to 0.08) |
| CT-P13 + MTX | | 0.63 (0.18 to 2.04) | 0.64 (0.20 to 1.97) | –0.02 (–0.12 to 0.03) |
| SB2 + MTX | | 0.48 (0.14 to 1.72) | 0.50 (0.16 to 1.68) | –0.03 (–0.13 to 0.02) |
| ABP501 + MTX | | 0.62 (0.13 to 3.31) | 0.64 (0.15 to 3.03) | –0.02 (–0.12 to 0.08) |
| CT-P13 + MTX | SB4 + MTX | 0.68 (0.19 to 2.47) | 0.69 (0.21 to 2.37) | –0.02 (–0.12 to 0.04) |
| SB2 + MTX | | 0.52 (0.14 to 1.91) | 0.54 (0.15 to 1.86) | –0.03 (–0.13 to 0.03) |
| ABP501 + MTX | | 0.67 (0.13 to 3.76) | 0.68 (0.15 to 3.41) | –0.02 (–0.12 to 0.09) |
| SB2 + MTX | CT-P13 + MTX | 0.77 (0.32 to 1.84) | 0.78 (0.33 to 1.79) | –0.01 (–0.05 to 0.03) |
| ABP501 + MTX | | 0.98 (0.23 to 4.70) | 0.98 (0.24 to 4.21) | –0.001 (–0.05 to 0.10) |
| ABP501 + MTX | SB2 + MTX | 1.28 (0.28 to 6.41) | 1.27 (0.30 to 5.70) | 0.01 (–0.04 to 0.11) |
| | | | | |
| Random-Effects Model | Residual Deviance | 68.49 vs. 75 data points | | |
| | Deviance Information Criteria | 394.513 | | |
| Fixed-Effect Model | Residual Deviance | 68.68 vs 75 data points | | |
| | Deviance Information Criteria | 393.243 | | |

ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; CERTO = certolizumab pegol; CrI = credible interval; CT-P13 = biosimilar infliximab; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; GOL = golimumab; HD203 = etanercept biosimilar; INF = infliximab; IV = intravenous; MTX = methotrexate; OR = odds ratio; RD = risk difference; RIT = rituximab; RR = relative risk; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator. Italicized results indicate a wide credible interval.

*Conventional Synthetic DMARD as a Common Comparator*

Six studies (five two-arm studies and one three-arm study)[101,144,151,163,172,249] were included that reported on the number of participants who developed SAEs. The evidence network involved 1,780 participants and six treatments, forming eight direct comparisons. Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in Figure 20; the odds ratios for all treatment comparisons with csDMARD monotherapy as the common comparator are available in Table 25. A staircase table of the results as odds ratios is presented in Appendix 10 (Table 97).

## Figure 20: Evidence Network: Serious Adverse Events (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




ADA = adalimumab; BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; IV = intravenous; RCT = randomized controlled trial; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab.

Participants receiving 4 mg of baricitinib in combination with csDMARD had statistically significantly lower odds of developing an SAE when compared with participants receiving adalimumab in combination with csDMARD (odds ratio = 0.10; 95% CrI, 0.01 to 0.87) and compared with etanercept in combination with csDMARD (odds ratio = 0.09; 95% CrI, 0.01 to 0.75). There were no other statistically significant comparisons of any treatments

compared with one another or with csDMARD monotherapy (Table 25). A staircase table of the results as odds ratios is also presented in Appendix 10.

## Table 25: Serious Adverse Events (Placebo + csDMARD): Odds Ratios, Relative Risks, and Risk Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ADA_STD + csDMARD | Placebo + csDMARD | 2.17 (0.55 to 11.04) | 2.10 (0.56 to 9.57) | 0.03 (–0.02 to 0.14) |
| ETN_STD | | 1.26 (0.19 to 8.74) | 1.25 (0.20 to 7.74) | 0.01 (–0.03 to 0.12) |
| ETN_STD + csDMARD | | 2.35 (0.67 to 9.82) | 2.27 (0.68 to 8.70) | 0.03 (–0.01 to 0.12) |
| TOC_8 (IV) + csDMARD | | 1.44 (0.53 to 4.06) | 1.43 (0.54 to 3.77) | 0.01 (–0.01 to 0.07) |
| BAR_4 + csDMARD | | 0.22 (0.02 to 1.13) | 0.22 (0.03 to 1.13) | –0.02 (–0.04 to 0.003) |
| ETN_STD | ADA_STD + csDMARD | 0.58 (0.07 to 3.89) | 0.59 (0.08 to 3.58) | –0.02 (–0.12 to 0.08) |
| ETN_STD + csDMARD | | 1.07 (0.32 to 3.61) | 1.07 (0.35 to 3.37) | 0.00 (–0.08 to 0.07) |
| TOC_8 (IV) + csDMARD | | 0.67 (0.10 to 3.79) | 0.68 (0.11 to 3.55) | –0.02 (–0.13 to 0.06) |
| BAR_4 + csDMARD | | 0.10 (0.01 to 0.87) | 0.10 (0.01 to 0.87) | –0.05 (–0.15 to –0.003) |
| ETN_STD + csDMARD | ETN_STD | 1.84 (0.39 to 10.80) | 1.79 (0.42 to 10.06) | 0.02 (–0.07 to 0.09) |
| TOC_8 (IV) + csDMARD | | 1.15 (0.13 to 10.24) | 1.15 (0.15 to 9.50) | 0.004 (–0.11 to 0.08) |
| BAR_4 + csDMARD | | 0.16 (0.01 to 2.26) | 0.17 (0.01 to 2.23) | –0.02 (–0.13 to 0.01) |
| TOC_8 (IV) + csDMARD | ETN_STD + csDMARD | 0.62 (0.11 to 3.09) | 0.63 (0.12 to 2.90) | –0.02 (–0.11 to 0.06) |
| BAR_4 + csDMARD | | 0.09 (0.01 to 0.75) | 0.09 (0.01 to 0.76) | –0.05 (–0.13 to –0.01) |
| BAR_4 + csDMARD | TOC_8 (IV) + csDMARD | 0.15 (0.01 to 1.02) | 0.15 (0.01 to 1.02) | –0.03 (–0.10 to 0.0004) |
| | | | | |
| Random-Effects Model | Residual Deviance | 11.6 vs. 13 data points | | |
| | Deviance Information Criteria | 64.912 | | |
| Fixed-Effect Model | Residual Deviance | 11.59 vs 13 data points | | |
| | Deviance Information Criteria | 64.838 | | |

ADA = adalimumab; BAR_4 = 4 mg baricitinib; CrI = credible interval; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; IV = intravenous; OR = odds ratio; RD = risk difference; RR = relative risk; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator.

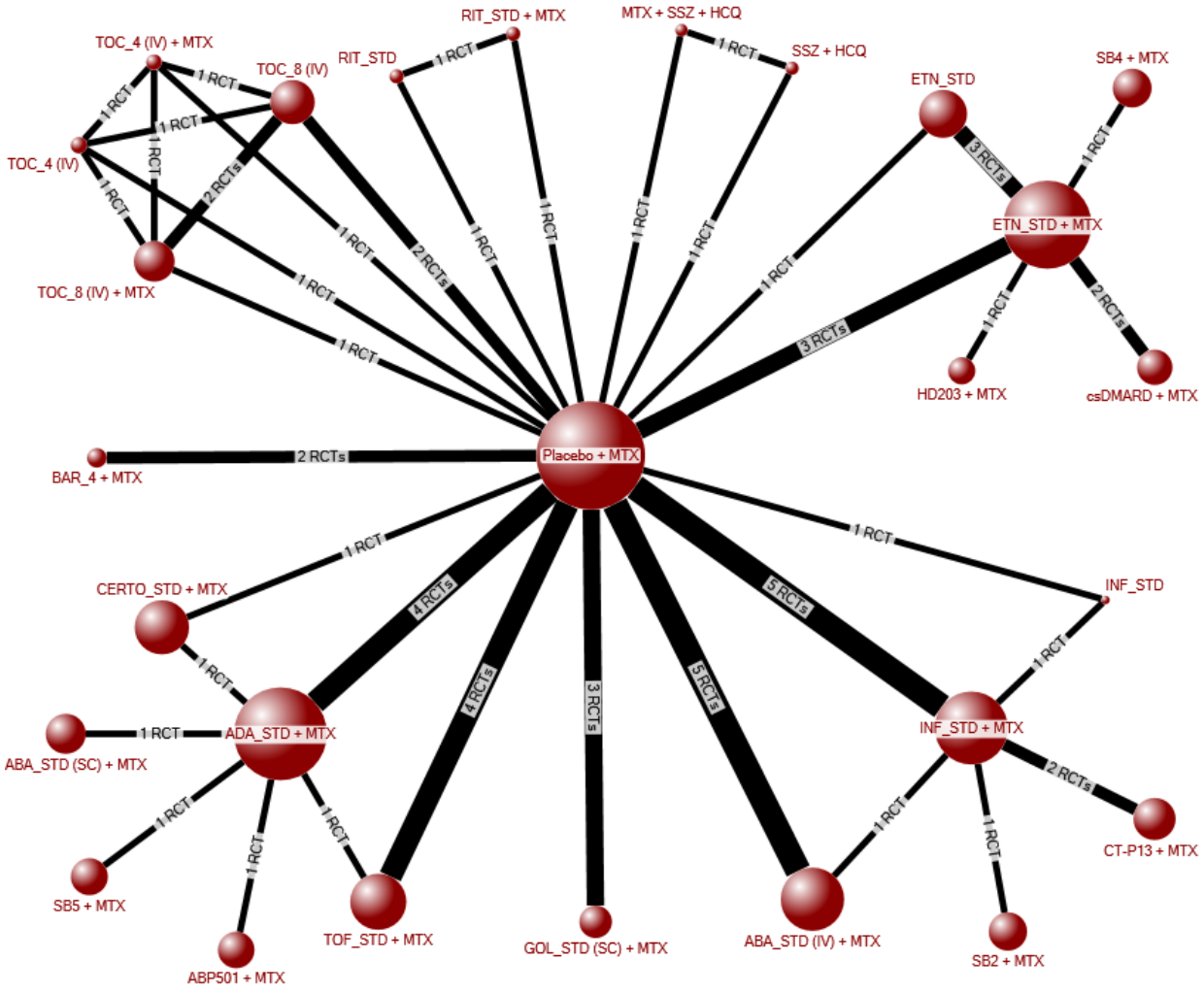
### Withdrawal due to Adverse Events

#### *Methotrexate as a Common Comparator*

A total of 43 studies[95,99,100,128,130,132,136,138,139,145,150,155,167,171,175,178,179,186,188,190,191,194,195,198,199,204,205,213,216,218,224,226,227,229,230,233,234,236,237,243,244,251,253] were included in the reference case NMA for the number of withdrawal due to adverse events (WDAEs) among inadequate responders to MTX. There were 64 direct comparisons in the evidence network based on 27 treatments. The studies consisted of 36 two-arm studies, six three-arm studies, and one five-arm study. The total number of participants contributing to the evidence network was 11,746. Assessment for consistency demonstrated that the model was consistent. A geometric

illustration of the evidence network is presented in Figure 21. The odds ratios for all treatment comparisons with placebo as the common comparator are available in Table 26.

## Figure 21: Evidence Network: Withdrawal due to Adverse Events (Placebo + Methotrexate)




ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; CT-P13 = biosimilar infliximab; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; HD203 = biosimilar etanercept; INF = infliximab; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; RIT = rituximab; SB2 = biosimilar infliximab; SB4 = biosimilar of etanercept; SB5 = biosimilar adalimumab; SC = subcutaneous; SSZ = sulfasalazine; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib.

There was insufficient evidence to detect a statistically significant difference in the odds of WDAEs for all treatments compared with MTX monotherapy, except for SB2 (biosimilar infliximab), which had higher odds of WDAEs in comparison with MTX monotherapy (odds ratio = 3.35; 95% CrI, 1.03 to 9.77).

Among the direct treatment comparisons, both etanercept in combination with MTX and biosimilar etanercept in combination with MTX (SB4) had lower odds of WDAEs compared with csDMARDs in combination with MTX (odds ratio = 0.33; 95% CrI, 0.11 to 0.89 and odds ratio = 0.25; 95% CrI, 0.06, 0.92). Tofacitinib in combination with MTX had higher odds of WDAEs compared with: etanercept in combination with MTX (odds ratio = 2.77; 95% CrI, 1.13, 6.58), SB4 (biosimilar etanercept) in combination with MTX (odds ratio = 0.28; 95% CrI, 0.08, 0.92), and SB5 (biosimilar adalimumab) in combination with MTX (odds ratio = 0.14; 95% CrI, 0.02, 0.81).

Both adalimumab in combination with MTX, and tofacitinib in combination with MTX, had higher odds of WDAEs compared with abatacept (SC) in combination with MTX (odds ratio = 2.91 [95% CrI, 1.27 to 6.84] and odds ratio = 4.30 [95% CrI, 1.34 to 14.22], respectively) (Table 26).

SB2 (biosimilar infliximab) in combination with MTX had higher odds of WDAEs compared with: SSZ and HCQ; triple-csDMARD therapy with MTX, SSZ, and HCQ; etanercept monotherapy and combination therapy with MTX; abatacept (IV and SC) in combination with MTX; 4 mg baricitinib in combination with MTX; HD203 (biosimilar etanercept) in combination with MTX; SB4 (biosimilar etanercept); and SB5 (biosimilar adalimumab) in combination with MTX. Another biosimilar, ABP501 (biosimilar adalimumab) in combination with MTX, had higher odds of WDAEs when compared with: double-csDMARD therapy with SSZ and HCQ, abatacept (SC) in combination with MTX, and SB5 (biosimilar adalimumab) in combination with MTX. Interestingly, SB5 (biosimilar adalimumab) in combination with MTX demonstrated statistically significantly lower odds of WDAEs compared with adalimumab in combination with MTX (odds ratio = 0.21; 95% CrI, 0.03 to 0.95) (Table 26).

## Table 26: Withdrawal Due to Adverse Events (Placebo + Methotrexate): Odds Ratios, Relative Risks, and Risk Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| csDMARD + MTX | Placebo + MTX | 2.03 (0.65 to 6.95) | 1.96 (0.66 to 5.80) | 0.03 (–0.01 to 0.16) |
| SSZ + HCQ | | 0.36 (0.06 to 1.66) | 0.37 (0.07 to 1.63) | –0.02 (–0.03 to 0.02) |
| MTX + SSZ + HCQ | | 0.42 (0.07 to 1.81) | 0.43 (0.08 to 1.76) | –0.02 (–0.03 to 0.02) |
| ETN_STD | | 0.79 (0.44 to 1.49) | 0.80 (0.45 to 1.47) | –0.01 (–0.02 to 0.02) |
| ETN_STD + MTX | | 0.68 (0.37 to 1.22) | 0.68 (0.38 to 1.21) | –0.01 (–0.02 to 0.01) |
| ABA STD (IV) + MTX | | 0.75 (0.36 to 1.56) | 0.75 (0.37 to 1.54) | –0.01 (–0.02 to 0.02) |
| ABA_STD (SC) + MTX | | 0.43 (0.14 to 1.35) | 0.44 (0.14 to 1.34) | –0.02 (–0.03 to 0.01) |
| ADA_STD + MTX | | 1.27 (0.60 to 2.75) | 1.26 (0.61 to 2.61) | 0.01 (–0.01 to 0.05) |
| TOF_STD + MTX | | 1.87 (0.96 to 3.62) | 1.82 (0.96 to 3.35) | 0.03 (–0.001 to 0.07) |
| TOC_4 (IV) | | 1.29 (0.32 to 5.44) | 1.28 (0.33 to 4.76) | 0.01 (–0.02 to 0.12) |
| TOC_8 (IV) | | 0.98 (0.31 to 3.00) | 0.98 (0.32 to 2.82) | –0.001 (–0.02 to 0.06) |
| TOC_4 (IV) + MTX | | 1.42 (0.37 to 6.17) | 1.40 (0.37 to 5.29) | 0.01 (–0.02 to 0.13) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| TOC_8 (IV) + MTX | | 1.43 (0.41 to 4.87) | 1.41 (0.41 to 4.36) | 0.01 (–0.02 to 0.11) |
| GOL_STD (SC) + MTX | | 1.04 (0.35 to 3.05) | 1.04 (0.36 to 2.87) | 0.001 (–0.02 to 0.06) |
| INF_STD + MTX | | 1.44 (0.69 to 2.87) | 1.42 (0.70 to 2.71) | 0.01 (–0.01 to 0.05) |
| INF_STD | | *3.01 (0.09 to 227.00)* | *2.82 (0.09 to 29.48)* | *0.06 (–0.03 to 0.85)* |
| CERTO_STD + MTX | | 1.12 (0.45 to 2.78) | 1.11 (0.46 to 2.63) | 0.004 (–0.02 to 0.05) |
| RIT_STD | | 2.73 (0.21 to 64.44) | 2.59 (0.22 to 21.99) | 0.05 (–0.03 to 0.64) |
| RIT_STD + MTX | | 1.00 (0.01 to 30.70) | 1.00 (0.01 to 15.91) | 0.0001 (–0.04 to 0.47) |
| BAR_4 + MTX | | 0.32 (0.02 to 2.00) | 0.32 (0.02 to 1.94) | –0.02 (–0.04 to 0.03) |
| HD203 + MTX | | 0.60 (0.19 to 1.95) | 0.61 (0.19 to 1.89) | –0.01 (–0.03 to 0.03) |
| SB4 + MTX | | 0.52 (0.19 to 1.42) | 0.53 (0.19 to 1.40) | –0.02 (–0.03 to 0.01) |
| CT-P13 + MTX | | 1.24 (0.49 to 3.08) | 1.23 (0.50 to 2.89) | 0.01 (–0.02 to 0.06) |
| SB2 + MTX | | 3.35 (1.03 to 9.77) | 3.11 (1.03 to 7.69) | 0.07 (0.001 to 0.21) |
| SB5 + MTX | | 0.26 (0.03 to 1.46) | 0.26 (0.03 to 1.44) | –0.02 (–0.04 to 0.01) |
| ABP501 + MTX | | 3.15 (0.64 to 17.95) | 2.94 (0.65 to 11.55) | 0.06 (–0.01 to 0.35) |
| SSZ + HCQ | csDMARD + MTX | 0.17 (0.02 to 1.17) | 0.18 (0.03 to 1.16) | –0.05 (–0.18 to 0.005) |
| MTX + SSZ + HCQ | | 0.20 (0.03 to 1.35) | 0.21 (0.03 to 1.33) | –0.05 (–0.18 to 0.01) |
| ETN_STD | | 0.39 (0.12 to 1.18) | 0.41 (0.14 to 1.18) | –0.04 (–0.16 to 0.004) |
| ETN_STD + MTX | | 0.33 (0.11 to 0.89) | 0.35 (0.13 to 0.89) | –0.04 (–0.16 to –0.003) |
| ABA_STD (IV) + MTX | | 0.37 (0.09 to 1.47) | 0.38 (0.11 to 1.45) | –0.04 (–0.17 to 0.01) |
| ABA_STD (SC) + MTX | | 0.21 (0.04 to 1.03) | 0.23 (0.05 to 1.03) | –0.05 (–0.18 to 0.001) |
| ADA_STD + MTX | | 0.62 (0.14 to 2.43) | 0.63 (0.16 to 2.35) | –0.02 (–0.16 to 0.04) |
| TOF_STD + MTX | | 0.93 (0.23 to 3.39) | 0.93 (0.26 to 3.19) | –0.004 (–0.14 to 0.06) |
| TOC_4 (IV) | | 0.64 (0.09 to 3.94) | 0.65 (0.11 to 3.59) | –0.02 (–0.15 to 0.09) |
| TOC_8 (IV) | | 0.48 (0.09 to 2.39) | 0.49 (0.10 to 2.29) | –0.03 (–0.16 to 0.04) |
| TOC_4 (IV) + MTX | | 0.70 (0.11 to 4.40) | 0.72 (0.13 to 3.92) | –0.02 (–0.15 to 0.11) |
| TOC_8 (IV) + MTX | | 0.71 (0.12 to 3.68) | 0.72 (0.14 to 3.38) | –0.02 (–0.15 to 0.09) |
| GOL_STD (SC) + MTX | | 0.52 (0.10 to 2.41) | 0.53 (0.11 to 2.31) | –0.03 (–0.16 to 0.04) |
| INF_STD + MTX | | 0.70 (0.16 to 2.74) | 0.71 (0.19 to 2.62) | –0.02 (–0.15 to 0.04) |
| INF_STD | | *1.44 (0.04 to 142.40)* | *1.39 (0.04 to 22.49)* | *0.02 (–0.14 to 0.82)* |
| CERTO_STD + MTX | | 0.54 (0.12 to 2.31) | 0.56 (0.14 to 2.23) | –0.03 (–0.16 to 0.04) |
| RIT_STD | | 1.30 (0.08 to 35.83) | 1.27 (0.09 to 13.90) | 0.02 (–0.14 to 0.60) |
| RIT_STD + MTX | | 0.47 (0.004 to 21.08) | 0.49 (0.004 to 10.18) | –0.03 (–0.16 to 0.44) |
| BAR_4 + MTX | | 0.15 (0.01 to 1.35) | 0.16 (0.01 to 1.33) | –0.05 (–0.18 to 0.01) |
| HD203 + MTX | | 0.30 (0.07 to 1.21) | 0.32 (0.08 to 1.20) | –0.04 (–0.17 to 0.01) |
| SB4 + MTX | | 0.25 (0.06 to 0.92) | 0.27 (0.08 to 0.92) | –0.05 (–0.17 to –0.002) |
| CT-P13 + MTX | | 0.60 (0.12 to 2.75) | 0.62 (0.14 to 2.63) | –0.02 (–0.16 to 0.04) |
| SB2 + MTX | | 1.61 (0.29 to 8.16) | 1.54 (0.32 to 6.73) | 0.03 (–0.11 to 0.19) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| SB5 + MTX | | 0.12 (0.01 to 1.01) | 0.13 (0.01 to 1.01) | –0.05 (–0.19 to 0.0003) |
| ABP501 + MTX | | 1.58 (0.21 to 11.29) | 1.52 (0.23 to 8.14) | 0.03 (–0.12 to 0.30) |
| MTX + SSZ + HCQ | SSZ + HCQ | 1.16 (0.18 to 7.26) | 1.16 (0.18 to 7.05) | 0.002 (–0.03 to 0.04) |
| ETN_STD | | 2.22 (0.45 to 13.75) | 2.18 (0.46 to 13.35) | 0.01 (–0.03 to 0.04) |
| ETN_STD + MTX | | 1.90 (0.37 to 11.30) | 1.88 (0.39 to 10.99) | 0.01 (–0.03 to 0.03) |
| ABA_STD (IV) + MTX | | 2.11 (0.40 to 13.20) | 2.08 (0.41 to 12.81) | 0.01 (–0.03 to 0.04) |
| ABA_STD (SC) + MTX | | 1.19 (0.17 to 9.40) | 1.19 (0.18 to 9.17) | 0.002 (–0.04 to 0.03) |
| ADA_STD + MTX | | 3.45 (0.62 to 23.77) | 3.35 (0.63 to 22.45) | 0.03 (–0.02 to 0.07) |
| TOF_STD + MTX | | 5.15 (0.98 to 32.81) | 4.90 (0.98 to 30.38) | 0.05 (–0.001 to 0.10) |
| TOC_4 (IV) | | 3.65 (0.47 to 28.99) | 3.52 (0.48 to 26.21) | 0.03 (–0.02 to 0.14) |
| TOC_8 (IV) | | 2.69 (0.41 to 20.27) | 2.63 (0.42 to 19.09) | 0.02 (–0.03 to 0.08) |
| TOC_4 (IV) + MTX | | 4.06 (0.53 to 36.39) | 3.90 (0.54 to 32.27) | 0.03 (–0.02 to 0.15) |
| TOC_8 (IV) + MTX | | 4.03 (0.58 to 30.40) | 3.88 (0.59 to 27.96) | 0.03 (–0.02 to 0.13) |
| GOL_STD (SC) + MTX | | 2.89 (0.45 to 23.61) | 2.82 (0.46 to 22.15) | 0.02 (–0.02 to 0.08) |
| INF_STD + MTX | | 3.97 (0.65 to 25.95) | 3.82 (0.66 to 24.43) | 0.03 (–0.02 to 0.07) |
| INF_STD | | *9.18 (0.17 to 771.10)* | *8.13 (0.17 to 152.70)* | *0.08 (–0.03 to 0.86)* |
| CERTO_STD + MTX | | 3.12 (0.52 to 22.19) | 3.04 (0.53 to 20.94) | 0.02 (–0.02 to 0.07) |
| RIT_STD | | *7.71 (0.37 to 254.20)* | *7.02 (0.38 to 98.97)* | *0.07 (–0.02 to 0.66)* |
| RIT_STD + MTX | | *2.77 (0.01 to 136.80)* | *2.69 (0.01 to 67.82)* | *0.02 (–0.03 to 0.49)* |
| BAR_4 + MTX | | 0.92 (0.04 to 10.29) | 0.92 (0.04 to 9.90) | –0.001 (–0.04 to 0.05) |
| HD203 + MTX | | 1.65 (0.26 to 13.70) | 1.63 (0.27 to 13.16) | 0.01 (–0.03 to 0.05) |
| SB4 + MTX | | 1.44 (0.23 to 10.63) | 1.43 (0.24 to 10.31) | 0.005 (–0.04 to 0.04) |
| CT-P13 + MTX | | 3.44 (0.51 to 24.05) | 3.34 (0.52 to 22.52) | 0.03 (–0.02 to 0.08) |
| SB2 + MTX | | 9.13 (1.27 to 71.14) | 8.22 (1.25 to 58.49) | 0.09 (0.01 to 0.23) |
| SB5 + MTX | | 0.71 (0.05 to 8.22) | 0.71 (0.06 to 8.00) | –0.003 (–0.05 to 0.04) |
| ABP501 + MTX | | *8.81 (1.03 to 101.50)* | *7.93 (1.03 to 74.08)* | *0.08 (0.001 to 0.36)* |
| ETN_STD | MTX + SSZ + HCQ | 1.88 (0.40 to 12.21) | 1.86 (0.41 to 11.82) | 0.01 (–0.03 to 0.04) |
| ETN_STD + MTX | | 1.61 (0.34 to 9.95) | 1.60 (0.35 to 9.71) | 0.01 (–0.04 to 0.03) |
| ABA_STD (IV) + MTX | | 1.81 (0.35 to 12.17) | 1.79 (0.37 to 11.79) | 0.01 (–0.03 to 0.04) |
| ABA_STD (SC) + MTX | | 1.03 (0.16 to 7.96) | 1.03 (0.17 to 7.74) | 0.0004 (–0.04 to 0.03) |
| ADA_STD + MTX | | 2.97 (0.56 to 20.37) | 2.89 (0.58 to 19.23) | 0.03 (–0.02 to 0.07) |
| TOF_STD + MTX | | 4.48 (0.87 to 28.63) | 4.26 (0.88 to 26.73) | 0.04 (–0.01 to 0.09) |
| TOC_4 (IV) | | 3.16 (0.41 to 29.03) | 3.06 (0.42 to 26.12) | 0.03 (–0.03 to 0.14) |
| TOC_8 (IV) | | 2.30 (0.39 to 19.30) | 2.25 (0.40 to 18.22) | 0.02 (–0.03 to 0.08) |
| TOC_4 (IV) + MTX | | 3.46 (0.46 to 33.30) | 3.32 (0.47 to 29.49) | 0.03 (–0.02 to 0.15) |
| TOC_8 (IV) + MTX | | 3.47 (0.54 to 29.91) | 3.34 (0.55 to 27.09) | 0.03 (–0.02 to 0.13) |
| GOL_STD (SC) + MTX | | 2.45 (0.40 to 20.76) | 2.39 (0.41 to 19.45) | 0.02 (–0.03 to 0.08) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| INF_STD + MTX | | 3.40 (0.70 to 22.16) | 3.28 (0.71 to 20.91) | 0.03 (–0.01 to 0.07) |
| INF_STD | | *8.03 (0.16 to 610.40)* | *7.09 (0.17 to 104.80)* | *0.08 (–0.03 to 0.86)* |
| CERTO_STD + MTX | | 2.64 (0.48 to 20.02) | 2.58 (0.50 to 18.92) | 0.02 (–0.02 to 0.07) |
| RIT_STD | | *6.72 (0.35 to 244.80)* | *6.13 (0.36 to 102.10)* | *0.07 (–0.02 to 0.66)* |
| RIT_STD + MTX | | *2.34 (0.01 to 141.70)* | *2.28 (0.01 to 75.68)* | *0.02 (–0.04 to 0.49)* |
| BAR_4 + MTX | | 0.79 (0.03 to 9.91) | 0.79 (0.03 to 9.54) | –0.002 (–0.05 to 0.05) |
| HD203 + MTX | | 1.45 (0.24 to 10.95) | 1.44 (0.25 to 10.52) | 0.01 (–0.04 to 0.05) |
| SB4 + MTX | | 1.26 (0.21 to 8.98) | 1.26 (0.22 to 8.73) | 0.003 (–0.04 to 0.03) |
| CT-P13 + MTX | | 2.97 (0.55 to 20.92) | 2.88 (0.57 to 19.57) | 0.02 (–0.02 to 0.08) |
| SB2 + MTX | | 7.94 (1.25 to 63.37) | 7.19 (1.24 to 52.51) | 0.08 (0.01 to 0.23) |
| SB5 + MTX | | 0.60 (0.05 to 6.56) | 0.61 (0.05 to 6.39) | –0.005 (–0.05 to 0.03) |
| ABP501 + MTX | | 7.63 (0.90 to 84.46) | 6.85 (0.90 to 60.21) | 0.08 (–0.003 to 0.36) |
| ETN_STD + MTX | ETN_STD | 0.85 (0.49 to 1.41) | 0.86 (0.50 to 1.40) | –0.004 (–0.02 to 0.01) |
| ABA_STD (IV) + MTX | | 0.94 (0.36 to 2.40) | 0.95 (0.37 to 2.34) | –0.001 (–0.03 to 0.03) |
| ABA_STD (SC) + MTX | | 0.55 (0.15 to 1.92) | 0.55 (0.15 to 1.88) | –0.01 (–0.04 to 0.02) |
| ADA_STD + MTX | | 1.59 (0.59 to 4.15) | 1.56 (0.60 to 3.93) | 0.01 (–0.02 to 0.06) |
| TOF_STD + MTX | | 2.37 (0.94 to 5.52) | 2.28 (0.94 to 5.12) | 0.03 (–0.002 to 0.08) |
| TOC_4 (IV) | | 1.60 (0.35 to 7.69) | 1.58 (0.36 to 6.75) | 0.01 (–0.02 to 0.13) |
| TOC_8 (IV) | | 1.22 (0.33 to 4.36) | 1.21 (0.34 to 4.06) | 0.01 (–0.03 to 0.06) |
| TOC_4 (IV) + MTX | | 1.78 (0.40 to 8.50) | 1.74 (0.41 to 7.30) | 0.02 (–0.02 to 0.14) |
| TOC_8 (IV) + MTX | | 1.79 (0.44 to 7.36) | 1.75 (0.45 to 6.52) | 0.02 (–0.02 to 0.11) |
| GOL_STD (SC) + MTX | | 1.32 (0.36 to 4.42) | 1.31 (0.37 to 4.15) | 0.01 (–0.02 to 0.07) |
| INF_STD + MTX | | 1.81 (0.66 to 4.52) | 1.77 (0.67 to 4.27) | 0.02 (–0.01 to 0.06) |
| INF_STD | | *3.86 (0.11 to 316.40)* | *3.58 (0.11 to 40.34)* | *0.07 (–0.03 to 0.85)* |
| CERTO_STD + MTX | | 1.40 (0.47 to 4.21) | 1.39 (0.48 to 3.97) | 0.01 (–0.02 to 0.06) |
| RIT_STD | | 3.39 (0.24 to 87.51) | 3.18 (0.25 to 30.54) | 0.06 (–0.03 to 0.65) |
| RIT_STD + MTX | | 1.25 (0.01 to 41.36) | 1.24 (0.01 to 22.33) | 0.01 (–0.04 to 0.47) |
| BAR_4 + MTX | | 0.40 (0.02 to 2.83) | 0.40 (0.02 to 2.73) | –0.01 (–0.04 to 0.04) |
| HD203 + MTX | | 0.76 (0.23 to 2.34) | 0.76 (0.24 to 2.27) | –0.01 (–0.03 to 0.03) |
| SB4 + MTX | | 0.66 (0.24 to 1.72) | 0.67 (0.24 to 1.69) | –0.01 (–0.03 to 0.02) |
| CT-P13 + MTX | | 1.56 (0.50 to 4.63) | 1.54 (0.51 to 4.34) | 0.01 (–0.02 to 0.07) |
| SB2 + MTX | | 4.18 (1.08 to 14.08) | 3.85 (1.08 to 11.23) | 0.07 (0.003 to 0.22) |
| SB5 + MTX | | 0.32 (0.04 to 2.04) | 0.33 (0.04 to 1.99) | –0.02 (–0.04 to 0.02) |
| ABP501 + MTX | | 4.00 (0.73 to 23.50) | 3.70 (0.74 to 15.47) | 0.07 (–0.01 to 0.35) |
| ABA_STD (IV) + MTX | ETN_STD + MTX | 1.11 (0.43 to 2.82) | 1.10 (0.44 to 2.74) | 0.002 (–0.02 to 0.03) |
| ABA_STD (SC) + MTX | | 0.64 (0.18 to 2.25) | 0.65 (0.18 to 2.20) | –0.01 (–0.03 to 0.02) |
| ADA_STD + MTX | | 1.87 (0.71 to 4.75) | 1.83 (0.72 to 4.48) | 0.02 (–0.01 to 0.06) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| TOF_STD + MTX | | 2.77 (1.13 to 6.58) | 2.66 (1.13 to 6.05) | 0.04 (0.004 to 0.08) |
| TOC_4 (IV) | | 1.92 (0.41 to 9.03) | 1.87 (0.42 to 7.84) | 0.02 (–0.02 to 0.13) |
| TOC_8 (IV) | | 1.43 (0.40 to 5.07) | 1.41 (0.41 to 4.74) | 0.01 (–0.02 to 0.07) |
| TOC_4 (IV) + MTX | | 2.10 (0.48 to 9.98) | 2.05 (0.48 to 8.61) | 0.02 (–0.02 to 0.14) |
| TOC_8 (IV) + MTX | | 2.10 (0.52 to 8.47) | 2.05 (0.52 to 7.49) | 0.02 (–0.01 to 0.12) |
| GOL_STD (SC) + MTX | | 1.53 (0.45 to 5.28) | 1.52 (0.45 to 4.92) | 0.01 (–0.02 to 0.07) |
| INF_STD + MTX | | 2.12 (0.81 to 5.34) | 2.06 (0.82 to 5.02) | 0.02 (–0.01 to 0.06) |
| INF_STD | | *4.54 (0.12 to 364.00)* | *4.20 (0.12 to 48.54)* | *0.07 (–0.03 to 0.86)* |
| CERTO_STD + MTX | | 1.63 (0.58 to 4.90) | 1.61 (0.58 to 4.60) | 0.01 (–0.01 to 0.06) |
| RIT_STD | | *3.97 (0.28 to 106.50)* | *3.71 (0.29 to 36.45)* | *0.06 (–0.02 to 0.65)* |
| RIT_STD + MTX | | 1.46 (0.01 to 49.20) | 1.45 (0.01 to 26.26) | 0.01 (–0.03 to 0.48) |
| BAR_4 + MTX | | 0.47 (0.02 to 3.21) | 0.48 (0.02 to 3.08) | –0.01 (–0.03 to 0.04) |
| HD203 + MTX | | 0.89 (0.32 to 2.51) | 0.89 (0.32 to 2.42) | –0.002 (–0.02 to 0.03) |
| SB4 + MTX | | 0.77 (0.33 to 1.77) | 0.77 (0.33 to 1.74) | –0.005 (–0.02 to 0.02) |
| CT-P13 + MTX | | 1.82 (0.61 to 5.53) | 1.78 (0.61 to 5.18) | 0.02 (–0.01 to 0.07) |
| SB2 + MTX | | 4.91 (1.32 to 16.77) | 4.50 (1.31 to 13.28) | 0.08 (0.01 to 0.22) |
| SB5 + MTX | | 0.38 (0.04 to 2.44) | 0.38 (0.04 to 2.38) | –0.01 (–0.03 to 0.03) |
| ABP501 + MTX | | 4.66 (0.86 to 27.43) | 4.29 (0.86 to 18.16) | 0.07 (–0.004 to 0.35) |
| ABA_STD (SC) + MTX | ABA_STD (IV) + MTX | 0.57 (0.16 to 2.17) | 0.58 (0.16 to 2.12) | –0.01 (–0.04 to 0.02) |
| ADA_STD + MTX | | 1.68 (0.59 to 4.68) | 1.66 (0.60 to 4.42) | 0.02 (–0.02 to 0.06) |
| TOF_STD + MTX | | 2.48 (0.93 to 6.39) | 2.40 (0.93 to 5.91) | 0.03 (–0.003 to 0.08) |
| TOC_4 (IV) | | 1.73 (0.34 to 9.08) | 1.70 (0.35 to 7.92) | 0.02 (–0.03 to 0.13) |
| TOC_8 (IV) | | 1.30 (0.32 to 5.02) | 1.29 (0.33 to 4.70) | 0.01 (–0.03 to 0.07) |
| TOC_4 (IV) + MTX | | 1.89 (0.38 to 9.81) | 1.84 (0.39 to 8.48) | 0.02 (–0.02 to 0.14) |
| TOC_8 (IV) + MTX | | 1.88 (0.42 to 8.31) | 1.84 (0.43 to 7.40) | 0.02 (–0.02 to 0.12) |
| GOL_STD (SC) + MTX | | 1.38 (0.35 to 5.19) | 1.37 (0.36 to 4.85) | 0.01 (–0.03 to 0.07) |
| INF_STD + MTX | | 1.91 (0.74 to 4.74) | 1.86 (0.75 to 4.47) | 0.02 (–0.01 to 0.06) |
| INF_STD | | *3.98 (0.11 to 310.70)* | *3.68 (0.11 to 41.98)* | *0.07 (–0.03 to 0.85)* |
| CERTO_STD + MTX | | 1.49 (0.46 to 4.67) | 1.47 (0.47 to 4.42) | 0.01 (–0.02 to 0.06) |
| RIT_STD | | 3.54 (0.26 to 92.53) | 3.31 (0.27 to 32.97) | 0.06 (–0.02 to 0.65) |
| RIT_STD + MTX | | 1.30 (0.01 to 44.01) | 1.29 (0.01 to 23.01) | 0.01 (–0.04 to 0.48) |
| BAR_4 + MTX | | 0.42 (0.02 to 2.94) | 0.42 (0.02 to 2.83) | –0.01 (–0.04 to 0.04) |
| HD203 + MTX | | 0.80 (0.21 to 3.26) | 0.81 (0.22 to 3.13) | –0.004 (–0.03 to 0.04) |
| SB4 + MTX | | 0.69 (0.21 to 2.40) | 0.69 (0.21 to 2.34) | –0.01 (–0.03 to 0.02) |
| CT-P13 + MTX | | 1.65 (0.54 to 4.97) | 1.62 (0.55 to 4.65) | 0.01 (–0.02 to 0.07) |
| SB2 + MTX | | 4.41 (1.21 to 15.07) | 4.05 (1.20 to 12.08) | 0.08 (0.01 to 0.22) |
| SB5 + MTX | | 0.35 (0.04 to 2.04) | 0.35 (0.04 to 1.99) | –0.02 (–0.04 to 0.02) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ABP501 + MTX | | 4.20 (0.76 to 27.13) | 3.88 (0.77 to 18.11) | 0.07 (–0.01 to 0.35) |
| ADA_STD + MTX | ABA_STD (SC) + MTX | 2.91 (1.27 to 6.84) | 2.83 (1.26 to 6.59) | 0.03 (0.01 to 0.06) |
| TOF_STD + MTX | | 4.30 (1.34 to 14.22) | 4.10 (1.33 to 13.23) | 0.04 (0.01 to 0.09) |
| TOC_4 (IV) | | 3.02 (0.49 to 17.58) | 2.92 (0.50 to 15.48) | 0.03 (–0.01 to 0.14) |
| TOC_8 (IV) | | 2.25 (0.42 to 11.24) | 2.21 (0.43 to 10.51) | 0.02 (–0.02 to 0.08) |
| TOC_4 (IV) + MTX | | 3.31 (0.56 to 19.58) | 3.20 (0.57 to 17.21) | 0.03 (–0.01 to 0.15) |
| TOC_8 (IV) + MTX | | 3.35 (0.58 to 18.18) | 3.23 (0.59 to 16.31) | 0.03 (–0.01 to 0.13) |
| GOL_STD (SC) + MTX | | 2.39 (0.48 to 11.73) | 2.34 (0.48 to 10.92) | 0.02 (–0.02 to 0.08) |
| INF_STD + MTX | | 3.29 (0.83 to 12.84) | 3.18 (0.84 to 12.05) | 0.03 (–0.01 to 0.07) |
| INF_STD | | *7.03 (0.19 to 611.30)* | *6.37 (0.19 to 87.43)* | *0.08 (–0.02 to 0.86)* |
| CERTO_STD + MTX | | 2.59 (0.76 to 8.78) | 2.53 (0.77 to 8.30) | 0.02 (–0.01 to 0.07) |
| RIT_STD | | *6.32 (0.33 to 193.90)* | *5.81 (0.33 to 71.95)* | *0.07 (–0.02 to 0.66)* |
| RIT_STD + MTX | | *2.39 (0.01 to 101.10)* | *2.34 (0.01 to 49.52)* | *0.02 (–0.03 to 0.49)* |
| BAR_4 + MTX | | 0.71 (0.03 to 6.18) | 0.71 (0.03 to 5.91) | –0.004 (–0.03 to 0.05) |
| HD203 + MTX | | 1.37 (0.28 to 7.45) | 1.37 (0.29 to 7.13) | 0.005 (–0.03 to 0.05) |
| SB4 + MTX | | 1.19 (0.27 to 5.49) | 1.19 (0.27 to 5.32) | 0.003 (–0.03 to 0.03) |
| CT-P13 + MTX | | 2.86 (0.65 to 12.77) | 2.78 (0.66 to 11.87) | 0.02 (–0.01 to 0.08) |
| SB2 + MTX | | 7.55 (1.51 to 38.07) | 6.85 (1.49 to 30.41) | 0.08 (0.01 to 0.23) |
| SB5 + MTX | | 0.59 (0.07 to 3.37) | 0.59 (0.07 to 3.28) | –0.01 (–0.03 to 0.03) |
| ABP501 + MTX | | 7.25 (1.46 to 45.23) | 6.57 (1.44 to 31.56) | 0.08 (0.01 to 0.36) |
| TOF_STD + MTX | ADA_STD + MTX | 1.48 (0.67 to 3.39) | 1.45 (0.69 to 3.19) | 0.02 (–0.02 to 0.06) |
| TOC_4 (IV) | | 1.04 (0.20 to 4.89) | 1.04 (0.21 to 4.35) | 0.001 (–0.05 to 0.11) |
| TOC_8 (IV) | | 0.78 (0.19 to 3.01) | 0.79 (0.20 to 2.85) | –0.01 (–0.06 to 0.05) |
| TOC_4 (IV) + MTX | | 1.14 (0.23 to 5.39) | 1.13 (0.24 to 4.74) | 0.01 (–0.05 to 0.13) |
| TOC_8 (IV) + MTX | | 1.14 (0.26 to 5.14) | 1.14 (0.27 to 4.59) | 0.01 (–0.05 to 0.10) |
| GOL_STD (SC) + MTX | | 0.83 (0.21 to 3.10) | 0.84 (0.22 to 2.92) | –0.01 (–0.06 to 0.06) |
| INF_STD + MTX | | 1.15 (0.39 to 3.24) | 1.14 (0.41 to 3.08) | 0.01 (–0.04 to 0.05) |
| INF_STD | | *2.51 (0.07 to 191.80)* | *2.35 (0.07 to 25.69)* | *0.05 (–0.06 to 0.84)* |
| CERTO_STD + MTX | | 0.88 (0.36 to 2.17) | 0.89 (0.37 to 2.09) | –0.004 (–0.04 to 0.04) |
| RIT_STD | | 2.12 (0.14 to 63.03) | 2.02 (0.15 to 22.10) | 0.04 (–0.05 to 0.64) |
| RIT_STD + MTX | | 0.82 (0.01 to 32.22) | 0.82 (0.01 to 16.68) | –0.01 (–0.07 to 0.47) |
| BAR_4 + MTX | | 0.25 (0.01 to 1.73) | 0.26 (0.01 to 1.69) | –0.03 (–0.07 to 0.02) |
| HD203 + MTX | | 0.48 (0.12 to 1.97) | 0.49 (0.13 to 1.92) | –0.02 (–0.06 to 0.03) |
| SB4 + MTX | | 0.41 (0.12 to 1.43) | 0.42 (0.13 to 1.41) | –0.02 (–0.07 to 0.01) |
| CT-P13 + MTX | | 0.99 (0.30 to 3.31) | 0.99 (0.31 to 3.12) | –0.001 (–0.05 to 0.06) |
| SB2 + MTX | | 2.62 (0.67 to 10.05) | 2.45 (0.69 to 8.07) | 0.06 (–0.02 to 0.21) |
| SB5 + MTX | | 0.21 (0.03 to 0.95) | 0.21 (0.03 to 0.95) | –0.03 (–0.07 to –0.002) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ABP501 + MTX | | 2.47 (0.63 to 12.75) | 2.32 (0.64 to 8.65) | 0.05 (–0.01 to 0.33) |
| TOC_4 (IV) | TOF_STD + MTX | 0.68 (0.15 to 3.37) | 0.70 (0.16 to 3.03) | –0.02 (–0.08 to 0.10) |
| TOC_8 (IV) | | 0.52 (0.13 to 1.94) | 0.54 (0.14 to 1.87) | –0.03 (–0.08 to 0.04) |
| TOC_4 (IV) + MTX | | 0.77 (0.16 to 3.80) | 0.78 (0.17 to 3.35) | –0.01 (–0.08 to 0.11) |
| TOC_8 (IV) + MTX | | 0.77 (0.19 to 3.11) | 0.78 (0.20 to 2.84) | –0.01 (–0.07 to 0.08) |
| GOL_STD (SC) + MTX | | 0.55 (0.16 to 1.90) | 0.57 (0.17 to 1.83) | –0.02 (–0.08 to 0.04) |
| INF_STD + MTX | | 0.77 (0.28 to 2.03) | 0.78 (0.30 to 1.95) | –0.01 (–0.07 to 0.04) |
| INF_STD | | *1.63 (0.05 to 128.20)* | *1.57 (0.05 to 17.22)* | *0.03 (–0.08 to 0.82)* |
| CERTO_STD + MTX | | 0.60 (0.21 to 1.69) | 0.62 (0.22 to 1.64) | –0.02 (–0.07 to 0.03) |
| RIT_STD | | 1.44 (0.10 to 37.89) | 1.41 (0.11 to 13.85) | 0.02 (–0.08 to 0.62) |
| RIT_STD + MTX | | 0.53 (0.004 to 19.75) | 0.55 (0.004 to 10.46) | –0.03 (–0.09 to 0.45) |
| BAR_4 + MTX | | 0.17 (0.01 to 1.17) | 0.18 (0.01 to 1.16) | –0.05 (–0.10 to 0.01) |
| HD203 + MTX | | 0.32 (0.08 to 1.27) | 0.33 (0.09 to 1.25) | –0.04 (–0.09 to 0.01) |
| SB4 + MTX | | 0.28 (0.08 to 0.92) | 0.29 (0.09 to 0.92) | –0.04 (–0.09 to –0.003) |
| CT-P13 + MTX | | 0.66 (0.21 to 2.11) | 0.67 (0.23 to 2.02) | –0.02 (–0.07 to 0.04) |
| SB2 + MTX | | 1.78 (0.45 to 6.41) | 1.70 (0.47 to 5.22) | 0.04 (–0.04 to 0.19) |
| SB5 + MTX | | 0.14 (0.02 to 0.81) | 0.14 (0.02 to 0.82) | –0.05 (–0.10 to –0.01) |
| ABP501 + MTX | | 1.69 (0.33 to 9.87) | 1.62 (0.34 to 6.74) | 0.04 (–0.05 to 0.31) |
| TOC_8 (IV) | TOC_4 (IV) | 0.74 (0.23 to 2.73) | 0.75 (0.24 to 2.65) | –0.01 (–0.09 to 0.03) |
| TOC_4 (IV) + MTX | | 1.12 (0.29 to 3.88) | 1.11 (0.31 to 3.64) | 0.004 (–0.07 to 0.08) |
| TOC_8 (IV) + MTX | | 1.10 (0.35 to 3.79) | 1.09 (0.37 to 3.59) | 0.004 (–0.07 to 0.07) |
| GOL_STD (SC) + MTX | | 0.82 (0.13 to 4.90) | 0.83 (0.14 to 4.64) | –0.01 (–0.12 to 0.06) |
| INF_STD + MTX | | 1.11 (0.23 to 5.38) | 1.10 (0.25 to 5.08) | 0.004 (–0.11 to 0.06) |
| INF_STD | | *2.37 (0.05 to 189.40)* | *2.21 (0.06 to 32.38)* | *0.05 (–0.10 to 0.82)* |
| CERTO_STD + MTX | | 0.85 (0.17 to 4.70) | 0.86 (0.19 to 4.47) | –0.01 (–0.12 to 0.05) |
| RIT_STD | | 2.16 (0.12 to 60.39) | 2.05 (0.13 to 22.43) | 0.04 (–0.10 to 0.62) |
| RIT_STD + MTX | | 0.76 (0.01 to 36.10) | 0.76 (0.01 to 15.42) | –0.01 (–0.12 to 0.46) |
| BAR_4 + MTX | | 0.23 (0.01 to 2.94) | 0.24 (0.01 to 2.83) | –0.03 (–0.14 to 0.03) |
| HD203 + MTX | | 0.47 (0.07 to 2.97) | 0.48 (0.08 to 2.88) | –0.02 (–0.13 to 0.03) |
| SB4 + MTX | | 0.40 (0.07 to 2.34) | 0.41 (0.08 to 2.29) | –0.02 (–0.13 to 0.02) |
| CT-P13 + MTX | | 0.95 (0.18 to 5.21) | 0.96 (0.20 to 4.93) | –0.002 (–0.11 to 0.06) |
| SB2 + MTX | | 2.59 (0.41 to 15.04) | 2.42 (0.44 to 12.45) | 0.06 (–0.07 to 0.20) |
| SB5 + MTX | | 0.19 (0.02 to 1.74) | 0.20 (0.02 to 1.71) | –0.03 (–0.14 to 0.01) |
| ABP501 + MTX | | 2.50 (0.29 to 22.69) | 2.34 (0.32 to 16.18) | 0.05 (–0.08 to 0.34) |
| TOC_4 (IV) + MTX | TOC_8 (IV) | 1.49 (0.42 to 4.82) | 1.46 (0.43 to 4.42) | 0.01 (–0.03 to 0.11) |
| TOC_8 (IV) + MTX | | 1.48 (0.62 to 3.46) | 1.45 (0.63 to 3.25) | 0.01 (–0.02 to 0.08) |
| GOL_STD (SC) + MTX | | 1.07 (0.23 to 5.10) | 1.07 (0.24 to 4.80) | 0.002 (–0.06 to 0.06) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| INF_STD + MTX | | 1.46 (0.38 to 5.73) | 1.44 (0.40 to 5.40) | 0.01 (–0.05 to 0.06) |
| INF_STD | | *3.14 (0.07 to 257.30)* | *2.90 (0.08 to 44.49)* | *0.06 (–0.05 to 0.84)* |
| CERTO_STD + MTX | | 1.13 (0.28 to 4.87) | 1.12 (0.29 to 4.61) | 0.004 (–0.05 to 0.06) |
| RIT_STD | | 2.95 (0.17 to 82.18) | 2.76 (0.18 to 28.67) | 0.05 (–0.05 to 0.64) |
| RIT_STD + MTX | | 1.02 (0.01 to 45.05) | 1.01 (0.01 to 18.55) | 0.0004 (–0.07 to 0.47) |
| BAR_4 + MTX | | 0.31 (0.02 to 3.01) | 0.32 (0.02 to 2.91) | –0.02 (–0.08 to 0.03) |
| HD203 + MTX | | 0.63 (0.12 to 3.15) | 0.64 (0.13 to 3.05) | –0.01 (–0.07 to 0.03) |
| SB4 + MTX | | 0.53 (0.12 to 2.58) | 0.54 (0.12 to 2.53) | –0.01 (–0.07 to 0.02) |
| CT-P13 + MTX | | 1.26 (0.30 to 5.47) | 1.25 (0.31 to 5.16) | 0.01 (–0.05 to 0.06) |
| SB2 + MTX | | 3.40 (0.68 to 16.51) | 3.14 (0.70 to 13.49) | 0.07 (–0.02 to 0.21) |
| SB5 + MTX | | 0.25 (0.02 to 1.99) | 0.26 (0.03 to 1.95) | –0.02 (–0.08 to 0.02) |
| ABP501 + MTX | | 3.27 (0.44 to 30.02) | 3.02 (0.46 to 20.12) | 0.06 (–0.03 to 0.35) |
| TOC_8 (IV) + MTX | TOC_4 (IV) + MTX | 1.00 (0.30 to 3.37) | 1.00 (0.33 to 3.21) | –0.0002 (–0.08 to 0.06) |
| GOL_STD (SC) + MTX | | 0.74 (0.12 to 4.10) | 0.75 (0.13 to 3.87) | –0.01 (–0.14 to 0.06) |
| INF_STD + MTX | | 1.00 (0.20 to 4.67) | 1.00 (0.23 to 4.44) | 0.00004 (–0.12 to 0.05) |
| INF_STD | | *2.14 (0.05 to 187.80)* | *2.00 (0.05 to 29.35)* | *0.04 (–0.11 to 0.83)* |
| CERTO_STD + MTX | | 0.76 (0.15 to 4.24) | 0.77 (0.17 to 4.03) | –0.01 (–0.13 to 0.05) |
| RIT_STD | | 1.95 (0.11 to 58.85) | 1.86 (0.12 to 21.97) | 0.04 (–0.10 to 0.62) |
| RIT_STD + MTX | | 0.69 (0.01 to 30.82) | 0.70 (0.01 to 14.08) | –0.01 (–0.13 to 0.45) |
| BAR_4 + MTX | | 0.21 (0.01 to 2.48) | 0.22 (0.01 to 2.41) | –0.03 (–0.16 to 0.03) |
| HD203 + MTX | | 0.42 (0.07 to 2.68) | 0.43 (0.08 to 2.60) | –0.02 (–0.15 to 0.03) |
| SB4 + MTX | | 0.36 (0.06 to 2.03) | 0.37 (0.07 to 1.99) | –0.03 (–0.15 to 0.02) |
| CT-P13 + MTX | | 0.87 (0.16 to 4.47) | 0.87 (0.18 to 4.25) | –0.01 (–0.13 to 0.06) |
| SB2 + MTX | | 2.33 (0.36 to 13.42) | 2.18 (0.40 to 11.06) | 0.05 (–0.08 to 0.20) |
| SB5 + MTX | | 0.18 (0.02 to 1.44) | 0.18 (0.02 to 1.42) | –0.03 (–0.16 to 0.01) |
| ABP501 + MTX | | 2.20 (0.26 to 22.18) | 2.07 (0.28 to 15.51) | 0.05 (–0.09 to 0.34) |
| GOL_STD (SC) + MTX | TOC_8 (IV) + MTX | 0.74 (0.14 to 3.94) | 0.75 (0.15 to 3.71) | –0.01 (–0.11 to 0.06) |
| INF_STD + MTX | | 0.99 (0.25 to 4.22) | 0.99 (0.27 to 4.02) | –0.0005 (–0.09 to 0.05) |
| INF_STD | | *2.14 (0.05 to 188.40)* | *2.01 (0.05 to 27.60)* | *0.04 (–0.09 to 0.83)* |
| CERTO_STD + MTX | | 0.76 (0.17 to 3.64) | 0.77 (0.19 to 3.48) | –0.01 (–0.11 to 0.05) |
| RIT_STD | | 1.99 (0.12 to 55.24) | 1.89 (0.13 to 20.00) | 0.04 (–0.09 to 0.63) |
| RIT_STD + MTX | | 0.68 (0.01 to 30.31) | 0.69 (0.01 to 13.66) | –0.01 (–0.11 to 0.45) |
| BAR_4 + MTX | | 0.21 (0.01 to 2.13) | 0.22 (0.01 to 2.08) | –0.03 (–0.13 to 0.03) |
| HD203 + MTX | | 0.42 (0.08 to 2.36) | 0.43 (0.09 to 2.29) | –0.02 (–0.12 to 0.03) |
| SB4 + MTX | | 0.36 (0.07 to 1.88) | 0.37 (0.08 to 1.85) | –0.03 (–0.12 to 0.02) |
| CT-P13 + MTX | | 0.86 (0.19 to 4.00) | 0.86 (0.21 to 3.78) | –0.01 (–0.10 to 0.05) |
| SB2 + MTX | | 2.27 (0.43 to 11.87) | 2.13 (0.46 to 9.88) | 0.05 (–0.06 to 0.20) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| SB5 + MTX | | 0.17 (0.02 to 1.44) | 0.18 (0.02 to 1.42) | –0.04 (–0.13 to 0.01) |
| ABP501 + MTX | | 2.26 (0.28 to 20.40) | 2.13 (0.30 to 14.09) | 0.05 (–0.08 to 0.33) |
| INF_STD + MTX | GOL_STD (SC) + MTX | 1.39 (0.37 to 5.05) | 1.37 (0.39 to 4.77) | 0.01 (–0.05 to 0.06) |
| INF_STD | | *2.92 (0.08 to 246.20)* | *2.71 (0.08 to 33.91)* | *0.06 (–0.05 to 0.84)* |
| CERTO_STD + MTX | | 1.08 (0.27 to 4.34) | 1.08 (0.29 to 4.12) | 0.003 (–0.06 to 0.06) |
| RIT_STD | | 2.58 (0.17 to 84.85) | 2.43 (0.18 to 31.28) | 0.05 (–0.05 to 0.64) |
| RIT_STD + MTX | | 0.95 (0.005 to 39.51) | 0.95 (0.01 to 21.49) | –0.001 (–0.07 to 0.47) |
| BAR_4 + MTX | | 0.30 (0.01 to 2.75) | 0.31 (0.01 to 2.66) | –0.02 (–0.08 to 0.03) |
| HD203 + MTX | | 0.59 (0.11 to 2.78) | 0.60 (0.12 to 2.69) | –0.01 (–0.07 to 0.03) |
| SB4 + MTX | | 0.50 (0.12 to 2.15) | 0.51 (0.12 to 2.11) | –0.02 (–0.07 to 0.02) |
| CT-P13 + MTX | | 1.18 (0.30 to 4.98) | 1.17 (0.32 to 4.67) | 0.01 (–0.06 to 0.06) |
| SB2 + MTX | | 3.15 (0.63 to 14.98) | 2.93 (0.65 to 12.13) | 0.06 (–0.02 to 0.21) |
| SB5 + MTX | | 0.24 (0.02 to 1.94) | 0.25 (0.03 to 1.90) | –0.02 (–0.08 to 0.02) |
| ABP501 + MTX | | 3.07 (0.44 to 23.13) | 2.85 (0.45 to 15.88) | 0.06 (–0.03 to 0.34) |
| INF_STD | INF_STD + MTX | *2.09 (0.06 to 156.10)* | *1.99 (0.07 to 20.52)* | *0.05 (–0.06 to 0.83)* |
| CERTO_STD + MTX | | 0.77 (0.24 to 2.49) | 0.78 (0.25 to 2.38) | –0.01 (–0.06 to 0.04) |
| RIT_STD | | 1.93 (0.14 to 46.27) | 1.85 (0.15 to 16.61) | 0.04 (–0.06 to 0.63) |
| RIT_STD + MTX | | 0.70 (0.005 to 22.99) | 0.71 (0.01 to 11.87) | –0.01 (–0.07 to 0.45) |
| BAR_4 + MTX | | 0.22 (0.01 to 1.63) | 0.22 (0.01 to 1.59) | –0.03 (–0.08 to 0.02) |
| HD203 + MTX | | 0.42 (0.11 to 1.65) | 0.44 (0.12 to 1.61) | –0.03 (–0.07 to 0.02) |
| SB4 + MTX | | 0.37 (0.11 to 1.26) | 0.38 (0.11 to 1.25) | –0.03 (–0.07 to 0.01) |
| CT-P13 + MTX | | 0.86 (0.51 to 1.57) | 0.86 (0.52 to 1.53) | –0.01 (–0.03 to 0.03) |
| SB2 + MTX | | 2.30 (0.94 to 5.65) | 2.16 (0.94 to 4.66) | 0.05 (–0.002 to 0.18) |
| SB5 + MTX | | 0.18 (0.02 to 1.16) | 0.19 (0.02 to 1.16) | –0.04 (–0.08 to 0.01) |
| ABP501 + MTX | | 2.25 (0.38 to 14.74) | 2.13 (0.39 to 9.89) | 0.05 (–0.04 to 0.33) |
| CERTO_STD + MTX | INF_STD | 0.36 (0.004 to 13.29) | 0.39 (0.03 to 12.71) | –0.06 (–0.84 to 0.05) |
| RIT_STD | | *0.89 (0.01 to 138.60)* | *0.90 (0.03 to 61.17)* | *–0.01 (–0.78 to 0.60)* |
| RIT_STD + MTX | | *0.28 (0.001 to 81.31)* | *0.32 (0.001 to 39.93)* | *–0.05 (–0.82 to 0.43)* |
| BAR_4 + MTX | | 0.09 (0.001 to 6.18) | 0.11 (0.004 to 6.04) | –0.08 (–0.86 to 0.03) |
| HD203 + MTX | | 0.20 (0.002 to 8.66) | 0.22 (0.01 to 8.35) | –0.07 (–0.85 to 0.03) |
| SB4 + MTX | | 0.17 (0.002 to 7.06) | 0.19 (0.01 to 6.90) | –0.07 (–0.86 to 0.02) |
| CT-P13 + MTX | | 0.41 (0.01 to 13.87) | 0.44 (0.04 to 13.15) | –0.05 (–0.84 to 0.06) |
| SB2 + MTX | | 1.09 (0.02 to 41.06) | 1.08 (0.09 to 34.46) | 0.01 (–0.75 to 0.19) |
| SB5 + MTX | | 0.08 (0.001 to 3.70) | 0.09 (0.003 to 3.65) | –0.08 (–0.86 to 0.02) |
| ABP501 + MTX | | 1.01 (0.01 to 52.34) | 1.01 (0.06 to 41.44) | 0.001 (–0.77 to 0.30) |
| RIT_STD | CERTO_STD + MTX | 2.32 (0.16 to 69.70) | 2.21 (0.17 to 25.89) | 0.04 (–0.05 to 0.63) |
| RIT_STD + MTX | | 0.88 (0.01 to 39.81) | 0.88 (0.01 to 20.06) | –0.004 (–0.07 to 0.47) |

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| BAR_4 + MTX | | 0.28 (0.01 to 2.08) | 0.29 (0.02 to 2.03) | –0.02 (–0.07 to 0.03) |
| HD203 + MTX | | 0.54 (0.13 to 2.39) | 0.55 (0.14 to 2.33) | –0.02 (–0.07 to 0.03) |
| SB4 + MTX | | 0.47 (0.12 to 1.75) | 0.48 (0.13 to 1.72) | –0.02 (–0.07 to 0.02) |
| CT-P13 + MTX | | 1.11 (0.30 to 4.18) | 1.11 (0.32 to 3.93) | 0.004 (–0.05 to 0.06) |
| SB2 + MTX | | 2.97 (0.67 to 12.36) | 2.76 (0.69 to 9.96) | 0.06 (–0.02 to 0.21) |
| SB5 + MTX | | 0.23 (0.03 to 1.41) | 0.24 (0.03 to 1.39) | –0.03 (–0.07 to 0.01) |
| ABP501 + MTX | | 2.81 (0.55 to 17.01) | 2.62 (0.56 to 11.75) | 0.06 (–0.02 to 0.34) |
| RIT_STD + MTX | RIT_STD | 0.39 (0.003 to 4.37) | 0.44 (0.003 to 3.82) | –0.03 (–0.44 to 0.15) |
| BAR_4 + MTX | | 0.11 (0.002 to 2.81) | 0.13 (0.004 to 2.74) | –0.07 (–0.66 to 0.02) |
| HD203 + MTX | | 0.22 (0.01 to 4.03) | 0.24 (0.02 to 3.91) | –0.06 (–0.65 to 0.03) |
| SB4 + MTX | | 0.20 (0.01 to 2.88) | 0.21 (0.02 to 2.84) | –0.06 (–0.66 to 0.02) |
| CT-P13 + MTX | | 0.44 (0.02 to 6.86) | 0.47 (0.05 to 6.49) | –0.04 (–0.63 to 0.06) |
| SB2 + MTX | | 1.17 (0.04 to 19.20) | 1.16 (0.11 to 16.25) | 0.01 (–0.56 to 0.19) |
| SB5 + MTX | | 0.09 (0.002 to 2.05) | 0.10 (0.005 to 2.02) | –0.07 (–0.66 to 0.01) |
| ABP501 + MTX | | 1.19 (0.03 to 27.47) | 1.17 (0.07 to 20.82) | 0.01 (–0.59 to 0.30) |
| BAR_4 + MTX | RIT_STD + MTX | 0.33 (0.003 to 57.26) | 0.34 (0.01 to 55.86) | –0.02 (–0.49 to 0.04) |
| HD203 + MTX | | 0.61 (0.01 to 78.74) | 0.62 (0.03 to 76.91) | –0.01 (–0.48 to 0.05) |
| SB4 + MTX | | 0.55 (0.01 to 69.67) | 0.56 (0.03 to 68.34) | –0.01 (–0.48 to 0.03) |
| CT-P13 + MTX | | *1.23 (0.04 to 189.70)* | *1.22 (0.07 to 180.80)* | *0.01 (–0.46 to 0.07)* |
| SB2 + MTX | | *3.33 (0.08 to 545.10)* | *3.06 (0.16 to 462.60)* | *0.06 (–0.39 to 0.21)* |
| SB5 + MTX | | 0.25 (0.004 to 49.13) | 0.26 (0.01 to 48.27) | –0.02 (–0.49 to 0.03) |
| ABP501 + MTX | | *3.26 (0.05 to 613.40)* | *2.98 (0.10 to 505.80)* | *0.05 (–0.42 to 0.34)* |
| HD203 + MTX | BAR_4 + MTX | 1.93 (0.22 to 42.00) | 1.91 (0.23 to 40.74) | 0.01 (–0.04 to 0.05) |
| SB4 + MTX | | 1.65 (0.20 to 37.03) | 1.64 (0.21 to 36.07) | 0.01 (–0.04 to 0.04) |
| CT-P13 + MTX | | 4.00 (0.50 to 85.01) | 3.87 (0.51 to 80.42) | 0.03 (–0.03 to 0.08) |
| SB2 + MTX | | 10.61 (1.12 to 245.10) | 9.54 (1.12 to 206.90) | 0.09 (0.005 to 0.23) |
| SB5 + MTX | | 0.80 (0.04 to 23.99) | 0.81 (0.05 to 23.41) | –0.002 (–0.05 to 0.04) |
| ABP501 + MTX | | *10.23 (0.92 to 260.30)* | *9.16 (0.93 to 207.50)* | *0.08 (–0.003 to 0.36)* |
| SB4 + MTX | HD203 + MTX | 0.86 (0.23 to 3.32) | 0.86 (0.23 to 3.24) | –0.003 (–0.04 to 0.02) |
| CT-P13 + MTX | | 2.01 (0.46 to 9.05) | 1.97 (0.48 to 8.50) | 0.02 (–0.03 to 0.07) |
| SB2 + MTX | | 5.45 (1.07 to 26.03) | 4.97 (1.07 to 21.29) | 0.08 (0.003 to 0.22) |
| SB5 + MTX | | 0.42 (0.04 to 3.37) | 0.43 (0.04 to 3.27) | –0.01 (–0.06 to 0.03) |
| ABP501 + MTX | | 5.35 (0.72 to 40.54) | 4.88 (0.73 to 28.21) | 0.07 (–0.01 to 0.36) |
| CT-P13 + MTX | SB4 + MTX | 2.35 (0.62 to 9.41) | 2.29 (0.63 to 8.79) | 0.02 (–0.01 to 0.08) |
| SB2 + MTX | | 6.32 (1.38 to 28.38) | 5.74 (1.36 to 22.73) | 0.08 (0.01 to 0.23) |
| SB5 + MTX | | 0.49 (0.05 to 3.62) | 0.49 (0.05 to 3.51) | –0.01 (–0.04 to 0.03) |
| ABP501 + MTX | | 6.09 (0.94 to 42.26) | 5.56 (0.94 to 28.86) | 0.08 (–0.002 to 0.36) |

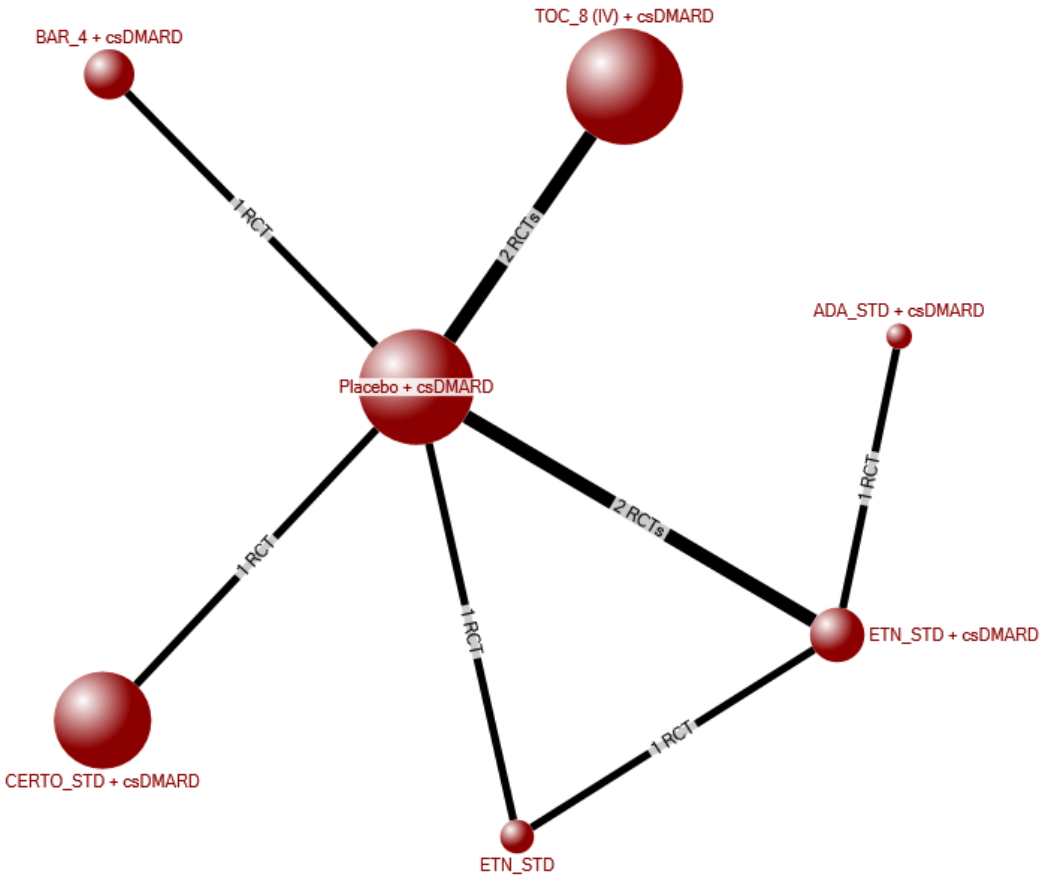
| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| SB2 + MTX | CT-P13 + MTX | 2.68 (0.89 to 7.56) | 2.49 (0.90 to 6.28) | 0.06 (–0.01 to 0.19) |
| SB5 + MTX | | 0.20 (0.02 to 1.45) | 0.21 (0.02 to 1.44) | –0.03 (–0.08 to 0.01) |
| ABP501 + MTX | | 2.62 (0.39 to 18.27) | 2.45 (0.41 to 12.38) | 0.05 (–0.04 to 0.34) |
| SB5 + MTX | SB2 + MTX | 0.08 (0.01 to 0.62) | 0.08 (0.01 to 0.63) | –0.09 (–0.23 to –0.02) |
| ABP501 + MTX | | 0.97 (0.14 to 7.70) | 0.97 (0.17 to 5.51) | –0.003 (–0.17 to 0.28) |
| ABP501 + MTX | SB5 + MTX | *12.82 (1.51 to 166.00)* | *11.39 (1.48 to 121.90)* | *0.08 (0.01 to 0.37)* |
| | | | | |
| Random-Effects Model | Residual Deviance | 91.31 vs. 95 data points | | |
| | Deviance Information Criteria | 460.223 | | |
| Fixed-Effect Model | Residual Deviance | 92.53 vs 95 data points | | |
| | Deviance Information Criteria | 459.252 | | |

ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; CrI = credible interval; CT-P13 = biosimilar infliximab; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; HD203 = biosimilar etanercept; INF = infliximab; IV = intravenous; MTX = methotrexate; OR = odds ratio; RD = risk difference; RIT = rituximab; RR = relative risk; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; SB5 = biosimilar adalimumab; SC = subcutaneous; SSZ = sulfasalazine; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator. Italicized results indicate a wide CrI.

### *Conventional Synthetic DMARD as a Common Comparator*

Seven studies (six two-arm studies and one three-arm study) were included for the reference case NMA with csDMARD monotherapy as the common comparator.[101,143,151,162,163,241,249] The evidence network involved 3,936 participants and seven treatments, forming nine direct comparisons. Assessment for consistency demonstrated that the model was consistent. A geometric illustration of the evidence network is presented in Figure 22; the odds ratios for all treatment comparisons with placebo as the common comparator are available in Table 27. A staircase table of the results as odds ratios is also presented in Appendix 10 (Table 98).

## Figure 22: Evidence Network: Withdrawal due to Adverse Events (Placebo + csDMARD)




ADA = adalimumab; BAR_4 = 4 mg baricitinib; CrI = credible interval; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; IV = intravenous; RCT = randomized controlled trial; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab.

Only etanercept monotherapy had statistically significantly higher odds of WDAE compared with csDMARD monotherapy (odds ratio = 3.46; 95% CrI, 1.07 to 13.18). There were no other statistically significant results for any of the comparisons of biologics or 4 mg baricitinib in terms of WDAEs (Table 27).

## Table 27: Withdrawal Due to Adverse Events (Placebo + csDMARD): Odds Ratios, Relative Risks, and Risk Differences for All Treatment Comparisons – Random-Effects Model

| Treatment | Reference | OR (95% CrI) | RR (95% CrI) | RD (95% CrI) |
|---|---|---|---|---|
| ETN_STD | Placebo + csDMARD | 3.46 (1.07 to 13.18) | 3.11 (1.07 to 9.08) | 0.10 (0.004 to 0.31) |
| ETN_STD + csDMARD | | 1.65 (0.53 to 6.03) | 1.60 (0.54 to 5.11) | 0.03 (–0.03 to 0.15) |
| ADA_STD + csDMARD | | 1.16 (0.24 to 6.08) | 1.15 (0.25 to 5.10) | 0.01 (–0.04 to 0.16) |
| TOC_8 (IV) + csDMARD | | 1.95 (0.98 to 4.05) | 1.87 (0.98 to 3.60) | 0.04 (–0.001 to 0.11) |
| CERTO_STD + csDMARD | | 1.47 (0.52 to 4.78) | 1.44 (0.53 to 4.14) | 0.02 (–0.02 to 0.13) |
| BAR_4 + csDMARD | | 1.00 (0.30 to 3.28) | 1.00 (0.31 to 2.99) | –0.0002 (–0.03 to 0.09) |
| ETN_STD + csDMARD | ETN_STD | 0.48 (0.18 to 1.29) | 0.52 (0.22 to 1.26) | –0.07 (–0.22 to 0.02) |
| ADA_STD + csDMARD | | 0.33 (0.08 to 1.39) | 0.37 (0.10 to 1.33) | –0.08 (–0.26 to 0.03) |
| TOC_8 (IV) + csDMARD | | 0.56 (0.12 to 2.25) | 0.60 (0.17 to 2.08) | –0.06 (–0.27 to 0.07) |
| CERTO_STD + csDMARD | | 0.43 (0.08 to 2.21) | 0.47 (0.11 to 2.03) | –0.07 (–0.29 to 0.07) |
| BAR_4 + csDMARD | | 0.28 (0.05 to 1.53) | 0.32 (0.07 to 1.47) | –0.09 (–0.30 to 0.03) |
| ADA_STD + csDMARD | ETN_STD + csDMARD | 0.70 (0.24 to 1.95) | 0.72 (0.26 to 1.81) | –0.02 (–0.08 to 0.07) |
| TOC_8 (IV) + csDMARD | | 1.18 (0.27 to 4.64) | 1.17 (0.31 to 4.15) | 0.01 (–0.12 to 0.11) |
| CERTO_STD + csDMARD | | 0.90 (0.17 to 4.37) | 0.91 (0.19 to 3.87) | –0.01 (–0.14 to 0.12) |
| BAR_4 + csDMARD | | 0.59 (0.10 to 3.04) | 0.61 (0.12 to 2.80) | –0.03 (–0.15 to 0.07) |
| TOC_8 (IV) + csDMARD | ADA_STD + csDMARD | 1.68 (0.28 to 9.60) | 1.62 (0.32 to 8.52) | 0.03 (–0.13 to 0.12) |
| CERTO_STD + csDMARD | | 1.29 (0.18 to 8.45) | 1.27 (0.21 to 7.44) | 0.01 (–0.14 to 0.13) |
| BAR_4 + csDMARD | | 0.86 (0.11 to 5.98) | 0.86 (0.13 to 5.48) | –0.01 (–0.16 to 0.09) |
| CERTO_STD + csDMARD | TOC_8 (IV) + csDMARD | 0.75 (0.21 to 2.96) | 0.77 (0.23 to 2.64) | –0.02 (–0.11 to 0.10) |
| BAR_4 + csDMARD | | 0.51 (0.12 to 2.00) | 0.53 (0.14 to 1.88) | –0.04 (–0.12 to 0.05) |
| BAR_4 + csDMARD | CERTO_STD + csDMARD | 0.67 (0.13 to 3.34) | 0.69 (0.14 to 3.08) | –0.02 (–0.14 to 0.08) |
| | | | | |
| Random-Effects Model | Residual Deviance | 14.01 vs. 15 data points | | |
| | Deviance Information Criteria | 87.491 | | |
| Fixed-Effect Model | Residual Deviance | 13.77 vs 15 data points | | |
| | Deviance Information Criteria | 86.891 | | |

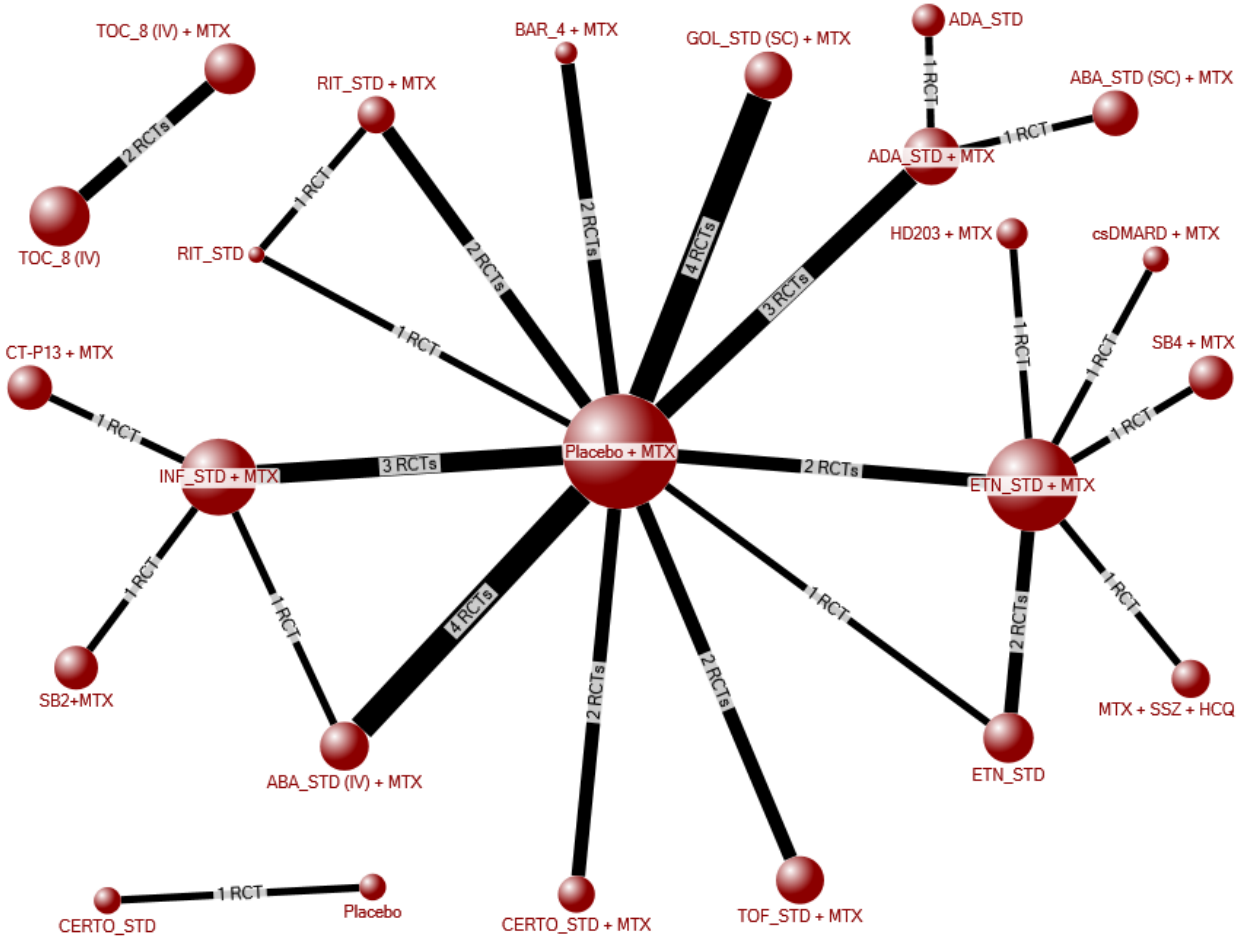
ADA = adalimumab; BAR_4 = 4 mg baricitinib; CrI = credible interval; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; IV = intravenous; OR = odds ratio; RD = risk difference; RR = relative risk; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab; vs. = versus.
Note: Results highlighted in green are statistically significant and favour the treatment. Results highlighted in red are statistically significant and favour the comparator.

## Mortality

### *Methotrexate as a Common Comparator*

A total of 35 studies reported mortality outcomes.[94,95,99,128,132,136,138,139,145,150,152,153,155,156,169,171,175,178,179,187,193,197,207,224,227,229,230,232,234,236,237,244,245,248,251] Of these, 20 reported no deaths in any treatment arm for the duration of the treatment period that was eligible for this analysis.[128,136,139,145,152,153,156,171,175,178,187,193,207,224,227,229,230,237,244,245,248] The treatments for studies with mortality data are visually represented in Figure 23. Outcome data on all eligible studies are represented graphically in Table 28.

**Figure 23: Evidence Network: Mortality (Placebo + Methotrexate)**




ABA = abatacept; ADA = adalimumab; BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; HD203 = biosimilar etanercept; INF = infliximab; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; RIT = rituximab; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; SC = subcutaneous; SSZ = sulfasalazine; STD = standard dose; TOC_8 (IV) = 8 mg/kg tocilizumab; TOF = tofacitinib.

A pairwise MA of two studies that compared infliximab in combination with MTX with MTX monotherapy showed no statistically significant difference in the occurrence of mortality (Peto odds ratio = 0.62; 95% CI, 0.11 to 3.67) (Figure 24). A third comparison arm in the trial by Schiff et al. was of standard dose abatacept in combination with MTX, which reported one death among 156 participants.[95] Another pairwise comparison based on two studies of etanercept in combination with MTX or etanercept alone found no statistically significant difference between these two active treatments in terms of deaths (Peto odds ratio = 1.93; 95% CI, 0.39 to 9.59) (Figure 25).

Two studies both compared 8 mg/kg tocilizumab monotherapy and 8 mg/kg tocilizumab in combination with MTX. In a pairwise MA, there was no statistically significant difference between the two treatments in terms of mortality (Peto odds ratio = 0.99; 95% CI, 0.14 to 7.04) (Figure 26).

Two studies compared a biosimilar etanercept with etanercept in combination with MTX. The first compared SB4 in combination with MTX with etanercept combination therapy; one death occurred in the biosimilar arm and none in the etanercept arm.[155] The second was of HD203 in combination with MTX. In that study, two deaths occurred in the etanercept combination arm and none in the biosimilar arm.[132]

Infliximab in combination with MTX was the comparator for two studies of different biosimilar infliximab drugs. Choe et al. reported one death in the infliximab combination arm and zero deaths in the SB2 in combination with MTX arm.[138] Yoo et al. reported one death in the infliximab combination arm and no deaths in the CT-P13 arm.[251]

Another study compared etanercept in combination with MTX with a csDMARD combination therapy involving MTX and another csDMARD; one patient in the etanercept arm died, but no participants died in the csDMARD combination arm.[179] A three-arm trial comparing rituximab combination therapy with MTX, rituximab monotherapy, and MTX monotherapy reported one death in the rituximab monotherapy arm and no deaths in the other treatment arms.[152]

A head-to-head study reported no deaths in the adalimumab monotherapy arm and two deaths in the 8 mg/kg tocilizumab monotherapy arm.[94] Another head-to-head study (AMPLE) had one death in both the SC abatacept and adalimumab arms after two years of treatment.[99]

## Table 28: Mortality Events, Concomitant Methotrexate

| Author, Year | Treatment 1 | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Bae, 2017 | ETN_STD + MTX | 2 | 146 | HD203 + MTX | 0 | 147 | | | |
| Tanaka, 2016 | Placebo + MTX | 0 | 49 | BAR_4 + MTX | 0 | 24 | | | |
| Choe, 2017 | INF_STD + MTX | 1 | 293 | SB2 + MTX | 0 | 290 | | | |
| Emery, 2017 | ETN_STD + MTX | 0 | 297 | SB4 + MTX | 1 | 298 | | | |
| Keystone, 2015 | Placebo + MTX | 0 | 98 | BAR_4 + MTX | 0 | 52 | | | |
| Li, 2016 | Placebo + MTX | 0 | 132 | GOL_STD (SC) + MTX | 0 | 131 | | | |
| Weinblatt, 2015 | Placebo + MTX | 0 | 61 | ADA_STD + MTX | 0 | 59 | | | |
| Yoo, 2016 | INF_STD + MTX | 1 | 300 | CT-P13 + MTX | 0 | 302 | | | |
| Yamamoto, 2014 | Placebo + MTX | 0 | 77 | CERTO_STD + MTX | 0 | 82 | | | |

| Author, Year | Treatment 1 | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Choy, 2012 | Placebo + MTX | 0 | 119 | CERTO_STD + MTX | 0 | 124 | | | |
| Abe, 2006 | Placebo + MTX | 0 | 47 | INF_STD + MTX | 0 | 49 | | | |
| Conaghan, 2013 | Placebo + MTX | 0 | 23 | ABA_STD (IV) + MTX | 0 | 27 | | | |
| Emery, 2010 | Placebo + MTX | 0 | 172 | RIT_STD + MTX | 0 | 170 | | | |
| Kim, 2012 | csDMARD + MTX | 0 | 103 | ETN_STD + MTX | 1 | 197 | | | |
| O'Dell, 2013 | MTX + SSZ + HCQ | 0 | 222 | ETN_STD + MTX | 0 | 219 | | | |
| Takeuchi, 2013 | Placebo + MTX | 0 | 66 | ABA_STD (IV) + MTX | 0 | 61 | | | |
| Tanaka, 2011 | Placebo + MTX | 0 | 28 | TOF_STD + MTX | 0 | 27 | | | |
| Tanaka, 2012 | Placebo + MTX | 0 | 88 | GOL_STD (SC) + MTX | 0 | 86 | | | |
| Chen, 2009 | Placebo + MTX | 0 | 12 | ADA_STD + MTX | 0 | 35 | | | |
| Kay, 2008 | Placebo + MTX | 0 | 34 | GOL_STD (SC) + MTX | 0 | 37 | | | |
| Keystone, 2009 | Placebo + MTX | 0 | 133 | GOL_STD (SC) + MTX | 0 | 89 | | | |
| Kremer, 2005 | Placebo + MTX | 0 | 119 | ABA_STD (IV) + MTX | 0 | 115 | | | |
| Maini, 1999 | Placebo + MTX | 3 | 88 | INF_STD + MTX | 1 | 86 | | | |
| Weinblatt, 1999 | Placebo + MTX | 0 | 30 | ETN_STD + MTX | 0 | 59 | | | |
| van Vollenhoven, 2011 | Placebo + MTX | 0 | 76 | ADA_STD + MTX | 0 | 79 | | | |
| van der Heijde, 2013 | Placebo + MTX | 0 | 160 | TOF_STD + MTX | 2 | 321 | | | |
| van Riel, 2006 | ETN_STD | 0 | 159 | ETN_STD + MTX | 2 | 155 | | | |
| Gabay, 2013 | ADA_STD | 0 | 162 | TOC_8 (IV) | 2 | 162 | | | |
| Schiff 2013 | ADA_STD + MTX | 1 | 328 | ABA_STD (SC) + MTX | 1 | 318 | | | |
| Kaneko 2016 | TOC_8 (IV) | 0 | 111 | TOC_8 (IV) + MTX | 1 | 115 | | | |
| Dougados 2013 | TOC_8 (IV) | 2 | 276 | TOC_8 (IV) + MTX | 1 | 277 | | | |
| Fleischmann 2009 | Placebo | 0 | 109 | CERTO_STD (SC) | 0 | 111 | | | |
| Edwards, 2004 | Placebo + MTX | 0 | 40 | RIT_STD | 1 | 40 | RIT_STD + MTX | 0 | 40 |
| Schiff, 2008 | Placebo + MTX | 0 | 110 | ABA_STD (IV) + MTX | 1 | 156 | INF_STD + MTX | 1 | 165 |
| van der Heijde, 2007 | Placebo + MTX | 1 | 228 | ETN_STD | 2 | 223 | ETN_STD + MTX | 2 | 231 |

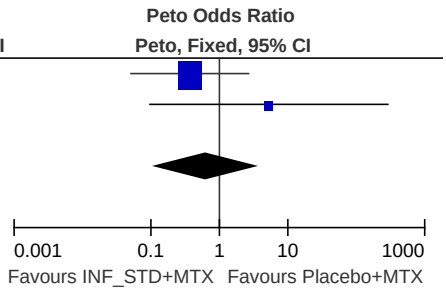
ABA = abatacept; ADA = adalimumab; BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; HD203 = biosimilar etanercept; INF = infliximab; IV = intravenous; MTX = methotrexate; RIT = rituximab; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; SC = subcutaneous; SSZ = sulfasalazine; STD = standard dose; TOC_8 (IV) = 8 mg/kg tocilizumab; TOF = tofacitinib.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

## Figure 24: Mortality (Infliximab with MTX Versus MTX Monotherapy): Meta-Analysis — Peto Odds Ratio

| Study or Subgroup | INF_STD+MTX Events | INF_STD+MTX Total | Placebo+MTX Events | Placebo+MTX Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Maini 1999 | 1 | 86 | 3 | 88 | 80.4% | 0.37 [0.05, 2.67] |
| Schiff 2008 | 1 | 165 | 0 | 110 | 19.6% | 5.29 [0.10, 289.29] |
| **Total (95% CI)** | | **251** | | **198** | **100.0%** | **0.62 [0.11, 3.67]** |
| Total events | 2 | | 3 | | | |

Heterogeneity: Chi² = 1.37, df = 1 (P = 0.24); I² = 27%

Test for overall effect: Z = 0.52 (P = 0.60)



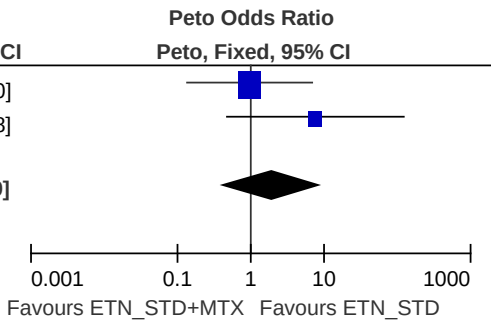

CI = confidence interval; INF = infliximab; MTX = methotrexate; STD = standard dose.

## Figure 25: Mortality (Etanercept with MTX Versus Etanercept Monotherapy): Meta-Analysis — Peto Odds Ratio

| Study or Subgroup | ETN_STD+MTX Events | ETN_STD+MTX Total | ETN_STD Events | ETN_STD Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| van der Heijde 2007 | 2 | 231 | 2 | 223 | 66.6% | 0.97 [0.14, 6.90] |
| van Riel 2006 | 2 | 155 | 0 | 159 | 33.4% | 7.63 [0.48, 122.58] |
| **Total (95% CI)** | | **386** | | **382** | **100.0%** | **1.93 [0.39, 9.59]** |
| Total events | 4 | | 2 | | | |

Heterogeneity: Chi² = 1.42, df = 1 (P = 0.23); I² = 30%

Test for overall effect: Z = 0.80 (P = 0.42)



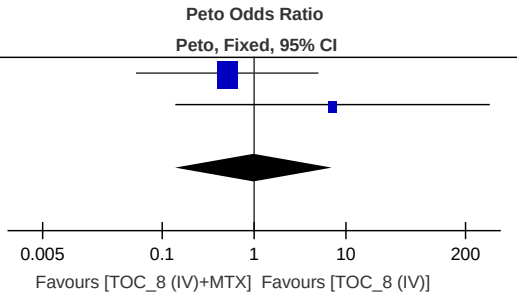

CI = confidence interval; ETN = etanercept; MTX = methotrexate; STD = standard dose.

## Figure 26: Mortality (8 mg/kg Tocilizumab Monotherapy Versus 8 mg/kg Tocilizumab with MTX: Meta-Analysis — Peto Odds Ratio)

| Study or Subgroup | TOC_8 (IV)+MTX Events | TOC_8 (IV)+MTX Total | TOC_8 (IV) Events | TOC_8 (IV) Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Dougados 2013 | 1 | 277 | 2 | 276 | 74.9% | 0.51 [0.05, 4.93] |
| Kaneko 2015 | 1 | 115 | 0 | 111 | 25.1% | 7.14 [0.14, 359.88] |
| **Total (95% CI)** | | **392** | | **387** | **100.0%** | **0.99 [0.14, 7.04]** |
| Total events | 2 | | 2 | | | |

Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² = 23%

Test for overall effect: Z = 0.01 (P = 0.99)

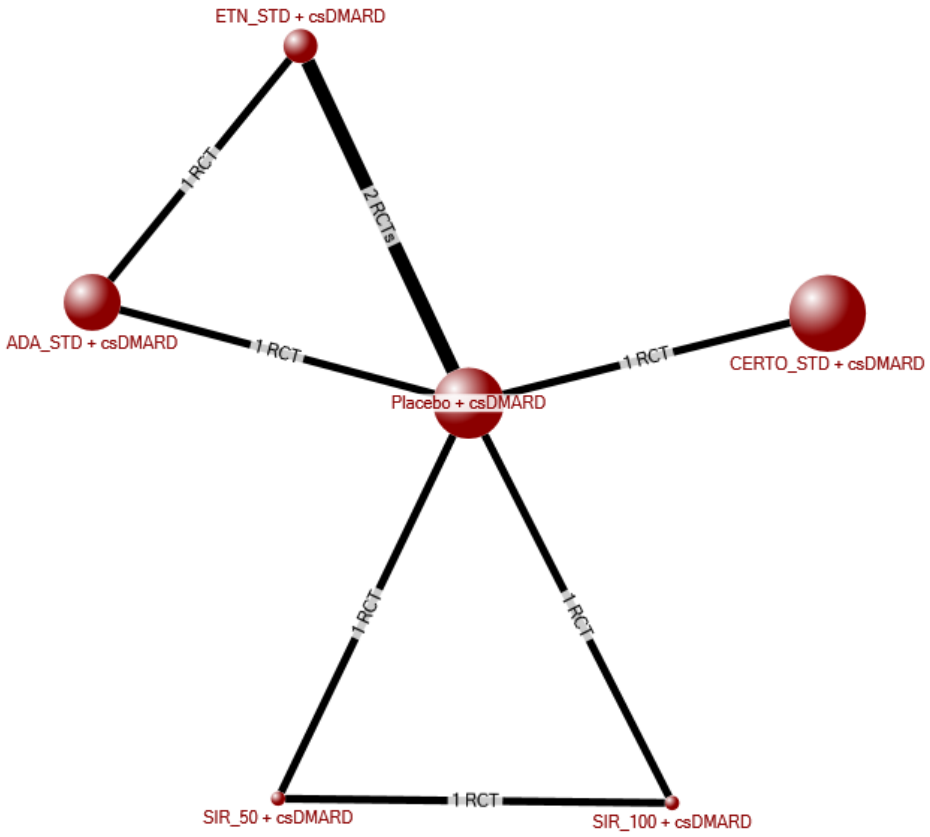



CI = confidence interval; MTX = methotrexate; TOC_8 = 8 mg/kg tocilizumab.

*Conventional Synthetic DMARD as a Common Comparator*

Seven trials treating 1,398 participants with concomitant csDMARD (either MTX or another csDMARD) reported on mortality.[101,143,158,163,172,196,217] Four of these trials had zero events for all treatment arms.[163,172,196,217] One participant receiving adalimumab in combination with a csDMARD died in a study where csDMARD monotherapy was the comparator.[158] Another study reported two deaths in the adalimumab in combination with csDMARD arm and no deaths in the etanercept in combination with csDMARD arm.[101] A three-arm trial compared etanercept in combination with sulfasalazine, etanercept monotherapy, and sulfasalazine monotherapy; during the eligible treatment period, one participant in the etanercept monotherapy arm died and no other deaths were reported in the other treatment arms.[143] A geometric illustration of the evidence network is available in Figure 27. Full mortality data on the included studies is presented in Table 29.

## Figure 27: Evidence Network: Mortality (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




ADA = adalimumab; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; RCT = randomized controlled trial; SIR_50 = 50 mg sirukumab; SIR_100 = 100 mg sirukumab; STD = standard dose.

## Table 29: Mortality Events, Concomitant Conventional Synthetic Disease-Modifying Antirheumatic Drug

| Author, Year | Treatment 1 | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Furst, 2003 | Placebo + csDMARD | 0 | 318 | ADA_STD + csDMARD | 1 | 318 | | | |
| Hobbs, 2015 | Placebo + csDMARD | 0 | 104 | ETN_STD + csDMARD | 0 | 106 | | | |
| Jobanputra, 2012 | ADA_STD + csDMARD | 2 | 60 | ETN_STD + csDMARD | 0 | 60 | | | |
| Kennedy, 2014 | Placebo + csDMARD | 0 | 43 | ADA_STD + csDMARD | 0 | 85 | | | |
| MacIsaac, 2014 | Placebo + csDMARD | 0 | 31 | INF_STD + csDMARD | 0 | 30 | | | |
| Combe, 2009 | Placebo + SSZ | 0 | 50 | ETN_STD | 1 | 103 | ETN_STD + SSZ | 0 | 101 |
| Smolen, 2014 | Placebo + csDMARD | 0 | 30 | SIR_100 + csDMARD | 0 | 30 | SIR_50 + csDMARD | 0 | 30 |

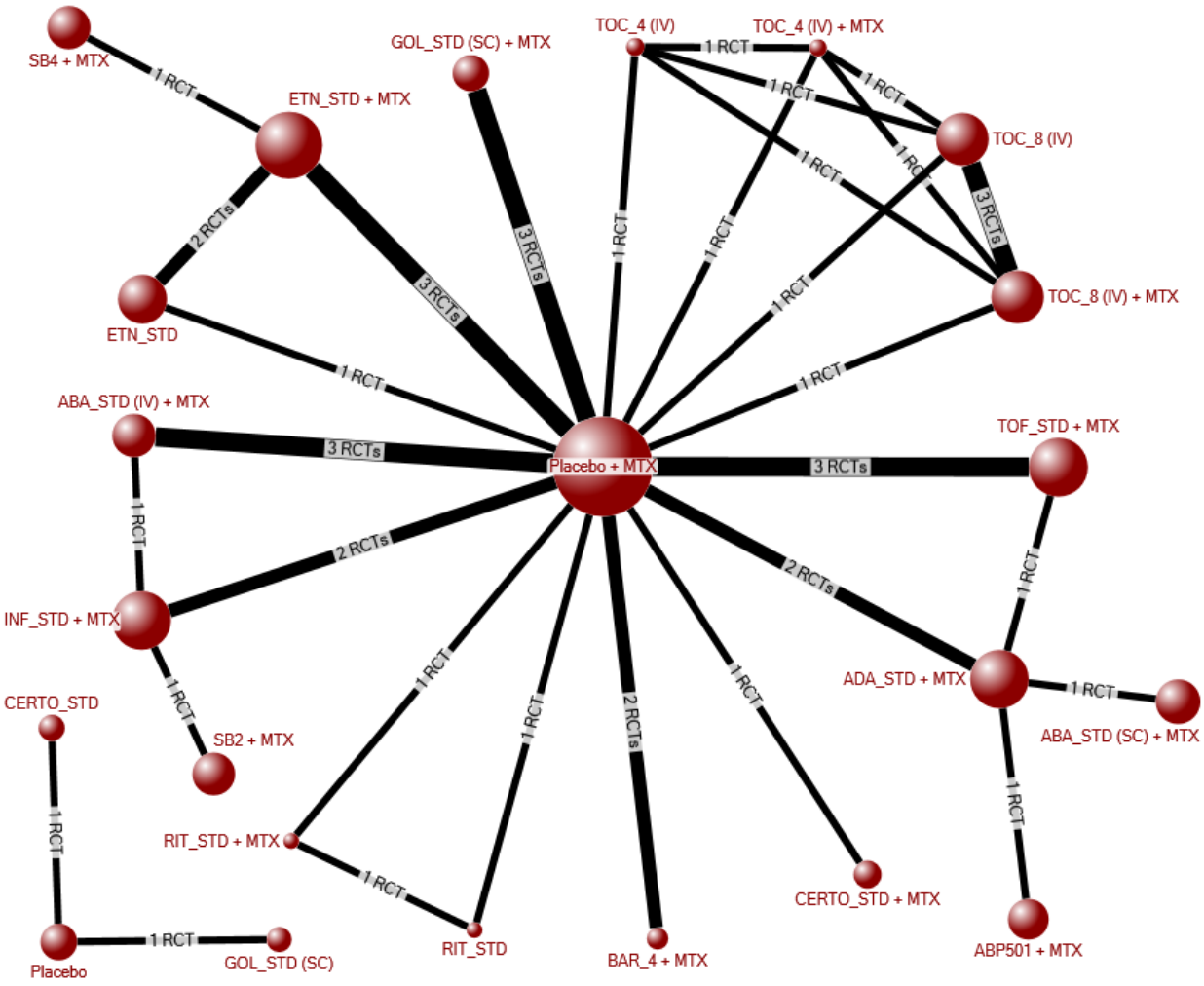
ADA = adalimumab; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; INF = infliximab; SIR_50 = 50 mg sirukumab; SIR_100 = 100 mg sirukumab; SSZ = sulfasalazine; STD = standard dose.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

### Serious Infections

#### *Methotrexate as a Common Comparator*

Twenty-seven studies consisting of 7,963 participants reported on the number of participants experiencing serious infections and involved MTX as the common comparator.[95,99,100,130,138,139,145,150,152,155,156,169,171,175,178,190,191,194,199,223,227,229,230,232,234,236,237] A geometric illustration of the evidence network is available in Figure 28. Full event data for these studies is reported in Table 30.

## Figure 28: Evidence Network: Serious Infections (Placebo + Methotrexate)




ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; ETN = etanercept; GOL = golimumab; INF = infliximab; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; RIT = rituximab; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib.

Six of the studies reported no serious infections among participants in all treatment arms.[145,178,190,227,229,230] In the five-arm CHARISMA trial, no participants developed a serious infection in any treatment arm, except those receiving 8 mg/kg tocilizumab in combination with MTX; three participants out of 50 in that arm developed one or more serious infections.[199] Another study reported zero events in the MTX monotherapy arm, but two participants with serious infections in the tofacitinib in combination with MTX arm.[234]

A pairwise MA of two trials of combination infliximab therapy with MTX compared with MTX monotherapy did not have a statistically significant result (Peto odds ratio = 0.71; 95% CI, 0.28 to 1.79) (Figure 29).[95,194] Two trials compared the combination therapy of tofacitinib

with MTX to MTX alone; the pooled results indicate there is no difference in the number of participants developing serious infections (Peto odds ratio = 2.19; 95% CI, (0.40 to 11.91) (Figure 30).[100,234] Another pairwise MA conducted with MTX monotherapy as the comparator involved two studies of SC golimumab in combination with MTX; no difference in the number of participants with serious infections was found (Peto odds ratio = 1.87; 95% CI, 0.31 to 11.14) (Figure 31).[171,175] There was no statistically significant difference in the number of serious infections based on the pairwise MA of etanercept in combination with MTX compared with MTX alone (Peto odds ratio = 0.88; 95% CI, 0.45 to 1.71) (Figure 32).[191,232] Two studies of adalimumab in combination with MTX compared with MTX monotherapy combined in a pairwise MA had insufficient evidence to demonstrate one treatment having fewer participants with serious infections versus another (Peto odds ratio = 1.29; 95% CI, 0.22 to 7.68) (Figure 33).[100,237]

There were two pairwise MAs that involved direct comparisons of biologic monotherapy versus combination therapy (Figures 33 and 34). The first involved two studies with etanercept in combination with MTX and etanercept monotherapy as the two treatments of interest; there was no statistically significant difference in the number of participants developing serious infections (Peto odds ratio = 1.03; 95% CI, 0.52 to 2.04) (Figure 34).[232,236] The second pairwise MA compared 8 mg/kg tocilizumab monotherapy and combination therapy with MTX among three studies, but there was no statistically significant difference between the treatments in terms of the number of participants with serious infections (Peto odds ratio = 1.14; 95% CI, 0.54 to 2.43) (Figure 35).[150,169,199]

Choy et al. conducted a study comparing certolizumab pegol in combination with MTX with MTX monotherapy; three (2.4%) participants in the certolizumab arm and two (1.7%) in the MTX arm developed a serious infection.[139] The number of participants with a serious infection in a three-arm study by Edwards et al. were as follows: zero events among those receiving rituximab in combination with MTX, two (5.0%) events in the rituximab monotherapy arm, and one (2.5%) event in the MTX monotherapy arm.[152]

Another study that reported cases of serious infection compared SB2 in combination with MTX to its reference product, infliximab, in combination with MTX. There were nine (3.1%) participants who developed a serious infection in the biosimilar infliximab with MTX arm and six (2.0%) participants who developed a serious infection in the infliximab in combination with MTX arm.[138] Emery et al. conducted a study of a head-to-head comparison between a biologic and a biosimilar, both in combination with MTX. They reported one (0.3%) participant with a serious infection in the SB4 (biosimilar etanercept) arm and four (1.3%) participants with serious infections in the etanercept arm.[155] Lastly, one study sponsored by Amgen reported five (1.9%) participants with serious infection in the biosimilar adalimumab in combination with MTX arm and three (1.1%) in the adalimumab in combination with MTX arm.[130] Despite the trials previously mentioned reporting cases of serious infection during the study period, the proportions in each treatment arm remained low and comparable from one trial to another.

The GO-MONO study reported one case of serious infection in the placebo arm and no cases in the SC golimumab monotherapy arm.[223] The FAST4WARD study reported no serious infections in the placebo arm and two cases in the certolizumab pegol monotherapy arm.[156] In the AMPLE study, after two years of treatment, there were 12 (3.8%) and 19 (5.8%) participants with a serious infection in the SC abatacept and adalimumab arms, respectively.[99]

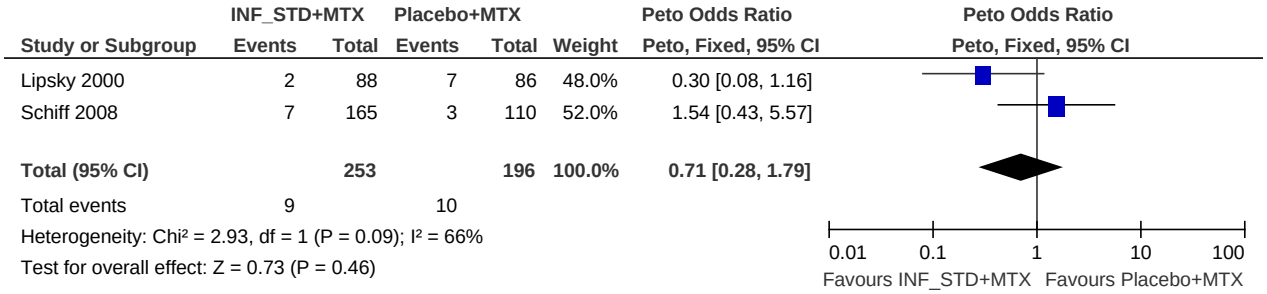
## Table 30: Serious Infections Events, Concomitant Methotrexate

| Author, Year | Trt 1 | n | N | Trt 2 | n | N | Trt 3 | n | N | Trt 4 | n | N | Trt 5 | n | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tanaka, 2016 | Placebo + MTX | 0 | 49 | BAR_4 + MTX | 0 | 24 | | | | | | | | | |
| Keystone, 2015 | Placebo + MTX | 0 | 98 | BAR_4 + MTX | 0 | 52 | | | | | | | | | |
| Conaghan, 2013 | Placebo + MTX | 0 | 23 | ABA_STD (IV) + MTX | 0 | 27 | | | | | | | | | |
| Kermer, 2003 | Placebo + MTX | 0 | 119 | ABA_STD (IV) + MTX | 0 | 115 | | | | | | | | | |
| Tanaka, 2011 | Placebo + MTX | 0 | 28 | TOF_STD + MTX | 0 | 27 | | | | | | | | | |
| Tanaka, 2012 | Placebo + MTX | 0 | 88 | GOL_STD (SC) + MTX | 0 | 86 | | | | | | | | | |
| van der Heijde, 2013t | Placebo + MTX | 0 | 160 | TOF_STD + MTX | 2 | 321 | | | | | | | | | |
| Kay, 2008 | Placebo + MTX | 1 | 34 | GOL_STD (SC) + MTX | 1 | 37 | | | | | | | | | |
| Keystone, 2009 | Placebo + MTX | 1 | 133 | GOL_STD (SC) + MTX | 2 | 89 | | | | | | | | | |
| Lan, 2004 | Placebo + MTX | 1 | 29 | ETN_STD + MTX | 1 | 29 | | | | | | | | | |
| van Vollenhoven, 2011 | Placebo + MTX | 1 | 76 | ADA_STD + MTX | 3 | 79 | | | | | | | | | |
| Choy, 2012 | Placebo + MTX | 2 | 119 | CERTO _STD + MTX | 3 | 124 | | | | | | | | | |
| van Riel, 2006 | ETN_STD | 2 | 159 | ETN_STD + MTX | 1 | 155 | | | | | | | | | |
| Amgen (Sponsor), 2016 | ADA_STD + MTX | 3 | 262 | ABP501 + MTX | 5 | 264 | | | | | | | | | |
| Emery, 2017 | ETN_STD + MTX | 4 | 297 | SB4 + MTX | 1 | 298 | | | | | | | | | |
| Choe, 2017 | INF_STD + MTX | 6 | 293 | SB2 + MTX | 9 | 290 | | | | | | | | | |
| Dougados, 2013 | TOC_8 (IV) | 6 | 276 | TOC_8 (IV) + MTX | 6 | 277 | | | | | | | | | |
| Lipsky, 2000 | Placebo + MTX | 7 | 86 | INF_STD + MTX | 2 | 88 | | | | | | | | | |
| Kaneko, 2016 | TOC_8 (IV) | 7 | 111 | TOC_8 (IV) + MTX | 6 | 115 | | | | | | | | | |
| Takeuchi, 2013 | Placebo | 1 | 105 | GOL_STD (SC) | 0 | 101 | | | | | | | | | |
| Fleischmann, 2009 | Placebo | 0 | 109 | CERTO _STD | 2 | 111 | | | | | | | | | |
| Schiff, 2013 | ADA_STD + MTX | 19 | 328 | ABA_STD (SC) + MTX | 12 | 318 | | | | | | | | | |
| van Vollenhoven, 2012 | Placebo + MTX | 1 | 108 | TOF_STD + MTX | 3 | 204 | ADA_ STD + MTX | 0 | 204 | | | | | | |
| Edwards, 2004 | Placebo + MTX | 1 | 40 | RIT_STD | 2 | 40 | RIT_S TD + MTX | 0 | 40 | | | | | | |
| Schiff, 2008 | Placebo + MTX | 3 | 110 | ABA_STD (IV) + MTX | 2 | 156 | INF_S TD | 7 | 165 | | | | | | |

| Author, Year | Trt 1 | n | N | Trt 2 | n | N | Trt 3 | n | N | Trt 4 | n | N | Trt 5 | n | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | + MTX | | | | | | | | |
| van der Heijde, 2007 | Placebo + MTX | 19 | 228 | ETN_STD | 15 | 223 | ETN_ STD + MTX | 17 | 231 | | | | | | |
| Maini, 2006 | Placebo + MTX | 0 | 49 | TOC_4 (IV) | 0 | 54 | TOC_ 8 (IV) | 0 | 52 | TOC_4 (IV) + MTX | 0 | 49 | TOC_8 (IV) + MTX | 3 | 5 0 |

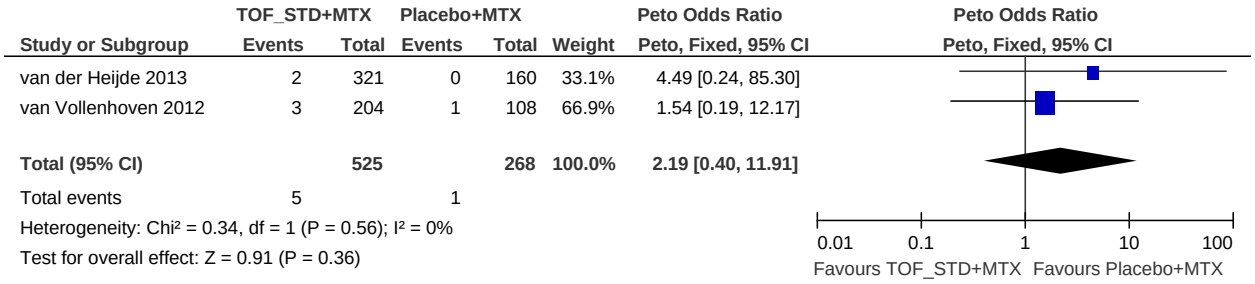
ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; BAR_4 = baricitinib 4 mg; CERTO = certolizumab pegol; ETN = etanercept; GOL = golimumab; INF = infliximab; IV = intravenous; MTX = methotrexate; RIT = rituximab; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; Trt = treatment.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

## Figure 29: Serious Infections (Infliximab with MTX Versus MTX Monotherapy): Meta-Analysis – Peto Odds Ratio




CI = confidence interval; INF = infliximab; MTX = methotrexate; STD = standard dose.

## Figure 30: Serious Infections (Tofacitinib with MTX Versus MTX Monotherapy): Meta-Analysis – Peto Odds Ratio



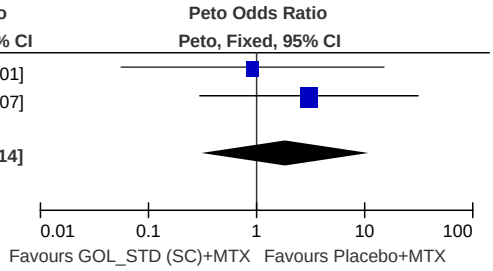

CI = confidence interval; MTX = methotrexate; STD = standard dose; TOF = tofacitinib.

## Figure 31: Serious Infections (Golimumab [SC] with MTX Versus MTX Monotherapy): Meta-Analysis – Peto Odds Ratio

| Study or Subgroup | GOL_STD (SC)+MTX Events | Total | Placebo+MTX Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Kay 2008 | 1 | 37 | 1 | 34 | 40.8% | 0.92 [0.06, 15.01] |
| Keystone 2009 | 2 | 89 | 1 | 133 | 59.2% | 3.05 [0.30, 31.07] |
| **Total (95% CI)** | | **126** | | **167** | **100.0%** | **1.87 [0.31, 11.14]** |
| Total events | 3 | | 2 | | | |

Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%

Test for overall effect: Z = 0.69 (P = 0.49)



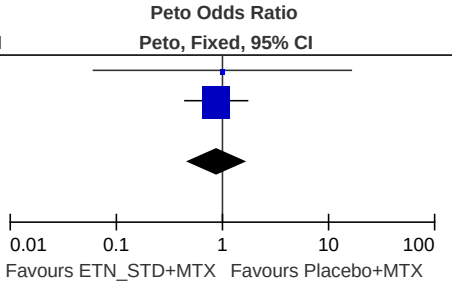

CI = confidence interval; GOL = golimumab; MTX = methotrexate; SC = subcutaneous; STD = standard dose.

## Figure 32: Serious Infections (Etanercept with MTX Versus MTX Monotherapy): Meta-Analysis – Peto Odds Ratio

| Study or Subgroup | ETN_STD+MTX Events | Total | Placebo+MTX Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Lan 2004 | 1 | 29 | 1 | 29 | 5.6% | 1.00 [0.06, 16.39] |
| van der Heijde 2007 | 17 | 231 | 19 | 228 | 94.4% | 0.87 [0.44, 1.73] |
| **Total (95% CI)** | | **260** | | **257** | **100.0%** | **0.88 [0.45, 1.71]** |
| Total events | 18 | | 20 | | | |

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%

Test for overall effect: Z = 0.38 (P = 0.71)



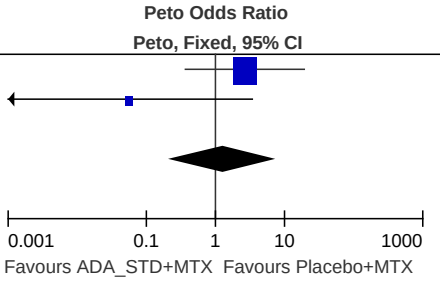

CI = confidence interval; ETN = etanercept; MTX = methotrexate; STD = standard dose.

## Figure 33: Serious Infections (Adalimumab with MTX Versus MTX Monotherapy): Meta-Analysis – Peto Odds Ratio

| Study or Subgroup | ADA_STD+MTX Events | Total | Placebo+MTX Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| van Vollenhoven 2011 | 3 | 79 | 1 | 76 | 81.2% | 2.67 [0.37, 19.31] |
| van Vollenhoven 2012 | 0 | 204 | 1 | 108 | 18.8% | 0.06 [0.00, 3.42] |
| **Total (95% CI)** | | **283** | | **184** | **100.0%** | **1.29 [0.22, 7.68]** |
| Total events | 3 | | 2 | | | |

Heterogeneity: Chi² = 2.75, df = 1 (P = 0.10); I² = 64%

Test for overall effect: Z = 0.28 (P = 0.78)



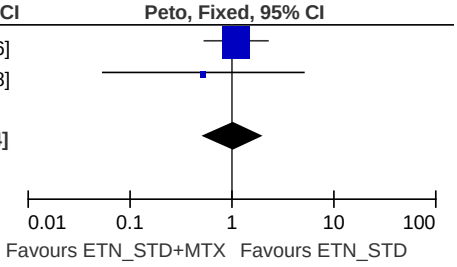

ADA = adalimumab; CI = confidence interval; MTX = methotrexate; STD = standard dose.

## Figure 34: Serious Infections (Etanercept with MTX Versus Etanercept Monotherapy): Meta-Analysis – Peto Odds Ratio

| | ETN_STD+MTX | | ETN_STD | | | Peto Odds Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | Peto, Fixed, 95% CI |
| van der Heijde 2007 | 17 | 231 | 15 | 223 | 90.9% | 1.10 [0.54, 2.26] |
| van Riel 2006 | 1 | 155 | 2 | 159 | 9.1% | 0.52 [0.05, 5.08] |
| **Total (95% CI)** | | **386** | | **382** | **100.0%** | **1.03 [0.52, 2.04]** |
| Total events | 18 | | 17 | | | |

Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%

Test for overall effect: Z = 0.08 (P = 0.93)



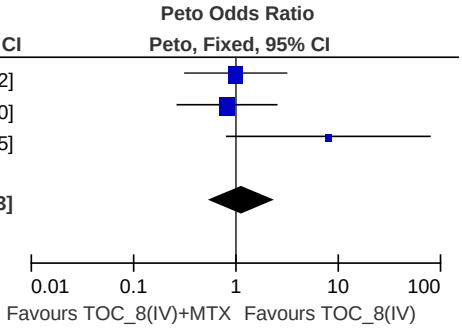

CI = confidence interval; ETN = etanercept; MTX = methotrexate; STD = standard dose.

## Figure 35: Serious Infections (8 mg/kg Tocilizumab [IV] with MTX Versus 8 mg/kg Tocilizumab IV] Monotherapy): Meta-Analysis – Peto Odds Ratio

| | TOC_8 (IV)+MTX | | TOC_8 (IV) | | | Peto Odds Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | Peto, Fixed, 95% CI |
| Dougados 2013 | 6 | 277 | 6 | 276 | 43.6% | 1.00 [0.32, 3.12] |
| Kaneko 2015 | 6 | 115 | 7 | 111 | 45.6% | 0.82 [0.27, 2.50] |
| Maini 2006 | 3 | 50 | 0 | 52 | 10.9% | 8.01 [0.81, 78.85] |
| **Total (95% CI)** | | **442** | | **439** | **100.0%** | **1.14 [0.54, 2.43]** |
| Total events | 15 | | 13 | | | |

Heterogeneity: Chi² = 3.19, df = 2 (P = 0.20); I² = 37%

Test for overall effect: Z = 0.35 (P = 0.73)

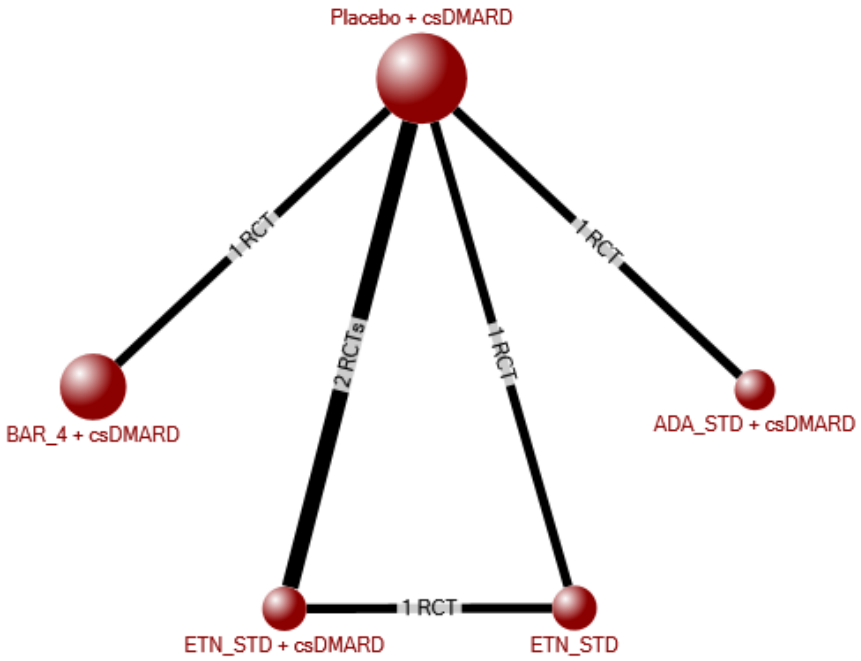



CI = confidence interval; MTX = methotrexate; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab.

### *Conventional Synthetic DMARD as a Common Comparator*

There were four studies with a total of 1,047 participants with csDMARD as a common comparator that reported on serious infection outcomes.[143,151,163,172] It was not possible to conduct an NMA because there were too many treatment arms with zero events. Pairwise MAs were also not possible because no two studies had the same comparison. Figure 36 presents the evidence network; the event data for the available studies are reported in Table 31.

## Figure 36: Evidence Network: Serious Infections (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




ADA = adalimumab; BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; RCT = randomized controlled trial; STD = standard dose.

One of the studies compared etanercept in combination with csDMARD with csDMARD monotherapy and reported zero events in either treatment arm.[163] Etanercept was also an intervention of interest in a three-arm trial comparing etanercept in combination with csDMARD, etanercept monotherapy, and csDMARD monotherapy.[143] In this trial, there were five (5.0%) participants in the etanercept combination arm, 11 (10.7%) in the etanercept monotherapy arm, and zero in the csDMARD monotherapy arm who developed a serious infection.[143] Participants in the etanercept monotherapy arm had statistically significantly higher odds of developing a serious infection compared with participants in the csDMARD monotherapy arm (Peto odds ratio = 4.90; 95% CI, 1.33 to 18.06).[143] A study comparing adalimumab in combination with csDMARD with csDMARD alone reported that only the adalimumab arm had cases of serious infection (n = 2, 2.4%).[172] Finally, the recent RA-BUILD trial of the oral tsDMARD baricitinib in combination with csDMARD versus csDMARD monotherapy reported a low number of cases, with two (0.9%) participants in the 4 mg baricitinib arm and three (1.3%) participants in the csDMARD monotherapy arm having a serious infection.[151]

## Table 31: Serious Infection Events, Concomitant csDMARDs

| Author, Year | Treatment 1 | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Hobbs, 2015 | Placebo + csDMARD | 0 | 104 | ETN_STD + csDMARD | 0 | 106 | | | |
| Kennedy, 2014 | Placebo + csDMARD | 0 | 43 | ADA_STD + csDMARD | 2 | 85 | | | |
| Dougados, 2017 | Placebo + csDMARD | 3 | 228 | BAR_4 + csDMARD | 2 | 227 | | | |
| Combe, 2009 | Placebo + csDMARD | 0 | 50 | ETN_STD | 11 | 103 | ETN_STD + csDMARD | 5 | 101 |

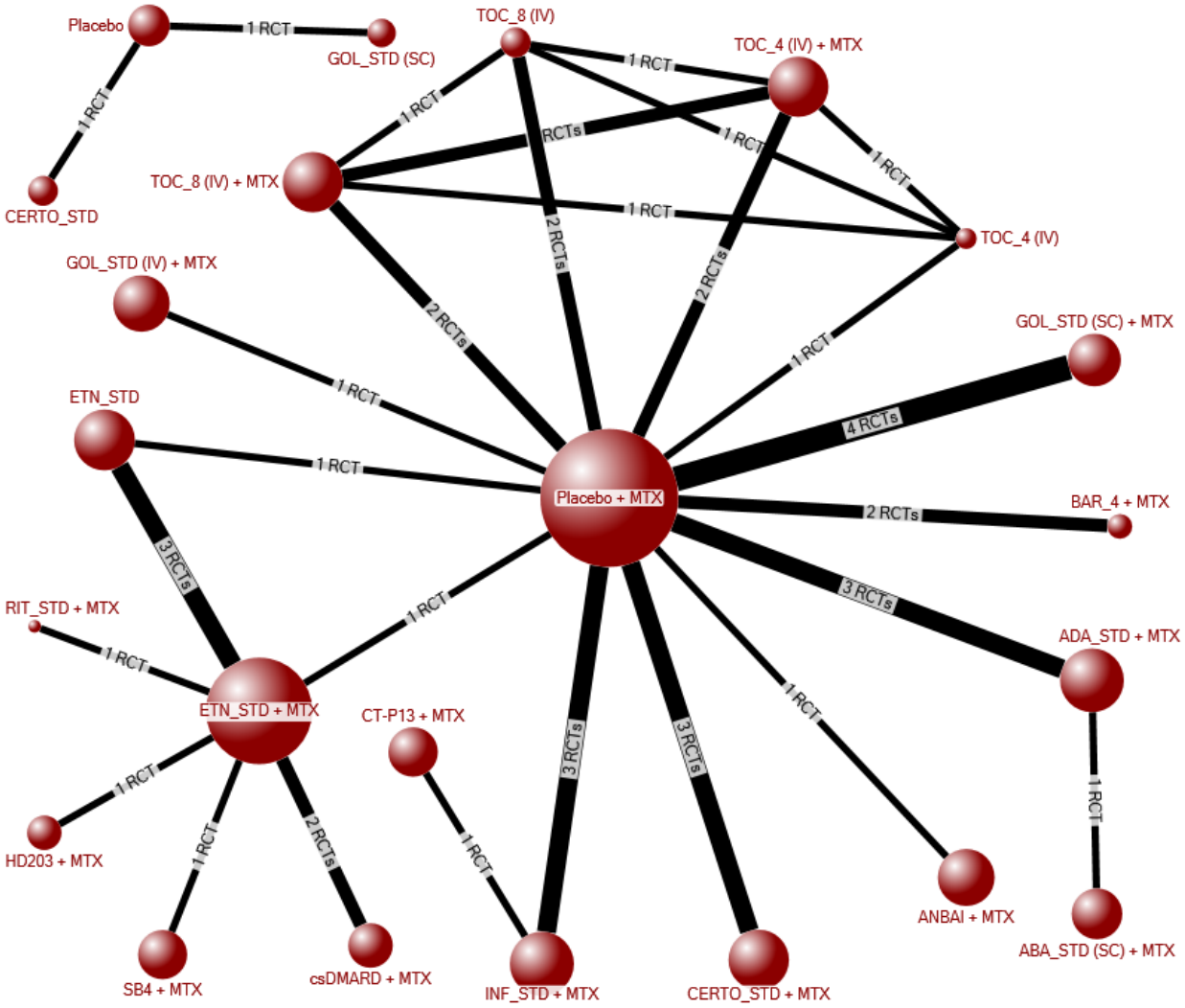
ADA = adalimumab; BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; STD = standard dose.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

### Tuberculosis

#### *Methotrexate as a Common Comparator*

Thirty-two studies with MTX as a common comparator reported on tuberculosis (TB) (active and latent) outcomes among a total of 8,711 participants.[98,99,128,132,136,137,139,155,156,168,171,175,178,179,181,185,193,195,199,204,214,223,227,229,232,236,237,240,245,248,251,253] Twenty-three of these studies reported zero cases of TB in all treatment arms.[98,128,137,139,156,168,171,175,178,179,181,185,193,195,199,204,223,227,229,236,240,245,248] With so many zero events, it was not possible to conduct an NMA. A geometric illustration of the evidence network is available in Figure 37. Descriptive analyses were used for the remaining studies. The event data for all studies reporting TB outcomes are reported in Table 32. One pairwise MA was possible based on two studies that compared adalimumab in combination with MTX with MTX monotherapy. The 95% CI was very wide because both arms had zero events in the MTX monotherapy arm, and it was not possible to detect any statistically significant difference in the number of cases of TB (Peto odds ratio = 5.44; 95% CI, 0.28 to 104.49) (Figure 38).[136,237]

## Figure 37: Evidence Network: Tuberculosis (Placebo + Methotrexate)




ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; ANBAI = Anbainuo (biosimilar etanercept); BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; GOL = golimumab; HD203 = biosimilar etanercept; INF = infliximab; MTX = methotrexate; RCT = randomized controlled trial; RIT = rituximab; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose; TOC_4 = 4 mg/kg tocilizumab; TOC_8 = 8 mg/kg tocilizumab.

One study comparing infliximab in combination with MTX versus MTX monotherapy found that one participant developed TB in the infliximab arm while no participants had TB in the MTX arm.[253] Infliximab was also the comparator in another study for CT-P13 (biosimilar infliximab); the number of participants with TB (latent and active) was high, with 22 cases (7.3%) in the CT-P13 arm and 20 (6.7%) in the infliximab arm.[251]. Smolen et al. compared certolizumab pegol in combination with MTX with MTX monotherapy and reported three and zero participants with tuberculosis in each arm, respectively.[214] A head-to-head study (AMPLE) compared SC abatacept and adalimumab over a two-year period; two participants in the adalimumab and none in the abatacept arm developed TB.

Three studies included etanercept, with different comparators. One was a three-arm study comparing etanercept in combination with MTX, etanercept monotherapy, and MTX monotherapy. The only case of TB that occurred in that study was in the etanercept combination arm.[232] A study by Emery et al. on SB4 (biosimilar etanercept) versus etanercept, both in combination with MTX, reported a somewhat high number of cases of TB in both arms: 13 cases (4.4%) in the biosimilar arm and 12 cases (4.0%) in the etanercept arm, respectively.[155] Bae et al. conducted a study of a different biosimilar etanercept (HD203) in combination with MTX compared with etanercept in combination with MTX; the numbers of participants who developed TB during the study were 14 (9.5%) and 8 (5.5%) in the HD203 and etanercept arms, respectively.[132]

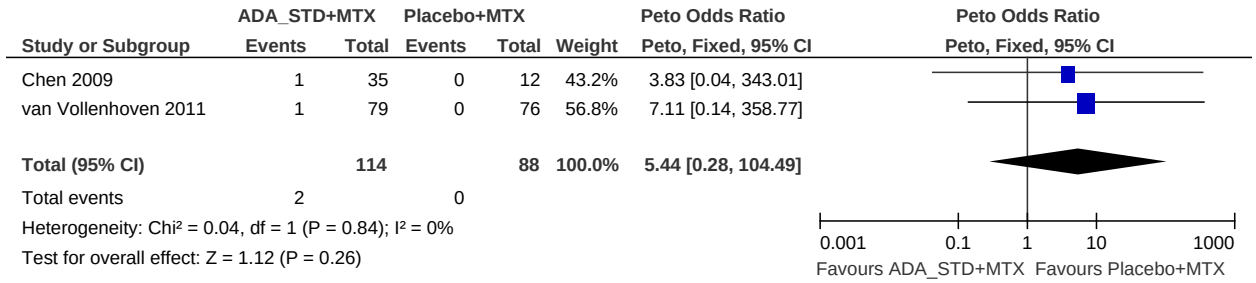
## Table 32: Tuberculosis Events, Concomitant Methotrexate

| Author, Year | Trt1 | n | N | Trt2 | n | N | Trt3 | n | N | Trt4 | n | N | Trt5 | n | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Li, 2016 | Placebo + MTX | 0 | 132 | GOL_STD (SC) + MTX | 0 | 131 | | | | | | | | | |
| Tanaka, 2016 | Placebo + MTX | 0 | 49 | BAR_4 + MTX | 0 | 24 | | | | | | | | | |
| Keystone, 2015 | Placebo + MTX | 0 | 98 | BAR_4 + MTX | 0 | 52 | | | | | | | | | |
| Weinblatt, 2015 | Placebo + MTX | 0 | 61 | ADA_STD + MTX | 0 | 59 | | | | | | | | | |
| Yamamoto, 2014 | Placebo + MTX | 0 | 77 | CERTO _STD + MTX | 0 | 82 | | | | | | | | | |
| Choy, 2012 | Placebo + MTX | 0 | 119 | CERTO _STD + MTX | 0 | 124 | | | | | | | | | |
| Weinblatt, 2013 | Placebo + MTX | 0 | 197 | GOL_STD (IV) + MTX | 0 | 395 | | | | | | | | | |
| Abe, 2006 | Placebo + MTX | 0 | 47 | INF_STD + MTX | 0 | 49 | | | | | | | | | |
| Kim, 2013 | Placebo + MTX | 0 | 72 | INF_STD + MTX | 0 | 71 | | | | | | | | | |
| Nishimoto, 2009 | Placebo + MTX | 0 | 64 | TOC_8 (IV) | 0 | 61 | | | | | | | | | |
| Tanaka, 2012 | Placebo + MTX | 0 | 88 | GOL_STD (SC) + MTX | 0 | 86 | | | | | | | | | |
| Kay, 2008 | Placebo + MTX | 0 | 34 | GOL_STD (SC) + MTX | 0 | 37 | | | | | | | | | |
| Keystone, 2009 | Placebo + MTX | 0 | 133 | GOL_STD (SC) + MTX | 0 | 89 | | | | | | | | | |
| Chen, 2016 | Placebo + MTX | 0 | 200 | ANBAI + MTX | 0 | 400 | | | | | | | | | |
| Kim, 2012 | csDMARD + MTX | 0 | 103 | ETN_STD + MTX | 0 | 197 | | | | | | | | | |
| Machado, 2014 | csDMARD + MTX | 0 | 142 | ETN_STD + MTX | 0 | 279 | | | | | | | | | |
| Kameda, 2010 | ETN_STD | 0 | 74 | ETN_STD + MTX | 0 | 77 | | | | | | | | | |
| van Riel, 2006 | ETN_STD | 0 | 159 | ETN_STD + MTX | 0 | 155 | | | | | | | | | |
| Gashi, 2014 | ETN_STD + MTX | 0 | 13 | RIT_STD + MTX | 0 | 20 | | | | | | | | | |
| Chen, 2009 | Placebo + MTX | 0 | 12 | ADA_STD + MTX | 1 | 35 | | | | | | | | | |

| Author, Year | Trt1 | n | N | Trt2 | n | N | Trt3 | n | N | Trt4 | n | N | Trt5 | n | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Smolen, 2009 | Placebo + MTX | 0 | 127 | CERTO _STD + MTX | 3 | 246 | | | | | | | | | |
| van Vollenhoven, 2011 | Placebo + MTX | 0 | 76 | ADA_STD + MTX | 1 | 79 | | | | | | | | | |
| Zhang, 2006 | Placebo + MTX | 0 | 86 | INF_STD + MTX | 1 | 87 | | | | | | | | | |
| Bae, 2017 | ETN_STD + MTX | 8 | 146 | HD203 + MTX | 14 | 147 | | | | | | | | | |
| Emery, 2017 | ETN_STD + MTX | 12 | 297 | SB4 + MTX | 13 | 298 | | | | | | | | | |
| Yoo, 2016 | INF_STD + MTX | 20 | 300 | CT-P13 + MTX | 22 | 302 | | | | | | | | | |
| Schiff, 2013 | ADA_STD + MTX | 2 | 328 | ABA_STD (SC) + MTX | 0 | 318 | | | | | | | | | |
| Takeuchi, 2012 | Placebo | 0 | 105 | GOL_STD (SC) | 0 | 101 | | | | | | | | | |
| Fleischmann, 2009 | Placebo | 0 | 109 | CERTO _STD | 0 | 111 | | | | | | | | | |
| Klareskog, 2004 | Placebo + MTX | 0 | 228 | ETN_STD | 0 | 223 | ETN_STD + MTX | 1 | 231 | | | | | | |
| Kremer, 2011 | Placebo + MTX | 0 | 393 | TOC_4 (IV) + MTX | 0 | 399 | TOC_8 (IV) + MTX | 0 | 398 | | | | | | |
| Maini, 2006 | Placebo + MTX | 0 | 49 | TOC_4 (IV) | 0 | 54 | TOC_8 (IV) | 0 | 52 | TOC_4 (IV) + MTX | 0 | 49 | TOC_8 (IV) + MTX | 0 | 50 |

ABA = abatacept; ABP501 = adalimumab biosimilar; ADA = adalimumab; ANBAI = Anbainuo (biosimilar etanercept); BAR_4 = baricitinib 4 mg; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; GOL = golimumab; HD203 = biosimilar infliximab; INF = infliximab; IV = intravenous; MTX = methotrexate; RIT = rituximab; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose; TOC_4 = tocilizumab 4 mg/kg; TOC_8 = tocilizumab 8 mg/kg; Trt = treatment.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

## Figure 38: Tuberculosis (Adalimumab with MTX Versus MTX Monotherapy): Meta-Analysis – Peto Odds Ratio

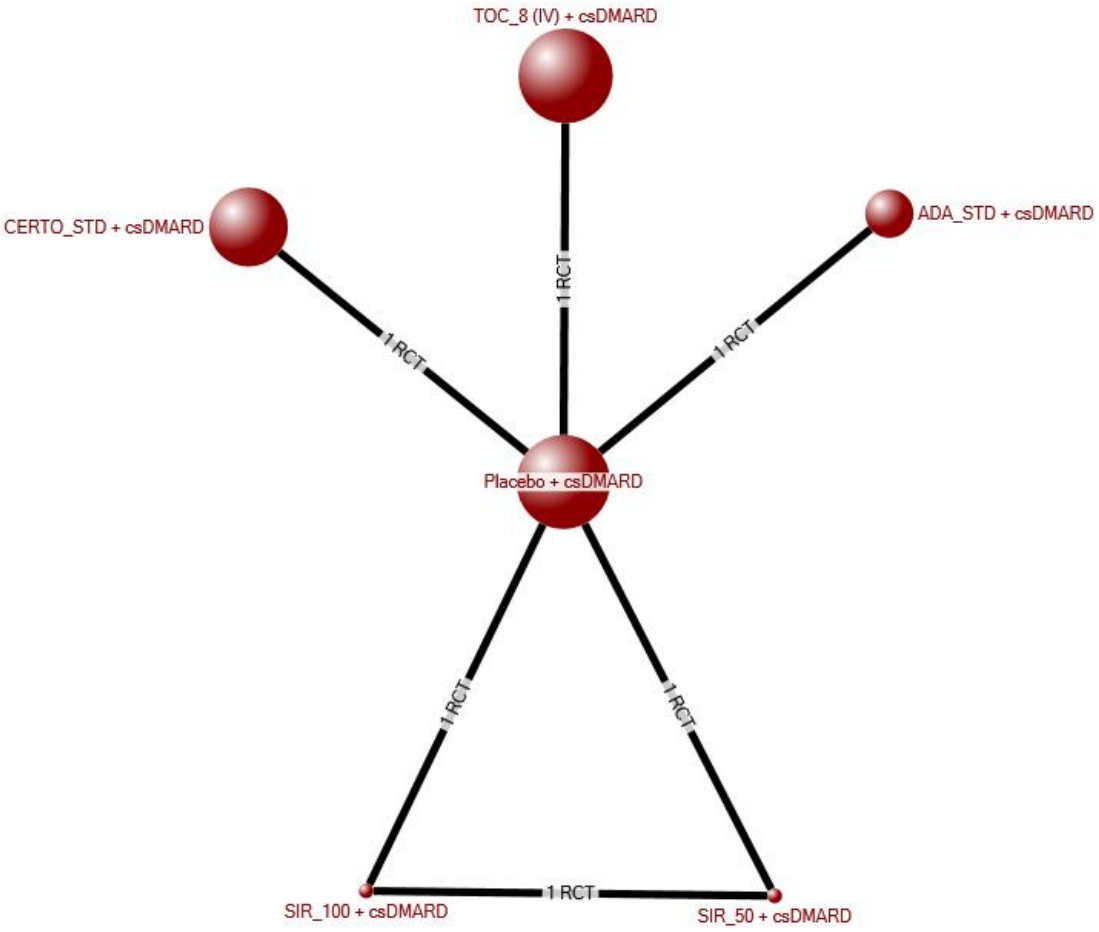



ADA = adalimumab; CI = confidence interval; MTX = methotrexate; STD = standard dose.

*Conventional Synthetic Disease-Modifying Antirheumatic Drug as a Common Comparator*

Four trials involving csDMARD as the common comparator and 2,556 total participants reported on tuberculosis outcomes.[158,162,217,249] There were no cases of TB reported in any treatment of these trials. A geometric illustration of the evidence network is available in Figure 39. Event data are available in Table 33.

## Figure 39: Evidence Network: Tuberculosis (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




ADA = adalimumab; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; IV = intravenous; SIR_100 = 100mg sirukumab; SIR_50 = 50 mg sirukumab; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab.

## Table 33: Tuberculosis Events, Concomitant Conventional Synthetic DMARD

| Author, Year | Treatment 1 | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Yazici 2012 | Placebo + csDMARD | 0 | 205 | TOC_8 (IV) + csDMARD | 0 | 409 | | | |
| Furst 2003 | Placebo + csDMARD | 0 | 318 | ADA_STD + csDMARD | 0 | 318 | | | |
| Genovese 2008 | Placebo + csDMARD | 0 | 414 | TOC_8 (IV) + csDMARD | 0 | 802 | | | |
| Smolen 2014 | Placebo + csDMARD | 0 | 30 | SIR_100 + csDMARD | 0 | 30 | SIR_50 + csDMARD | 0 | 30 |

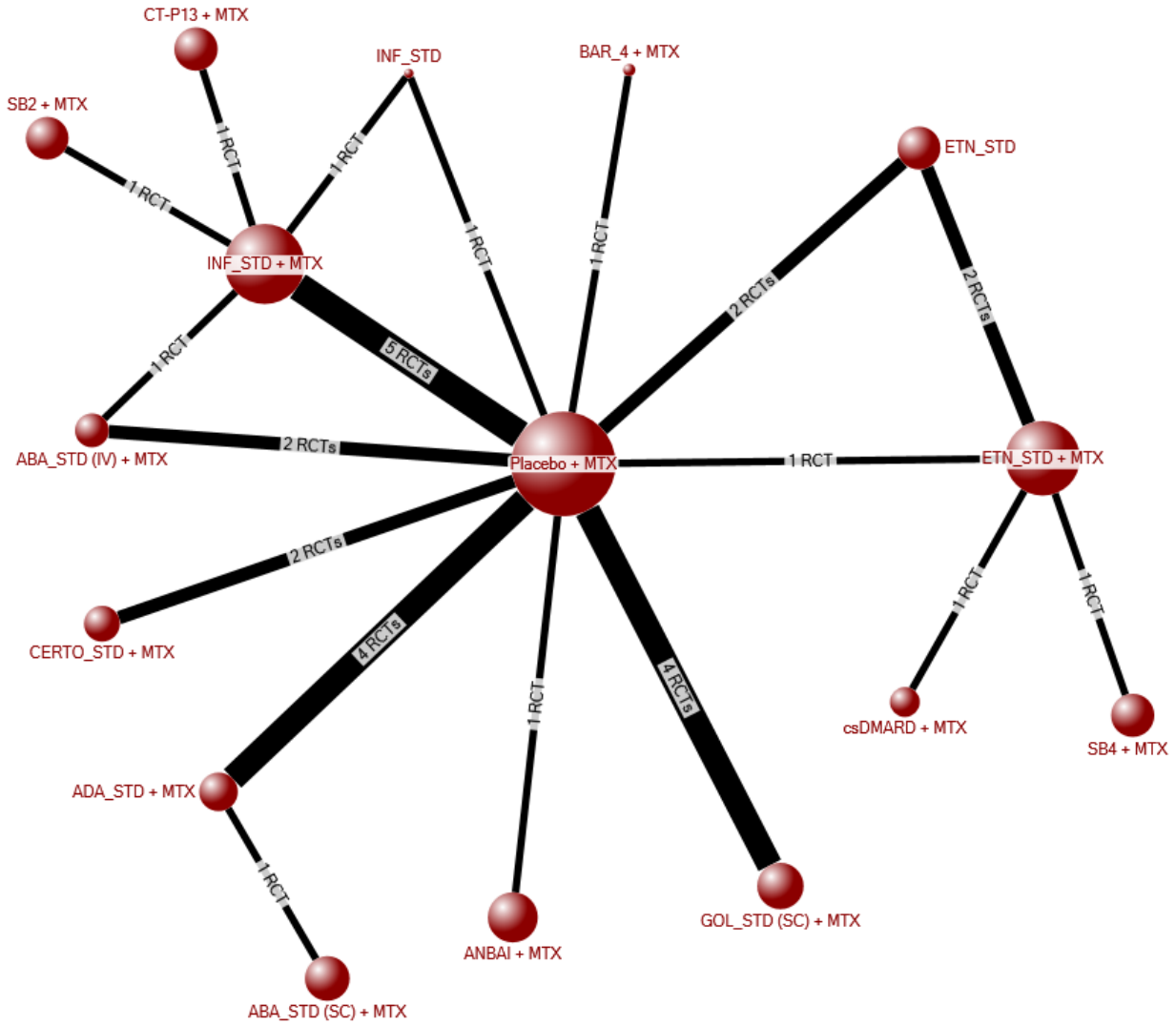
ADA = adalimumab; csDMARD = conventional synthetic disease-modifying antirheumatic drug; IV = intravenous; SIR_100 = 100mg sirukumab; SIR_50 = 50 mg sirukumab; STD = standard dose; TOC_8 = 8 mg/kg tocilizumab.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

### Cancer

#### *Methotrexate as a Common Comparator*

A total of 27 RCTs in which MTX monotherapy was the common comparator reported on cancer outcomes with 7,374 participants contributing data.[95,99,136-139,145,155,156,167,171,175,180,181,193,195,197,198,223,227,229,233,237,245,248,250,253] Nineteen of these trials had zero events in all treatment arms for the duration of the treatment period eligible for our analysis.[136,137,139,145,156,171,175,180,193,195,197,198,223,227,229,237,245,248,253] A geometric illustration of the evidence network is presented in Figure 40. The number of cancer events in each study is reported in Table 34.

## Figure 40: Evidence Network: Cancer (Placebo + Methotrexate)




ABA = abatacept; ADA = adalimumab; ANBAI = Anbainuo (biosimilar etanercept); BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; GOL = golimumab; INF = infliximab; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose.

Two trials compared etanercept monotherapy and combination therapy with MTX. A pooled estimate of the treatment effects indicates that there is no statistically significant difference between etanercept monotherapy and combination therapy (95% CI, 0.69 to 11.22)[167,233] (Figure 41). In a direct comparison of SB4 (biosimilar etanercept) with etanercept, both in combination with MTX, the etanercept arm had one case of cancer and the biosimilar arm reported three cases (Emery 2017).[155] The three-arm trial by van der Heijde et al. from 2006 reported five cases of cancer in the etanercept monotherapy and etanercept in combination with MTX arms (2.2% each) and two cases in the MTX monotherapy arm (0.9%).

A pairwise MA was conducted on two trials that compared infliximab in combination with MTX versus MTX monotherapy. The results were not statistically significant (95% CI, 0.10 to 5.41)[95,181] (Figure 42). The study by Schiff et al. published in 2008 was a three-arm trial where the third treatment arm was abatacept. That arm had one participant develop cancer.[95] In a study by Choe et al. (2015), two participants in the arm where patients received SB2 (biosimilar infliximab) in combination with MTX developed cancer during the study period, but none of the participants in the infliximab in combination with MTX arm developed cancer. In a study that directly compared infliximab with CT-P13 (biosimilar infliximab), both in combination with MTX, the infliximab arm reported two cases of cancer.[250] Lastly, the AMPLE study compared treatment with adalimumab and SC abatacept, both with concomitant MTX, over a two-year period. Seven patients in each arm (2.1% and 2.2% of participants, respectively) developed cancer.[99]

Overall, the number of participants who developed cancer was very low across all trials. Even in those trials where there were cases, the proportion was low and was comparable between the treatment and control arms.

## Table 34: Cancer Events, Concomitant Methotrexate

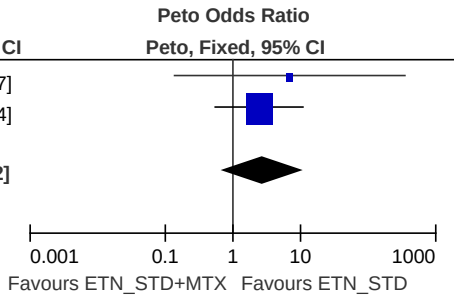
| Author, Year | Treatment | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Choe 2017 | INF_STD + MTX | 0 | 293 | SB2 + MTX | 2 | 290 | | | |
| Tanaka 2016 | Placebo + MTX | 0 | 49 | BAR_4 + MTX | 0 | 24 | | | |
| Li 2016 | Placebo + MTX | 0 | 132 | GOL_STD (SC) + MTX | 0 | 131 | | | |
| Weinblatt 2015 | Placebo + MTX | 0 | 61 | ADA_STD + MTX | 0 | 59 | | | |
| Kim 2007 | Placebo + MTX | 0 | 63 | ADA_STD + MTX | 0 | 65 | | | |
| Yamamoto 2014 | Placebo + MTX | 0 | 77 | CERTO_STD + MTX | 0 | 82 | | | |
| Choy 2012 | Placebo + MTX | 0 | 119 | CERTO_STD + MTX | 0 | 124 | | | |
| Conaghan 2013 | Placebo + MTX | 0 | 23 | ABA_STD (IV) + MTX | 0 | 27 | | | |
| Kim 2013 | Placebo + MTX | 1 | 72 | INF_STD + MTX | 0 | 71 | | | |
| Tanaka 2012 | Placebo + MTX | 0 | 88 | GOL_STD (SC) + MTX | 0 | 86 | | | |
| Chen 2009 | Placebo + MTX | 0 | 12 | ADA_STD + MTX | 0 | 35 | | | |
| Kay 2008 | Placebo + MTX | 0 | 34 | GOL_STD (SC) + MTX | 0 | 37 | | | |
| Keystone 2009 | Placebo + MTX | 0 | 133 | GOL_STD (SC) + MTX | 0 | 89 | | | |
| Maini 1999 | Placebo + MTX | 0 | 88 | INF_STD + MTX | 0 | 86 | | | |
| van Vollenhoven 2011 | Placebo + MTX | 0 | 76 | ADA_STD + MTX | 0 | 79 | | | |
| Zhang 2006 | Placebo + MTX | 0 | 86 | INF_STD + MTX | 0 | 87 | | | |
| Chen 2016 | Placebo + MTX | 0 | 200 | ANBAI + MTX | 0 | 400 | | | |
| Machado 2014 | csDMARD + MTX | 0 | 143 | ETN_STD + MTX | 0 | 281 | | | |
| Kameda 2010 | ETN_STD | 0 | 71 | ETN_STD + MTX | 1 | 76 | | | |
| Emery 2017 | ETN_STD + MTX | 1 | 297 | SB4 + MTX | 3 | 298 | | | |
| Yoo 2013 | INF_STD + MTX | 2 | 301 | CT-P13 + MTX | 0 | 301 | | | |

| Author, Year | Treatment | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Takeuchi 2013 | Placebo | 0 | 105 | GOL_STD (SC) | 0 | 101 | | | |
| Fleischmann 2009 | Placebo | 0 | 109 | CERTO_STD | 0 | 111 | | | |
| Schiff 2013 | ADA_STD + MTX | 7 | 328 | ABA_STD (SC) + MTX | 7 | 318 | | | |
| Maini 1998 | Placebo + MTX | 0 | 14 | INF_STD | 0 | 14 | INF_STD + MTX | 0 | 15 |
| Schiff 2008 | Placebo + MTX | 1 | 110 | ABA_STD (IV) + MTX | 1 | 156 | INF_STD + MTX | 2 | 165 |
| van der Heijde 2006 | Placebo + MTX | 2 | 228 | ETN_STD | 5 | 223 | ETN_STD + MTX | 5 | 231 |

ABA = abatacept; ADA = adalimumab; ANBAI = Anbainuo (biosimilar etanercept); BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; GOL = golimumab; INF = infliximab; IV = intravenous; MTX = methotrexate; SB2 = biosimilar infliximab; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

## Figure 41: Cancer (Etanercept MTX Versus Etanercept Monotherapy): Meta-Analysis – Peto Odds Ratio

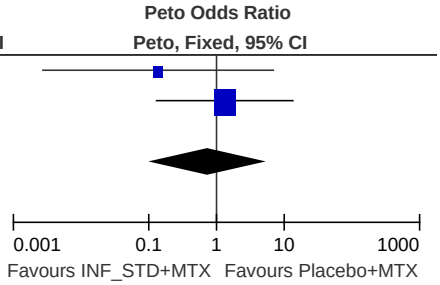
| | ETN_STD+MTX | | ETN_STD | | | Peto Odds Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | Peto, Fixed, 95% CI |
| Kameda 2010 | 1 | 76 | 0 | 71 | 12.6% | 6.92 [0.14, 349.47] |
| van der Heijde 2006 | 5 | 223 | 2 | 228 | 87.4% | 2.44 [0.55, 10.84] |
| **Total (95% CI)** | | **299** | | **299** | **100.0%** | **2.78 [0.69, 11.22]** |
| Total events | 6 | | 2 | | | |
| Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.44 (P = 0.15) | | | | | | |




CI = confidence interval; etanercept; MTX = methotrexate; STD = standard dose.

## Figure 42: Cancer (Infliximab with MTX Versus MTX Monotherapy): Meta-Analysis – Peto Odds Ratio

| | INF_STD+MTX | | Placebo+MTX | | | Peto Odds Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | Peto, Fixed, 95% CI |
| Kim 2013 | 0 | 71 | 1 | 72 | 25.9% | 0.14 [0.00, 6.92] |
| Schiff 2008 | 2 | 165 | 1 | 110 | 74.1% | 1.32 [0.13, 13.44] |
| **Total (95% CI)** | | **236** | | **182** | **100.0%** | **0.74 [0.10, 5.41]** |
| Total events | 2 | | 2 | | | |
| Heterogeneity: Chi² = 0.95, df = 1 (P = 0.33); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.30 (P = 0.76) | | | | | | |



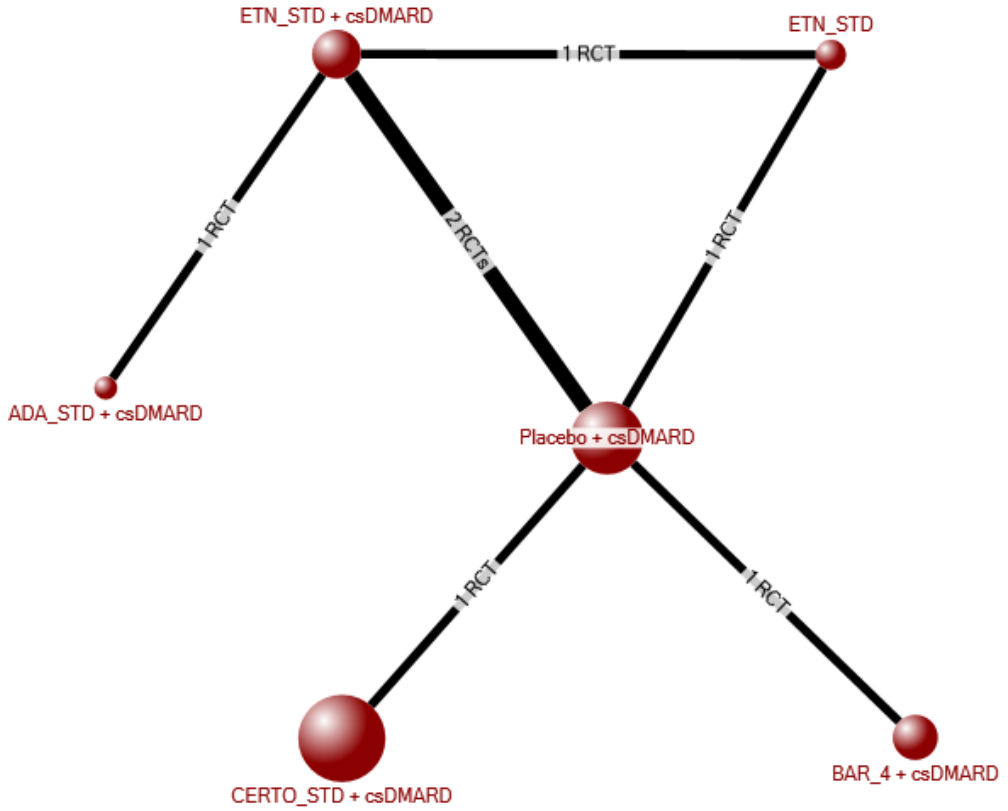

CI = confidence interval; INF = infliximab; MTX = methotrexate; STD = standard dose.

*Conventional Synthetic DMARD as a Common Comparator*

There were four trials with a total of 1,039 participants that reported on cancer outcomes with csDMARDs as the common comparator.[101,143,151,163] A geometric illustration of the evidence network is available in Figure 43. Results for the number of cancer events in these studies are reported in Table 35.

One study reported zero events in both the etanercept with csDMARD monotherapy arm and the csDMARD monotherapy arm.[163] Another study that used csDMARD monotherapy as the comparator reported one case of cancer in the arm combining 4 mg baricitinib with csDMARD.[151] In the RED SEA trial, one participant developed cancer in each of the etanercept in combination with csDMARD and adalimumab in combination with csDMARD arms.[101] A three-arm trial lasting two years reported zero cases of cancer in the arms with SSZ monotherapy and etanercept in combination with SSZ and two cases (out of 103 participants) in the etanercept monotherapy arm.[143]

## Figure 43: Evidence Network: Cancer (Placebo + Conventional Synthetic Disease-Modifying Antirheumatic Drug)




ADA = adalimumab; BAR_4 = 4 mg baricitinib; CERTO = certolizumab pegol; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; RCT = randomized controlled trial; STD = standard dose.

## Table 35: Cancer Event Data, Concomitant Conventional Synthetic Disease-Modifying Antirheumatic Drug

| Author, Year | Trt 1 | n | N | Trt 2 | n | N | Trt 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Jobanputra 2012 | ETN_STD + csDMARD | 1 | 60 | ADA_STD + csDMARD | 1 | 60 | | | |
| Hobbs 2015 | Placebo + csDMARD | 0 | 104 | ETN_STD + csDMARD | 0 | 106 | | | |
| Dougados 2017 | Placebo + csDMARD | 0 | 228 | BAR_4 + csDMARD | 1 | 227 | | | |
| Combe 2009 | Placebo + SSZ | 0 | 50 | ETN_STD | 2 | 103 | ETN_STD + SSZ | 0 | 101 |

ADA = adalimumab; BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; SSZ = sulfasalazine; STD = standard dose; Trt = treatment.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

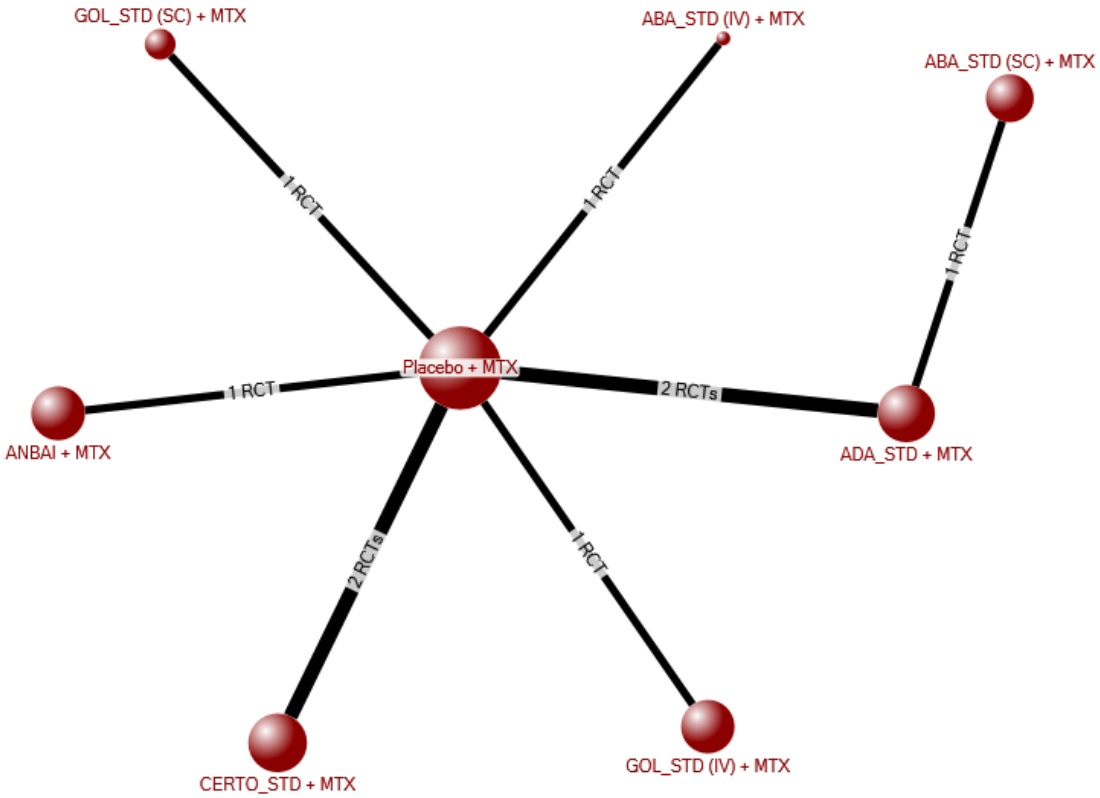
### Leukemia

*Methotrexate as a Common Comparator*

A total of eight RCTs[137,145,174,180,193,245,246,248] permitted concomitant treatment with MTX and reported leukemia outcomes, with 3,150 participants contributing data. A geometric illustration of the evidence network is available in Figure 44.

Two studies compared certolizumab pegol in combination with MTX versus MTX monotherapy. Two studies also compared adalimumab in combination with MTX versus MTX monotherapy. One study each of golimumab (SC), golimumab (IV), abatacept (IV), and Anbainuo (biosimilar etanercept), all in combination with MTX, was compared with MTX monotherapy. All of these studies reported no leukemia events for the eligible time period for analysis. There was only one case of leukemia reported in the SC abatacept arm of the AMPLE study after two years of treatment; there were no cases in the adalimumab arm (Table 36).[99]

## Figure 44: Evidence Network: Leukemia (Placebo + MTX)




ABA = abatacept; ADA = adalimumab; ANBAI = Anbainuo (biosimilar etanercept); CERTO = certolizumab pegol; GOL = golimumab; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; SC = subcutaneous; STD = standard dose.

## Table 36: Leukemia Event Data, Concomitant Methotrexate

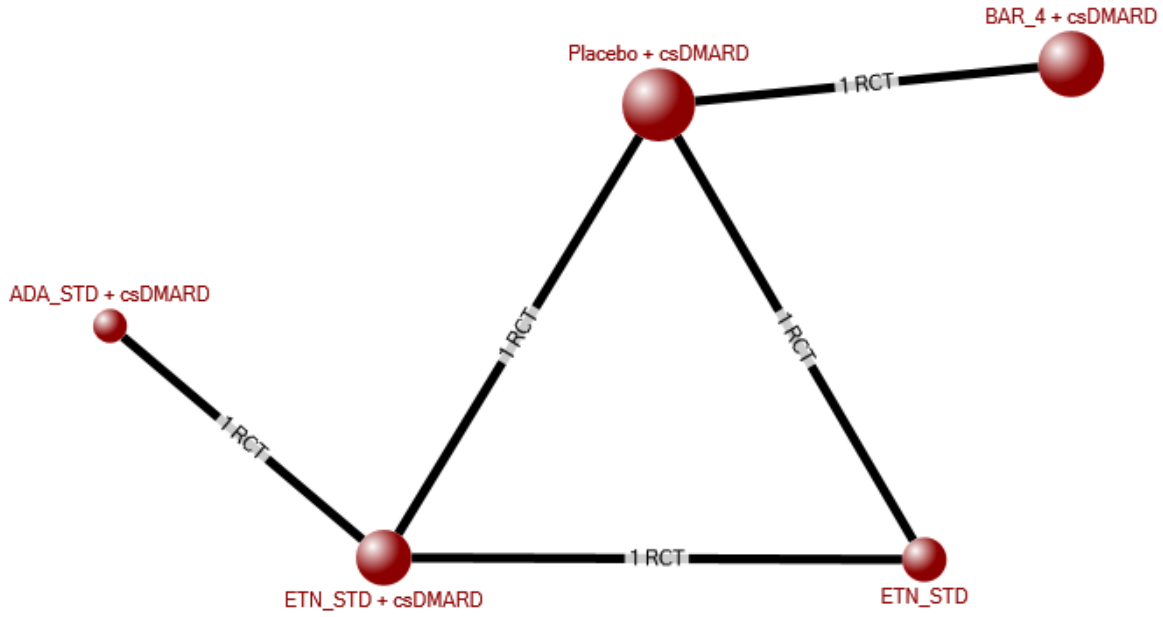
| Author, Year | Treatment 1 | n | N | Treatment 2 | n | N |
|---|---|---|---|---|---|---|
| Li 2016 | Placebo + MTX | 0 | 132 | GOL_STD (SC) + MTX | 0 | 131 |
| Weinblatt 2015 | Placebo + MTX | 0 | 61 | ADA_STD + MTX | 0 | 59 |
| Weinblatt 2014 | Placebo + MTX | 0 | 197 | GOL_STD (IV) + MTX | 0 | 395 |
| Kim 2007 | Placebo + MTX | 0 | 63 | ADA_STD + MTX | 0 | 65 |
| Yamamoto 2014 | Placebo + MTX | 0 | 77 | CERTO_STD + MTX | 0 | 82 |
| Conaghan 2013 | Placebo + MTX | 0 | 23 | ABA_STD (IV) + MTX | 0 | 27 |
| Keystone 2008 | Placebo + MTX | 0 | 199 | CERTO_STD + MTX | 0 | 393 |
| Chen 2016 | Placebo + MTX | 0 | 200 | ANBAI + MTX | 0 | 400 |
| Schiff 2013 | ADA_STD + MTX | 0 | 328 | ABA_STD (SC) + MTX | 1 | 318 |

ABA = abatacept; ADA = adalimumab; ANBAI = Anbainuo (biosimilar etanercept); CERTO = certolizumab pegol; IV = intravenous; GOL = golimumab; MTX = methotrexate; SC = subcutaneous; STD = standard dose.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

*Conventional Synthetic DMARD as a Common Comparator*

A total of three RCTs[101,143,151] of a biologic or tsDMARD in combination with a csDMARD and reported leukemia outcomes. A geometric illustration of the evidence network is available in Figure 45. One study comparing 4 mg baricitinib in combination with a csDMARD versus csDMARD monotherapy reported no leukemia events during the treatment period eligible for analysis.[151] In a direct comparison of etanercept and adalimumab, both in combination with a csDMARD, the etanercept arm reported one case of leukemia out of 60 participants.[101] In a three-arm trial of etanercept monotherapy, etanercept in combination with SSZ, and SSZ monotherapy, one out of 103 participants in the etanercept monotherapy arm developed leukemia during the study[143] (Table 37).

## Figure 45: Evidence Network: Leukemia (Placebo + csDMARD)




ADA = adalimumab; BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; RCT = randomized controlled trial; STD = standard dose.

## Table 37: Leukemia Event Data, Conventional Synthetic Disease-Modifying Antirheumatic Drug

| Author, Year | Treatment 1 | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Jobanputra 2012 | ETN_STD + csDMARD | 1 | 60 | ADA_STD + csDMARD | 0 | 60 | | | |
| Dougados 2017 | Placebo + csDMARD | 0 | 228 | BAR_4 + csDMARD | 0 | 227 | | | |
| Combe 2009 | Placebo +SSZ | 0 | 50 | ETN_STD | 1 | 103 | ETN_STD + SSZ | 0 | 101 |

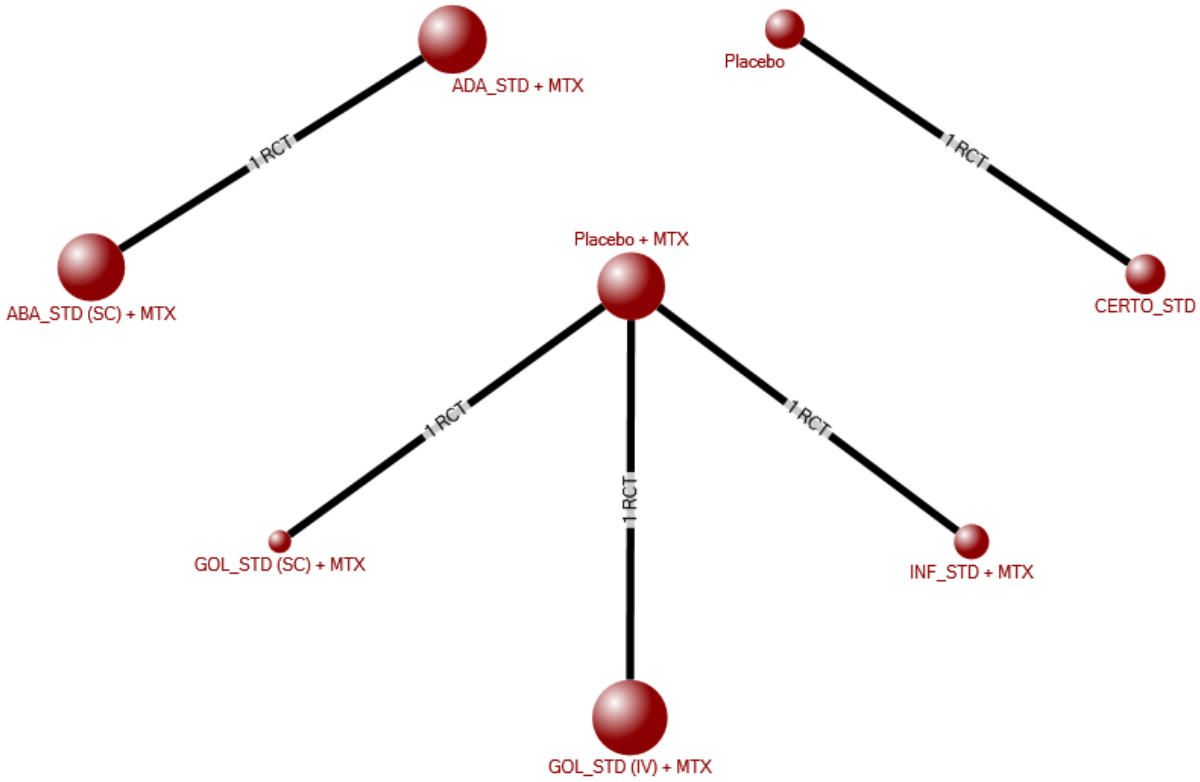
ADA = adalimumab; BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; SSZ = sulfasalazine; STD = standard dose.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

### Lymphoma

*Methotrexate as a Common Comparator*

There were five RCTs in total that reported on lymphoma outcomes,[156,171,197,240] with three focusing on combination therapy with MTX and one investigating monotherapy of certolizumab pegol compared with no treatment. A total of 1,703 participants contributed data. Figure 46 illustrates the connections between treatments in the studies. The AMPLE trial reported one case of lymphoma in the SC abatacept arm and zero cases in the adalimumab arm after two years of treatment.[99] There were no cases of lymphoma in the four other studies during the treatment period analyzed (Table 38).

**Figure 46: Evidence Network: Lymphoma (Placebo + Methotrexate)**




ABA = abatacept; ADA = adalimumab; GOL = golimumab; INF = infliximab; MTX = methotrexate; RCT = randomized controlled trial; SC = subcutaneous; STD = standard dose.

## Table 38: Lymphoma Event Data

| Author | Treatment 1 | n | N | Treatment 2 | n | N |
|---|---|---|---|---|---|---|
| Weinblatt 2013 | Placebo + MTX | 0 | 197 | GOL_STD (IV) + MTX | 0 | 395 |
| Kay 2998 | Placebo + MTX | 0 | 34 | GOL_STD (SC) + MTX | 0 | 37 |
| Maini 1999 | Placebo + MTX | 0 | 88 | INF_STD + MTX | 0 | 86 |
| Fleischmann 2009 | Placebo | 0 | 109 | CERTO_STD | 0 | 111 |
| Schiff 2013 | ABA_STD (SC) + MTX | 1 | 318 | ADA_STD + MTX | 0 | 328 |

ABA = abatacept; ADA = adalimumab; CERTO = certolizumab pegol; GOL = golimumab; INF = infliximab; MTX = methotrexate; SC = subcutaneous; STD = standard dose.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

### *Conventional Synthetic DMARD as a Common Comparator*

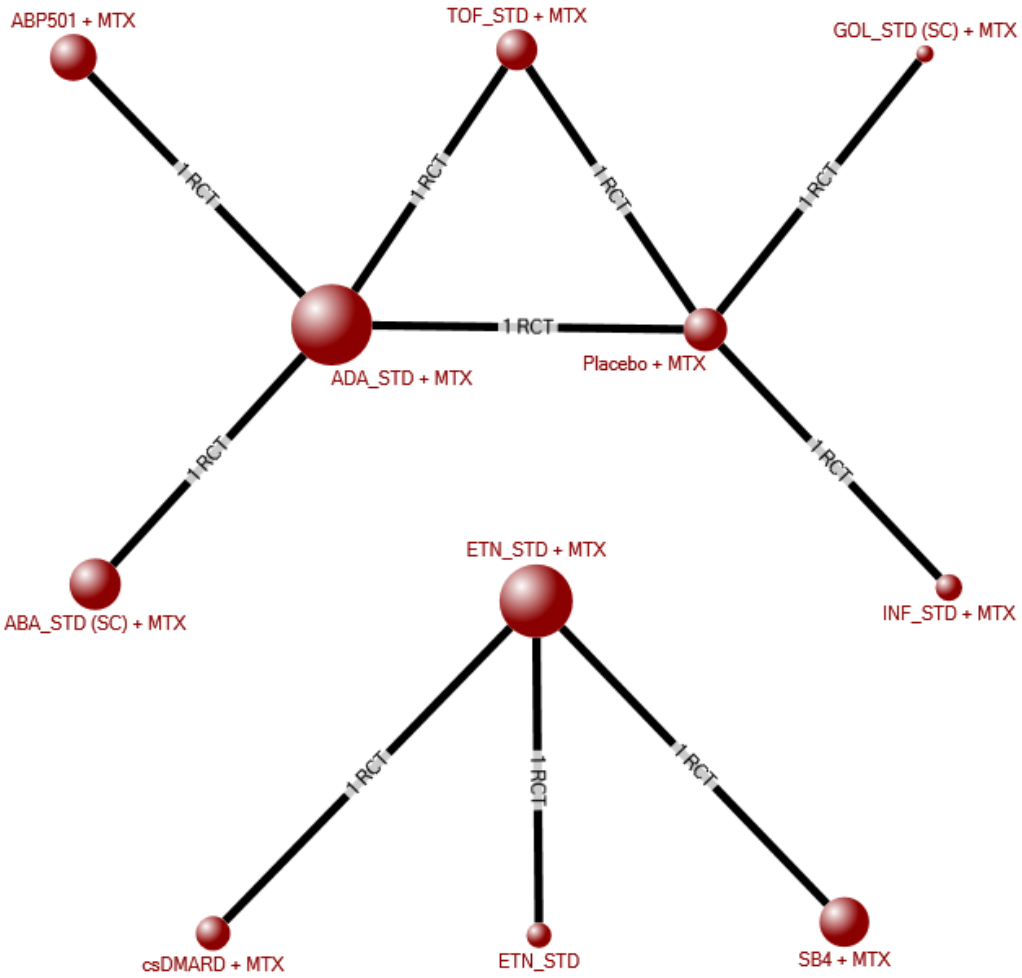
There were no included studies with csDMARD as a common comparator that reported lymphoma outcomes.

## Congestive Heart Failure

### *Methotrexate as a Common Comparator*

A total of eight RCTs reported on congestive heart failure with 2,329 participants contributing data.[99,100,130,155,167,171,195,253] Figure 47 provides an illustration of the treatments with data available. Three of these studies reported no events in any treatment arm.[100,195,253] Etanercept in combination with MTX was compared with etanercept monotherapy in one study; the combination therapy arm had one event during the study.[167] A different study also reported one event in the arm of etanercept in combination with MTX while the SB4 (biosimilar etanercept) arm had no reports of congestive heart failure.[155] Golimumab (SC) in combination with MTX had one event in a study that compared it with MTX monotherapy.[171] In a head-to-head comparison trial of adalimumab and ABP501 (biosimilar adalimumab), both in combination with MTX, there was one case of congestive heart failure in the adalimumab arm.[130] The AMPLE study comparing the standard dose of adalimumab in combination with MTX with SC abatacept at 125 mg per week (SC) in combination with MTX reported one case of congestive heart failure in each treatment arm after two years.[99]

## Figure 47: Evidence Network: Congestive Heart Failure (Concomitant MTX)




ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; GOL = golimumab; INF = infliximab; MTX = methotrexate; RCT = randomized controlled trial; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose; TOF = tofacitinib.

## Table 39: Congestive Heart Failure Events, Concomitant Methotrexate

| Author, Year | Treatment 1 | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Machado 2014 | csDMARD + MTX | 0 | 143 | ETN_STD + MTX | 0 | 281 | | | |
| Kameda 2010 | ETN_STD | 0 | 76 | ETN_STD + MTX | 1 | 71 | | | |
| Emery 2017 | ETN_STD+MTX | 1 | 297 | SB4 + MTX | 0 | 299 | | | |
| Kay 2008 | Placebo + MTX | 0 | 34 | GOL_STD (SC) + MTX | 1 | 37 | | | |
| Zhang 2006 | Placebo + MTX | 0 | 86 | INF_STD + MTX | 0 | 87 | | | |
| Amgen (Sponsor) 2016 | ADA_STD + MTX | 1 | 262 | ABP501 + MTX | 0 | 264 | | | |
| Schiff 2013 | ADA_STD + MTX | 1 | 328 | ABA_STD (SC) + MTX | 1 | 318 | | | |
| van Vollenhoven 2012 | Placebo + MTX | 0 | 108 | TOF_STD + MTX | 0 | 204 | ADA_STD + MTX | 0 | 204 |

ABA = abatacept; ABP501 = biosimilar adalimumab; ADA = adalimumab; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; GOL = golimumab; INF = infliximab; MTX = methotrexate; SB4 = biosimilar etanercept; SC = subcutaneous; STD = standard dose; TOF = tofacitinib.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

### *Conventional Synthetic DMARD as a Common Comparator*

There were no included studies with csDMARD as a common comparator that reported congestive heart failure data.

## Major Adverse Cardiac Events

### *Methotrexate as a Common Comparator*

There were no included studies with MTX as a common comparator that reported major adverse cardiac events (MACE) outcomes.

### *Conventional Synthetic DMARD as Common Comparator*

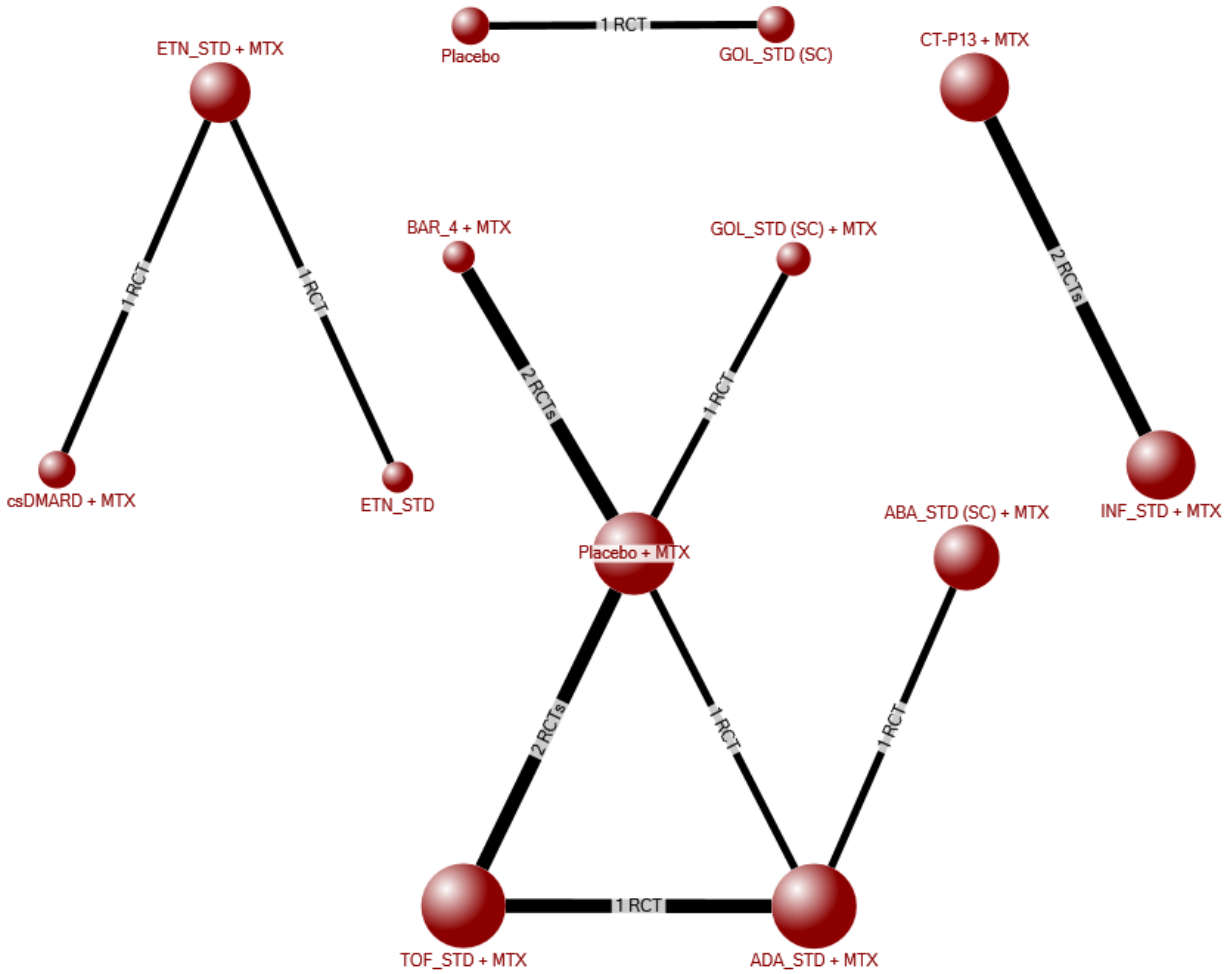
Only one study reported on MACE outcomes. It included 455 participants for this outcome.[151] The study compared 4 mg baricitinib in combination with a csDMARD with csDMARD monotherapy. Two participants out of 228 in the csDMARD monotherapy arm, and zero participants out of 227 in the 4 mg baricitinib combination arm, experienced a MACE.[151]

## Herpes Zoster

### *Methotrexate as a Common Comparator*

A total of 11 trials[99,100,167,178,179,223,226,227,229,234,250] reported herpes zoster outcomes (Figure 48). Table 40 reports the full event data for herpes zoster. There were 4,719 participants contributing data to this outcome. It was possible to analyze the studies by Takeuchi et al. (2015) and Yoo et al. (2013) in a pairwise MA because they both compared infliximab and CT-P13 (infliximab), both in combination with MTX.[226,250] In this comparison, there was no statistically significant difference between the treatments in terms of the number of herpes zoster cases (1.02; 95% CI, 0.25 to 4.13) (Figure 49).

## Figure 48: Evidence Network: Herpes Zoster (Placebo + MTX)




ABA = abatacept; ADA = adalimumab; BAR_4 = 4 mg baricitinib; CT-P13 = biosimilar infliximab; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ETN = etanercept; GOL = golimumab; INF = infliximab; MTX = methotrexate; SC = subcutaneous; STD = standard dose; TOF = tofacitinib.

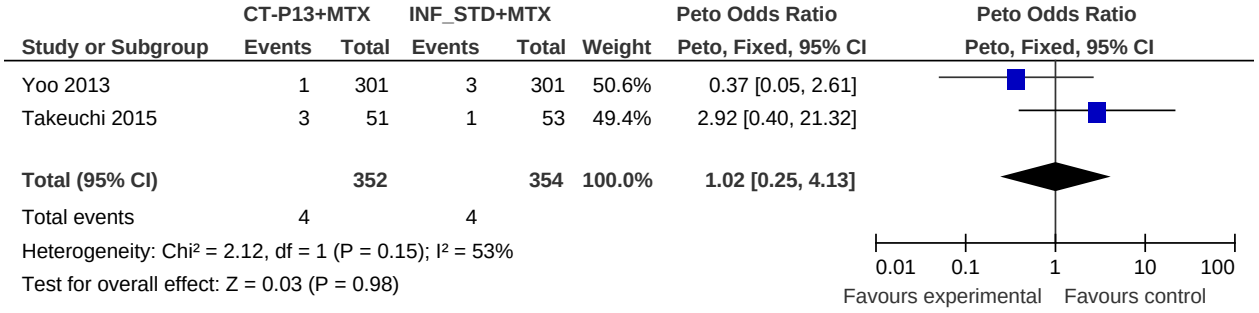
Four trials had zero events in both arms.[100,178,227,229] There were two cases of herpes zoster in a trial of etanercept in combination with MTX and a combination of a csDMARD with MTX,[179] as well as one case of herpes zoster when it was compared with etanercept monotherapy.[167] In a comparison against MTX monotherapy, three participants receiving tofacitinib in combination with MTX developed herpes zoster during the 12-week period prior to the treatment switch adaptation.[234] In another trial, one participant receiving no treatment developed herpes zoster; there were no cases in the golimumab (SC) monotherapy arm (Table 40).[223] Two-year data from the AMPLE study indicated that nine patients (2.8%) in the SC abatacept and six patients (1.8%) in the adalimumab arms developed herpes zoster.[99]

## Table 40: Herpes Zoster Events, Concomitant Methotrexate

| Author | Treatment 1 | n | N | Treatment 2 | n | N | Treatment 3 | n | N |
|---|---|---|---|---|---|---|---|---|---|
| Tanaka 2012 | Placebo + MTX | 0 | 88 | GOL_STD (SC) + MTX | 0 | 86 | | | |
| van der Heijde 2013 | Placebo + MTX | 0 | 160 | TOF_STD + MTX | 3 | 321 | | | |
| Tanaka 2016 | Placebo + MTX | 0 | 49 | BAR_4 + MTX | 0 | 24 | | | |
| Keystone 2015 | Placebo + MTX | 0 | 98 | BAR_4 + MTX | 0 | 52 | | | |
| Takeuchi 2015 | INF_STD + MTX | 1 | 53 | CT-P13 + MTX | 3 | 51 | | | |
| Yoo 2013 | INF_STD + MTX | 3 | 301 | CT-P13 + MTX | 1 | 301 | | | |
| Kim 2012 | csDMARD + MTX | 0 | 103 | ETN_STD + MTX | 2 | 197 | | | |
| Takeuchi 2013 | Placebo | 1 | 105 | GOL_STD (SC) | 0 | 101 | | | |
| Kameda 2010 | ETN_STD | 0 | 71 | ETN_STD + MTX | 1 | 76 | | | |
| Schiff 2014 | ADA_STD + MTX | 6 | 328 | ABA_STD (SC) + MTX | 9 | 318 | | | |
| van Vollenhoven 2012 | Placebo + MTX | 0 | 108 | ADA_STD + MTX | 0 | 204 | TOF_STD + MTX | 0 | 204 |

ABA = abatacept; ADA = adalimumab; BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT-P13 = biosimilar infliximab; ETN = etanercept; GOL = golimumab; INF = infliximab; MTX = methotrexate; SC = subcutaneous; STD = standard dose; TOF = tofacitinib.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

## Figure 49: Herpes Zoster (CT-P13 [Biosimilar Etanercept] with MTX Versus Infliximab with MTX): Meta-Analysis – Peto Odds Ratio




CI = confidence interval; CT-P13 = biosimilar infliximab; INF = infliximab; MTX = methotrexate; STD = standard dose.

### *Conventional Synthetic DMARD as a Common Comparator*

A total of two trials[151,158] had data available for herpes zoster outcomes with csDMARD monotherapy as the comparator. There were 1,091 participants contributing data to herpes zoster outcomes. One case of herpes zoster occurred in a participant receiving adalimumab in combination with a csDMARD versus zero events in the comparator arm.[158] The other study reported three cases of the outcome among participants receiving 4 mg baricitinib versus zero events in the csDMARD monotherapy arm[151] (Table 41).

## Table 41: Herpes Zoster Events, Concomitant Conventional Synthetic DMARD

| Author | Treatment 1 | n | N | Treatment 2 | n | N |
|---|---|---|---|---|---|---|
| Furst 2003 | Placebo + csDMARD | 0 | 318 | ADA_STD + csDMARD | 1 | 318 |
| Dougados 2017 | Placebo + csDMARD | 0 | 228 | BAR_4 + csDMARD | 3 | 227 |

ADA = adalimumab; BAR_4 = 4 mg baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; STD = standard dose.
Note: Data are reported as the number of events (n) and the number of participants in each treatment arm (N).

### Heterogeneity

Statistical heterogeneity was assessed for individual pairwise comparisons from studies forming each NMA. For NMAs with MTX as the common comparator, ACR 20, 50, 70, DAS 28, HAQ-DI, remission, SF-36 PCS and MCS, pain, and fatigue all had moderate to substantial heterogeneity present that could affect the mixed treatment comparisons in each NMA. Thus, the results should be interpreted with caution. However, there was minimal risk of heterogeneity for the WDAE and SAE outcomes.

Among NMAs with csDMARD as the common comparator, there was moderate to substantial heterogeneity present in a majority of direct comparisons for the outcomes ACR 20, ACR 50, and DAS 28. There was minimal risk of heterogeneity for the ACR 70, WDAE, and SAE NMA results.

### Publication Bias

A total of 10 NMAs could be assessed for publication bias because there were at least 10 trials available for the funnel plot. Of these, the ACR 20, ACR 50, and ACR 70 and remission in the NMAs with MTX as the common comparator were asymmetric in the funnel plots. These outcomes were also found to have moderate to substantial heterogeneity in some of their direct pairwise comparisons, with at least two studies reporting the same pairwise comparison. It is possible that the asymmetry present is due to the heterogeneity that was detected among the included studies or it could be due to publication bias.

There was no asymmetry for the outcomes DAS 28, HAQ-DI, fatigue, pain, WDAE, and SAE with MTX as the common comparator or for ACR 20 with csDMARDs as a common comparator. Thus, it is unlikely that publication bias is affecting the results of these NMAs.

### Sensitivity Analyses

A total of six types of sensitivity analyses were planned a priori (see Section 5.8.1). These were:

1) imputed standard errors for studies with no measure of dispersion (e.g., standard deviation, standard error) available; standard errors were imputed by taking the median standard error from other studies included in the evidence network;
2) included only studies published before the year 2007;
3) included only studies published from the year 2007 onwards;
4) included only studies that used end-of-treatment data from adaptive design trials;
5) included only studies that explicitly mentioned that included patients had IR MTX rather than IR to any csDMARD before study entry; and
6) included only studies with an overall low ROB.

The sensitivity analysis involving the restriction to studies with overall low ROB could not be conducted because there were too few studies to form an evidence network. All continuous outcomes involving studies without any measure of dispersion had median standard errors imputed across studies. The other sensitivity analyses were all conducted on the primary outcomes of the ACR 50 and WDAE. The sensitivity analysis using end-of-treatment data from adaptive design trials (number four in the list of sensitivity analyses) was also conducted for radiographic progression, since it is an outcome that requires longer time points to detect a difference in effect.

Five other types of sensitivity analyses were identified as important considerations through the review process and were conducted as post hoc sensitivity analyses:

- an analysis that included patients who were IR MTX and biologic-naive
- an analysis excluding studies that were conducted in Asian patients only
- an analysis of only studies that were conducted in Asian patients only
- a restricted time point analysis of end of treatment (or adaptive time point) data from week 12 to week 16
- an analysis excluding triple-csDMARD therapy studies published before 2000.

All of these post hoc sensitivity analyses were conducted on the primary outcomes of the ACR 50 and WDAE.

All sensitivity analyses were assessed for the NMAs with MTX as the common comparator and any csDMARD as the common comparator. Both a summary of the sensitivity analyses and full results for individual sensitivity analyses are presented in Appendix 8.

### *Methotrexate as a Common Comparator*

Full results for all 10 sensitivity analyses for ACR 50 with MTX as a common comparator are presented in Appendix 8 in tables 47 to 56. The reference case for the ACR 50 model had minimal changes based on the following sensitivity analyses: all treatment doses and a restricted time point analysis of results between week 12 and week 16 (see Appendix 8, Table 46 for a summary of results and tables 47 and 52 for full results).

The percentage of direct comparisons with different results (between the reference case and sensitivity analysis) ranged from 5% to 16%. These differences represented slight shifts in the upper and/or lower limits of the CrIs between the reference case model and the sensitivity analysis for:

1) studies published before the year 2007 (Table 48);
2) studies published from the year 2007 onward (Table 49);
3) end-of-treatment data used for adaptive design trials (Table 50);
4) patients who were IR MTX and not IR to another csDMARD (Table 51);
5) patients who were IR MTX and biologic-naive (Table 53);
6) excluding Asian-only trials (Table 54);
7) including only Asian-only trials (Table 55); and
8) excluding triple-csDMARD therapy studies published before the year 2000 (Table 56).

Importantly, there were very few cases (0% to 2.5% of comparisons) in these sensitivity analyses where a statistically significant result in the reference case favouring the treatment

became statistically significant in the sensitivity analysis favouring the control. There were also very few cases where a statistically significant result in the reference case favouring the control became statistically significant in the sensitivity analysis favouring the treatment (Appendix 8, Table 46).

Results for sensitivity analyses with the WDAE showed very few differences compared with the results from the reference case (Appendix 8, Table 46). In particular, there were no cases where a statistically significant result in the reference case favouring the treatment or control changed in the sensitivity analyses. Full results for each of the sensitivity analyses on WDAE with MTX as a common comparator are presented in tables 57 to 66.

The sensitivity analysis using end-of-treatment data for all studies (including for adaptive design studies) on radiographic progression had a model that yielded very wide CrIs as well as nonsensical point estimates (results not shown). In contrast, the reference case model was found to be both stable and consistent. Sensitivity analyses for DAS28, HAQ-DI, pain, fatigue, and SF-36 PCS and MCS were conducted to assess the impact of imputing missing standard errors from studies that reported no measure of dispersion. Results for these sensitivity analyses for DAS28, pain, fatigue, and SF-36 PCS and MCS showed no substantive changes compared with the reference case (see Appendix 8, Table 46 for the summary results and tables 67 to 72 for full results for each continuous outcome). The sensitivity analysis for HAQ-DI and pain shifted some results that were statistically significant in favour of the treatment in the reference case to lose statistical significance. However, the CrIs were both close to the line of non-significance, and only a small shift resulted in the change. For example, certain effect estimates were slightly statistically significant in the reference case and became slightly non-statistically significant in the sensitivity analysis; or, slightly non-statistically significant effect estimates in the reference case became slightly statistically significant in the sensitivity analysis.

*Conventional Synthetic Disease-Modifying Antirheumatic Drug as a Common Comparator*

Five sensitivity analyses were conducted for ACR 50:

1) inclusion of all drug doses (Table 74);
2) studies published from 2007 onwards (Table 75);
3) inclusion of end-of-treatment data for adaptive design trials (Table 76);
4) use of a restricted time point analysis with 12-week to 16-week data (Table 77); and
5) studies that included only patients who were IR MTX and also biologic-naive (Table 78).

There were no substantive changes to the results when results of the sensitivity analyses were compared with the reference case. (See Appendix 8, Table 73 for a summary of results and tables 74 to 78 for full results of the sensitivity analyses.)

There were no substantive changes to the results of the sensitivity analysis for DAS28 and HAQ-DI to impute missing standard errors from studies compared with the reference case. (See Appendix 8, Table 73 for a summary of results and tables 82 and 83 for full results of the sensitivity analyses.)

The sensitivity analyses conducted for WDAE were: inclusion of all treatment doses, inclusion of end-of-treatment data for adaptive design trials, and use of a restricted time

point analysis with 12-week to 16-week data. Results for these three sensitivity analyses for WDAE showed no substantive changes to the results when compared with the reference case. (See Appendix 8, Table 73 for a summary of results and tables 79 to 81 for full results of the sensitivity analyses.)

## Discussion

The objective of this report was to investigate the comparative benefits and harms of drugs for the treatment of RA in individuals with an IR to MTX. Results for NMAs, pairwise MAs, and descriptive analyses are reported for any comparisons of biologics with each other (including biosimilars), with csDMARD combination therapy (double or triple), with tsDMARDs, or with either MTX monotherapy or csDMARD monotherapy. To the authors' knowledge, this was the first comprehensive systematic review and NMA that included mono-, double-, and triple-csDMARD therapies, as well as biologics, tsDMARDs, and biosimilars as monotherapies and in combination with csDMARDs.

A total of 98 unique studies were included in this review, along with 41 companion publications. A majority of included studies permitted concomitant therapy with MTX and had 12 outcomes that could be analyzed by NMA. The largest of these NMAs were for ACR 20, ACR 50, and ACR 70, with more than 37, 31, and 29 treatments included, respectively; HAQ-DI with 21 treatments; DAS 28 with 31 treatments; WDAE with 27 treatments; and SAE with 22 treatments included. Other outcomes had 19 or fewer treatments. There were far fewer studies (and treatments) with csDMARDs as the concomitant therapy. Therefore, not as many NMAs could be conducted on the outcomes of interest, and those that could be analyzed were much smaller — with fewer than 10 treatments — and lacked the power to detect statistically significant differences among treatments being compared.

No studies in which participants could receive concomitant treatment with MTX reported on the outcome of MACEs. No studies permitting concomitant treatment with a csDMARD reported on the outcomes of radiographic progression, lymphoma, or congestive heart failure.

Assessment of the ROB of included studies revealed that more than half of studies poorly reported random sequence generation and allocation concealment, and as a result, were considered to have an unclear ROB. In addition, high ROB was most prevalent within the domains of incomplete outcome data for efficacy (42%) followed by incomplete outcome data for safety (28%). Blinding of subjective outcomes mostly had an unclear ROB (53%) because the methods used to maintain blinding were not adequately reported. In terms of overall quality when considering all domains, only 10 studies were assessed to have low ROB.

The company that makes sirukumab withdrew all applications to regulatory agencies in October 2017(after analysis for this review was completed) when the FDA did not approve the drug and requested further clinical data on it.[57] Therefore, the results on sirukumab from this review may no longer be relevant to clinical practice, since it will not go through the regulatory approval process.

## Policy Implications

Questions of interest were gathered from the federal, provincial, and territorial drug plans regarding the use of drugs for treating RA. Specifically, the drug plans were interested in the following:

1. For patients whose response to MTX is less than optimal, should a biologic be added to MTX, should a biologic be prescribed alone, or should other csDMARDs be added or substituted for MTX?
2. For patients who cannot tolerate MTX because of an adverse event (AE) or a contraindication, should csDMARDs, alone or in combination, be tried ahead of a biologic?
3. What is the relative efficacy of double-csDMARD therapy compared with triple-csDMARD therapy?
4. For patients who are inadequately treated with a biologic (alone or with MTX), what should be tried next?
5. What is the place in therapy of tofacitinib and other JAK inhibitors?
6. What are the benefits and harms of innovator biologics and SEBs (biosimilars)?

To make this project manageable, the scope was limited to patients in whom treatment with MTX has failed or who are intolerant to MTX. This review excluded patients with early or mild disease, csDMARD-naive patients, patients with comorbidities, or patients with a poor prognosis. Treatments of interest were identified through consultation with the federal, provincial, and territorial jurisdictions, and were approved by Health Canada or advanced in the development process.

The overarching policy question was determined to be: *In patients with moderate to severe RA in whom treatment with MTX has failed, or who are intolerant to MTX, what is the optimal drug therapy?*

We have addressed the questions related to the most effective treatment for patients with moderate to severe RA who are inadequately treated due to treatment failure or intolerance with MTX, or who are intolerant to MTX due to an AE or a contraindication. Additionally, we have addressed the question related to the place of therapy of tsDMARDs after an IR to MTX. We were able to partially address the questions on the relative efficacy of double- and triple-csDMARD therapy, as well as the comparative evidence for double- and triple-csDMARD therapy versus a biologic alone or in combination with MTX among treatment-experienced patients with moderate to severe RA.

The question on what should be tried next for patients with moderate to severe RA who are inadequately treated due to treatment failure or intolerance with a biologic (alone or with MTX) was out of scope of the current review because studies where treatment had failed or where patients were intolerant to a biologic were excluded. We were also unable to address the question pertaining to whether csDMARD monotherapy or double-csDMARD therapy should be second-line therapy following MTX failure as first-line therapy; this is because the available studies were not clear on whether patients entering the study were starting second-line therapy or if they were on third- or even fourth-line therapy.

Based on the objective, the policy questions, and selection criteria for this report, the focus was on individual treatments rather than on drug classes (e.g., TNF inhibitors, IL-6 inhibitors, etc.) or treatment strategies.

## Interpretation of Systematic Review Results

### Methotrexate as a Common Comparator

Sufficient data were available for NMAs of the following outcomes: disease response (ACR 20, ACR 50, and ACR 70), disease activity (DAS 28), disability (HAQ-DI), remission (DAS 28 < 2.6), radiographic progression, HRQoL (SF-36 PCS and MCS), fatigue, pain, SAEs, and WDAEs. Studies of double- and triple-csDMARD therapies had data available only for ACR 20, ACR 50, ACR 70, DAS 28 (double-csDMARD only), remission (double-csDMARD only), pain, radiographic progression, SAE (double-csDMARD only), and WDAE.

#### *Efficacy Outcomes*

CADTH asked what RA patients and their families would like drug therapies to achieve. Total disease remission without significant joint damage and impact on their lives is a key outcome that was mentioned, with the recognition that this might not be possible: *"Remission, but I'm not keeping my hopes up, as I know that's not always how it works out."*

For those in whom total remission may be unrealistic, the goal is to have the lowest disease activity possible so as to be able to live a life that is as productive and pain-free as possible. Specifically, desired outcomes are reductions in fatigue, inflammation, joint damage and disfigurement, pain, stiffness, and depression; reduced frequency of major flares; and increased mobility and cognitive function.

#### *ACR 50*

Thirty-one treatments, including MTX monotherapy, csDMARD combinations (any csDMARD + MTX, MTX + SSZ, MTX + HCQ, SSZ + HCQ, and MTX + SSZ + HCQ), all biologics, tofacitinib, 4 mg baricitinib, 150 mg and 200 mg sarilumab, and all biosimilars for this review were compared in the NMA for the primary outcome of ACR 50. All of the biologics and tsDMARDs in combination with MTX demonstrated statistically significantly higher odds of ACR 50 response compared with MTX monotherapy, and this is supported by the findings of previous NMAs.[88,89,258,259] Of the biologic monotherapies that were included, only 8 mg/kg tocilizumab had statistically significantly higher odds of ACR 50 response than MTX monotherapy, which was found in another NMA that compared biologics and tofacitinib in combination with MTX as well as monotherapies.[258] Another NMA of only biologic monotherapies by Tarp et al. found that etanercept monotherapy had statistically significantly higher odds of ACR 50 compared with MTX monotherapy (odds ratio = 1.54; 95% CI, 1.03 to 2.32).[260] Our point estimates were comparable, and their result may have reached statistical significance because CIs are generally narrower than CrIs, as evidenced by our slightly wider estimate (odds ratio = 1.76; 95% CrI, 0.93 to 3.54). There was insufficient evidence to detect a statistically significant difference in ACR 50 response when comparing biologic monotherapies (etanercept, 4 mg/kg tocilizumab, 8 mg/kg tocilizumab, and rituximab) with one another, as has been found in three previous NMAs of these biologic monotherapies.[258,260,261]

Triple-csDMARD therapy (MTX, HCQ, and SSZ) was favoured over double-csDMARD therapy (MTX and SSZ or any csDMARD with MTX) for achieving disease response. Results from one of the previous NMAs by Hazlewood et al. indicated there was more evidence to support triple-csDMARD therapy over the biologics abatacept (IV), infliximab, and 4 mg/kg tocilizumab, all in combination with MTX.[88] In our review, we found no statistically significant difference between triple-csDMARD therapy and MTX combination therapy with abatacept (IV), infliximab, or 4 mg/kg tocilizumab (odds ratio = 0.47 [95% CrI, 0.11 to 1.74]; odds ratio = 0.34 [95% CrI, 0.08 to 1.29], and odds ratio = 0.31 [95% CrI, 0.07 to 1.21], respectively) or any of the other biologics, biosimilars, or tsDMARDs in the analysis. Our review included 57 studies to their 45 studies, and we had different eligibility criteria for included studies, which may have influenced the difference in results of the network.

Additionally, of the 57 trials in our ACR 50 NMA, there were only two csDMARD therapy trials with eligible data,[205,206] which means the evidence comparing triple-csDMARD therapy with biologics is limited. Based on the results from our review, triple-csDMARD therapy has greater benefit for disease response compared with double-csDMARD therapy (any csDMARD with MTX or MTX with SSZ), etanercept monotherapy, and 4 mg/kg tocilizumab monotherapy. The NICE guidelines recommend the use of csDMARD combination therapy; the ACR guidelines recommend it as one option for patients with IR MTX.[262,263] Fleischmann et al. conducted an NMA comparing triple-csDMARD therapy with the drug class of TNF inhibitors in combination with MTX. The random-effects model had better fit than the fixed-effects model and the results demonstrated no statistically significant difference between the two treatments in terms of ACR 50 response after six months and one year of therapy.[264] Similarly, no difference could be detected in this review in terms of disease response based on the ACR 50 between triple therapy with csDMARDs and biologics, biosimilars, or tsDMARDs in combination with MTX.

When comparing the efficacy of biologic monotherapy versus combination therapy with a biologic or biosimilar and MTX, most biologics as monotherapy included in the analysis (i.e., etanercept, 4 mg/kg tocilizumab, rituximab) had no difference, or at times, lower odds of patients achieving disease response, except for 8 mg/kg tocilizumab. Biologic combinations with MTX that had higher odds than biologic monotherapies included etanercept, golimumab (SC), and certolizumab pegol, as well as the tsDMARD tofacitinib in combination with MTX. However, there was insufficient evidence to identify which biologic, biosimilar, or tsDMARD in combination with MTX had the most efficacy compared with the other biologics, biosimilars, or tsDMARDs in combination with MTX. Other NMAs in patients with IR to MTX also found no statistically significant results in the head-to-head comparisons of biologics in combination with MTX.[89,258,265,266] The ACR guidelines recommend either biologic monotherapy or combination therapy with MTX for patients with IR MTX;[13] the results from this review for the ACR 50 may indicate that a biologic in combination with MTX may be more effective than biologics as monotherapy. Some of the CrIs for comparisons for disease response were wide. While the NMA by Hazlewood et al. also reported wide CrIs for ACR 50 results,[88] the results for our analysis should be interpreted with caution.

Biosimilars etanercept (HD203 or Anbainuo) in combination with MTX demonstrated a greater disease response compared with double-csDMARD therapy (csDMARDs + MTX and HCQ + SSZ) and etanercept monotherapy (but not etanercept in combination with MTX). SB4, another biosimilar etanercept, also had higher odds of disease response compared with csDMARDs + MTX and etanercept monotherapy. With the current evidence, it is not possible to draw definitive conclusions on the comparative efficacy of biosimilars versus their reference biologic (and other biologics) because there are still a limited number of

studies available. However, given that biosimilars are a growing area of research and drug approval, more data on the comparative efficacy versus biologics will become available to assist with decision-making in the future.

*Disease Severity (DAS28)*

Thirty-one treatments were included for the NMA of DAS28; this represented most of the eligible treatments for this review (some being included as monotherapy and/or combination therapy with MTX). Four biologics in combination with MTX (abatacept [IV], 8 mg/kg tocilizumab, certolizumab pegol and rituximab) and 8 mg/kg tocilizumab monotherapy demonstrated greater improvement in disease severity based on the DAS28 scale versus the comparator MTX monotherapy, to which patients had an IR. There was insufficient evidence based on statistical significance to detect a difference in the efficacy of the other biologics combined with MTX versus MTX monotherapy, but there was a trend toward statistical significance. The Cochrane review by Hazlewood et al. also reported statistically significant reductions in disease severity for these treatments, but did not include certolizumab pegol in combination with MTX in the NMA due to concerns about ROB.[267] Their review also found statistically significant results for infliximab in combination with MTX, 4 mg/kg tocilizumab in combination with MTX, and adalimumab in combination with MTX, all compared with MTX monotherapy. The difference in these statistically significant results compared with the results of our review (which did not find any statistically significant difference for these comparisons) may be due to the variations in the treatments included for each network.

Of all the comparisons of one biologic, biosimilar, or tsDMARD to another, 8 mg/kg tocilizumab in combination with MTX had greater benefits in terms of reducing disease severity than etanercept monotherapy, and had nearly favourable results compared with etanercept in combination with MTX, adalimumab in combination with MTX, infliximab in combination with MTX, and tofacitinib in combination with MTX. Rituximab in combination with MTX was nearly favoured over etanercept monotherapy. There were no other statistically significant or potentially clinically important differences between biologics, biosimilars, and tsDMARDs as monotherapy or as combination therapy with MTX. No evidence was available for double- and triple-csDMARD therapies, as there were no included studies with DAS28 data for these treatments.

*Disability (HAQ-DI)*

> Some Arthritis Society respondents explained to CADTH that they had modest hopes for improvement: “a few days a week that the pain would be controlled” or “to sleep soundly through an entire night” or “walking farther than one aisle in the supermarket” or “allow pain-free use of my hands.”

Twenty-one treatments had data available for the NMA on HAQ-DI. Treatments that were not present were: all double- and triple-csDMARD therapies, etanercept (monotherapy and combination therapy), adalimumab monotherapy, infliximab monotherapy, certolizumab pegol monotherapy, 4 mg/kg tocilizumab monotherapy, tofacitinib monotherapy, golimumab (SC) monotherapy, two biosimilar etanercept drugs in combination with MTX (HD203 and SB4), and biosimilars of adalimumab in combination with MTX (SB5 and ABP501).

Results for the HAQ-DI, demonstrated that most treatments were more effective than MTX monotherapy, including monotherapy with 8 mg/kg tocilizumab and rituximab, and MTX in combination with the following: abatacept (IV and SC), adalimumab, tofacitinib, 4 mg/kg tocilizumab, 8 mg/kg tocilizumab, golimumab (SC and IV), infliximab, certolizumab pegol, 150 mg and 200 mg sarilumab, 4 mg baricitinib, Anbainuo (biosimilar etanercept), and CT-P13 (biosimilar infliximab). These results are expected, since patients in these studies were IR MTX, and the findings are similar to the results compared with MTX in three other NMAs that considered the same treatments as our review.[265,268,269] The Cochrane review by Hazlewood et al. also reported statistically significant results that match the ones previously discussed, except for 4 mg/kg tocilizumab (mean difference = -0.18 [95% CrI, –0.37 to 0.01] versus mean difference = –0.36 [95% CrI, –0.50 to –0.22] in our review).[267] The discrepancy may be related to the different treatments included in each NMA; for example, our NMA included biosimilars and biologic monotherapies, whereas the Cochrane review did not, including instead gold and cyclosporine (both in combination with MTX).

When comparing biologics and tsDMARDs with one another, there were no statistically significant differences between them. The head-to-head comparisons of biologics were also found to have no statistically significant difference in other NMAs.[264,265,268,269] However, the evidence suggests that 8 mg/kg tocilizumab monotherapy has greater benefit than adalimumab in combination with MTX, infliximab in combination with MTX, rituximab in combination with MTX, 150 mg sarilumab in combination with MTX, SB2 (biosimilar infliximab) in combination with MTX, and ZRC-3197 (biosimilar adalimumab) in combination with MTX based on clinically important differences (mean difference point estimates were larger than the minimal clinically important difference of 0.22). The evidence suggests that combination therapy of 8 mg/kg tocilizumab and MTX may also be more beneficial than combination therapy of rituximab and MTX, based on clinical importance.

Anbainuo (biosimilar etanercept) in combination with MTX demonstrated greater benefit in terms of disability compared with several other biologics (abatacept [SC] in combination with MTX, adalimumab in combination with MTX, 4 mg/kg tocilizumab in combination with MTX, golimumab [SC and IV routes] in combination with MTX, infliximab in combination with MTX, certolizumab pegol in combination with MTX, rituximab in combination with MTX, and 150 mg and 200 mg sarilumab), tsDMARDs (tofacitinib in combination with MTX and 4 mg baricitinib in combination with MTX), and the biosimilars SB2 (biosimilar infliximab) and ZRC-3197 (biosimilar adalimumab), both in combination with MTX. These results were both statistically significant and had point estimates larger than the minimal clinically important difference for HAQ-DI. One study published in 2016 compared Anbainuo against MTX monotherapy and it had unclear ROB overall.[137] To the authors' knowledge, there were no other NMAs that included this treatment in their evidence networks. Since the quality of the study providing this evidence is unclear, results for the benefits of Anbainuo in combination with MTX should be interpreted with caution.

Mixed treatment comparison evidence for CT-P13 demonstrated its superiority in terms of disability compared with its reference product (i.e., infliximab in combination with MTX). While biosimilars are designed to be noninferior to the reference product, it is likely that an outcome such as the ACR 20 was used to test efficacy, so it is possible that the biosimilar may have more (or less) benefit in other efficacy outcomes compared with the reference product.

While the Cochrane review by Singh et al. found there were statistically significant comparisons between biologic drug classes,[89] it is likely that our results were not statistically

significant because the power is decreased with fewer patients in each individual treatment node. In either case, there is insufficient evidence based on statistical significance to identify one biologic, biosimilar, or tsDMARD as a preferred option for reducing disability over another biologic, biosimilar, or tsDMARD.

*Remission*

A total of 19 treatments had eligible data for the NMA of remission. Missing treatments were: all double- and triple-csDMARD therapies (except for csDMARD + MTX), adalimumab monotherapy, infliximab monotherapy, certolizumab pegol monotherapy, golimumab (SC) monotherapy, golimumab (IV) in combination with MTX, tofacitinib monotherapy, 4 mg/kg tocilizumab monotherapy, Anbainuo (biosimilar etanercept) in combination with MTX, and biosimilars adalimumab (SB5, ZRC-3107, and ABP501) in combination with MTX.

As expected for studies of patients in whom treatment with MTX had failed or who were intolerant to MTX, most treatments had higher odds of remission compared with MTX monotherapy. Most of the results of the comparative efficacy among biologics and biosimilars were not statistically significant and were also unlikely to be clinically different from one another. Two other NMAs also found no statistically significant differences between treatments.[264,265] One recent NMA by Fleischmann et al. reported on remission outcomes (using DAS28 < 2.6). In contrast to this review, they investigated the comparative efficacy of all TNF inhibitors in combination with MTX versus triple-csDMARD –therapy. Their results indicated no statistically significant difference between the treatment categories.[264] Another NMA that included just four studies in the NMA of remission (DAS28 < 2.6) reported results that were similar to our review, with golimumab in combination with MTX and infliximab in combination with MTX having higher odds of remission compared with MTX monotherapy (odds ratio = 14.40 [95% CI, 5.34 to 38.79] and odds ratio = 5.20 [95% CI, 1.51 to 17.89], respectively).[265] The authors also reported no statistically significant difference in any head-to-head comparisons of the three included treatments (golimumab monotherapy, golimumab in combination with MTX, and infliximab in combination with MTX).[265] These same head-to-head comparisons were also not found to be statistically significant in our review, except for golimumab monotherapy, which was not in this outcome because none of the included studies with this treatment reported remission data.

Comparisons against etanercept monotherapy revealed that several biologics in combination with MTX were favoured in terms of remission: etanercept, abatacept (IV and SC), adalimumab, 4 mg/kg tocilizumab, 8 mg/kg tocilizumab, golimumab (SC), infliximab, certolizumab pegol, and 4 mg baricitinib. Monotherapy with 8 mg/kg tocilizumab also demonstrated higher odds of remission compared with etanercept monotherapy. Compared with etanercept combination therapy with MTX, only 8 mg/kg tocilizumab combination therapy with MTX had higher odds of remission. More results are needed to determine the comparative efficacy of 8 mg/kg tocilizumab in combination with MTX compared with the other biologics, tsDMARDs, and biosimilars.

With improvements in their health, respondents to the Arthritis Society hoped to continue working, to start or raise families, and to be more active parents, employees, and members of society. “I was so sick with arthritis that I was not the mom I wanted to be, and this had a long-term effect on my kids and my husband.” “Pain-free life would equal different job opportunities for me.”

Others had difficulty even imagining such a future: “Such a far-off goal. I can barely comprehend. It would mean more than anything.”

## Health-Related Quality of Life

Both the physical and mental component score NMAs for HRQoL included nine treatments: MTX monotherapy, biologics in combination with MTX (adalimumab, golimumab [SC and IV]), infliximab, certolizumab pegol, and abatacept [IV]), tofacitinib in combination with MTX, and biosimilar infliximab (CT-P13) in combination with MTX.

As expected, the results indicated that all treatments in the NMA (i.e., MTX combination therapy with abatacept [IV], tofacitinib, adalimumab, golimumab [SC and IV], infliximab, certolizumab pegol, and CT-P13 [biosimilar infliximab]) were more effective than MTX monotherapy for physical HRQoL (SF-36 PCS). However, in terms of mental HRQoL (SF-36 MCS), only the combination of MTX with either abatacept (IV), tofacitinib, golimumab (IV), or certolizumab pegol demonstrated greater benefit than MTX monotherapy. Comparisons of the biologics, biosimilars, and tsDMARD with one another had insufficient evidence to indicate one treatment having greater benefit than the others in terms of either physical or mental HRQoL. To the authors’ knowledge, there were no other reviews that conducted an NMA on HRQoL outcomes with which these findings can be compared. One study by Gartlehner et al. in 2006 was unable to conduct an NMA, but reported that in the studies, they assessed there was a significant improvement in quality of life for patients receiving biologics compared with those in the control arms.[270]

Improved ability to complete simple daily activities could allow individuals with RA to participate in social activities and lead to a better state of mental health. *“I would not be angry all the time. Living in a chronic state of pain and exhaustion causes a state of little patience. I would love to be able to exercise and enjoy the outdoors without it taking away valuable energy levels and causing even more pain.”*

### *Pain*

Seventeen treatments of interest had eligible data for the NMA for pain. Included treatments were: 10 mg LEF monotherapy, double-csDMARD therapy (SSZ and HCQ), triple-csDMARD therapy (MTX, SSZ, and HCQ), adalimumab monotherapy, certolizumab pegol monotherapy, biologics in combination with MTX (etanercept, adalimumab, certolizumab pegol, abatacept [IV], and 150 mg and 200 mg sarilumab), tofacitinib monotherapy, tofacitinib in combination with MTX, 4 mg baricitinib in combination with MTX, and biosimilar adalimumab (ZRC-3197) in combination with MTX.

In terms of pain reduction, both certolizumab pegol and 200 mg sarilumab in combination with MTX demonstrated higher odds of pain reduction compared with double-csDMARD therapy with SSZ and HCQ, based on statistical significance and a large effect size. Certolizumab pegol in combination with MTX was also found to have greater benefit than adalimumab monotherapy and tofacitinib monotherapy. Another NMA that compared the drug class of TNF inhibitors with triple-csDMARD therapy found no statistically significant differences in pain reduction.[264] In contrast, our results are on the individual drug level, and indicate that one TNF inhibitor (certolizumab pegol in combination with MTX) had greater pain reduction than another TNF inhibitor (adalimumab monotherapy). However, these findings should be interpreted with caution, because three of the studies involving certolizumab had a high ROB overall[220,247,248] and one had unclear ROB overall.[156]

A comparison of our results with those from Hazlewood et al. indicates that, for the treatments that were analyzed in both our NMA and theirs, etanercept, abatacept (IV), adalimumab, and tofacitinib (all in combination with MTX) had statistically significant results versus MTX monotherapy.[267] Our analysis also indicated that certolizumab pegol in combination with MTX, 150 mg and 200 mg sarilumab in combination with MTX, and 4 mg baricitinib in combination with MTX had higher odds of pain reduction compared with MTX monotherapy. These treatments were not included in the analysis for the other review. To the authors' knowledge, there were no other NMAs reporting on the outcome of pain; thus, there is nothing to compare our results against on indirect evidence of biologics, tsDMARDs, and biosimilars.

> With reduced pain and/or fatigue, those with RA hoped to continue normal activities: "to do things without suffering later on for your efforts," and "to be independent."
>
> "It would mean not budgeting my energy so I can complete necessary tasks. It would mean not scheduling my week around a day of being sick from my methotrexate dose."

### *Fatigue*

There were 13 treatments in the NMA for fatigue that were all combination therapies with MTX: etanercept, adalimumab, certolizumab pegol, golimumab (SC and IV), abatacept (IV), 4 mg/kg and 8 mg/kg tocilizumab, 150 mg and 200 mg sarilumab, tofacitinib, and biosimilar etanercept (HD203).

Only tofacitinib in combination with MTX and certolizumab pegol in combination with MTX were found to have a statistically significant improvement in fatigue compared with MTX monotherapy, with a moderate and large effect size, respectively. This differed from the Cochrane review by Hazlewood et al., in which their NMA demonstrated statistically significant results over MTX monotherapy for golimumab (SC and IV) in combination with MTX, 4 mg/kg tocilizumab in combination with MTX, 8 mg/kg tocilizumab in combination with MTX, and rituximab in combination with MTX (none of the included studies of rituximab had eligible data for this review). These differences are likely a result of the variation in treatments included in the evidence networks; only our NMA involved 150 mg and 200 mg sarilumab, HD203 (biosimilar etanercept), and certolizumab pegol, whereas only their NMA included abatacept (SC) in combination with MTX.[267]

Results for fatigue did not demonstrate any statistically significant difference in benefit between biologics, biosimilars, or tsDMARDs. There was no evidence available on double or

triple-csDMARD therapies, which was also the case for the other review.[267] Additionally, there were no data on biologic monotherapies; thus, an assessment of the treatment options used by patients who have an intolerance to MTX could not be made. There were no other reviews with NMA results for fatigue on head-to-head comparisons of biologics, tsDMARDs, and biosimilars with which to compare the results from this review.

### *Radiographic Progression*

Only seven treatments were represented in the NMA for radiographic progression, likely because longer studies were not as common and we analyzed adaptive design trials based on data at the time of adaptation. Included treatments were: any csDMARD in combination with MTX, triple-csDMARD –therapy (MTX, SSZ, and HCQ), etanercept monotherapy, etanercept in combination with MTX, infliximab in combination with MTX, and biosimilar infliximab (CT-P13) in combination with MTX. The results did not include any adaptive design studies because they did not have any radiographic progression data available before the time of adaptation. Therefore, the results are based on a smaller subset of studies' end-of-treatment data.

There were no statistically significant results for any comparisons in the evidence network on radiographic progression, and none of the results indicated any clear trend in favour of one treatment compared with another. These were similar to the findings on radiographic progression from the Cochrane review by Hazlewood et al. in that there were no statistically significant differences in any treatment compared with MTX monotherapy.[267] In contrast, a review that assessed the modified Total Sharp Scale for radiographic progression among patients with IR MTX found that TNF inhibitors in combination with MTX had greater reduction (i.e., improvement) (mean difference = 2.61; 95% CI, –4.08 to –1.14) on the Sharp and modified Total Sharp Scale at two years than MTX or csDMARD therapy.[264] This difference may be due in part to the fact that our review analyzed adaptive design trials at the time of adaptation (e.g., 12 weeks or 16 weeks); thus, it had a limited quantity of included data with longer time points for an outcome that requires more long-term follow-up to detect differences. However, it may also be due to the methods of their review, including: 1) use of a mixed population of patients who were naive to MTX and patients with an IR to MTX,[264] while our review focused specifically on patients who had an IR to MTX; and 2) limited studies available with data on radiographic progression at two years, as was found in a different NMA that had only five studies with longer-term radiographic progression data.[270] It should also be noted that the results between their random-effects and fixed-effects NMA models conflicted, with only the latter demonstrating a statistically significant difference.[264]

### *Safety Outcomes*

One respondent to the Arthritis Society summarized her experience with RA drugs by saying that, “if it gave me two heads, I would have taken it.” Several respondents described the fear and necessity of balancing benefits and harms of treatment. “The side effects we do suffer, we do so willingly, because life without medication is not a life to wish on your worst enemy.” Another respondent said, “The cost and the way I feel don’t seem worth it. Unfortunately, I have no alternative.”

CAPA noted that many patients live with multiple comorbidities and take medications for other diseases along with those for RA. As one respondent put it, RA therapies “frequently result in the need to take other medications (which have their own side effects) for side effects. I am now also on a PPI, stool softener, laxative and folic acid all because of side effects from RA drugs. However, I am sincerely grateful for the progress in RA disease control achieved because of the RA medications.”

Several individuals expressed deep concern over the long-term risks of treatment. Although out of scope for this project, CAPA emphasized the need to include existing Canadian biologic registries and RA cohort data for CADTH to better appreciate the risks and benefits of RA treatments. CAPA also highlighted the need for greater research regarding the safety of RA medications for women who are pregnant, trying to get pregnant, or breastfeeding.

Among safety outcomes, there was insufficient evidence to detect a difference for any treatment comparisons for mortality or the notable harms identified in the protocol, namely: serious infections, TB, cancer, leukemia, lymphoma, congestive heart failure, MACEs, and herpes zoster. Of note, among the studies reporting TB outcomes, three studies reported high percentages of events (ranging from about 4% to 10%). Two studies reported latent TB outcomes, which would explain the higher number of TB cases compared with most studies that report only active TB cases.[132,251]

There were very few deaths or cases of leukemia or lymphoma. There were few cases of herpes zoster in most studies except the AMPLE study. However, the AMPLE study reported results over a two-year period; it is expected that there would be more cases with longer exposure, yet the proportion of cases in each arm was low.[99] Of the outcomes that were analyzed by descriptive analysis, serious infection was the outcome with the highest number of cases. This is reasonable, as serious infections are a more common safety event among patients after shorter-term treatment than other safety events (e.g., cancer, mortality, herpes zoster).

### *Serious Adverse Events*

The NMA for SAEs was fairly large, with 22 treatments. Missing treatments were: most double- and triple-csDMARD therapies (MTX and SSZ, MTX and HCQ, SSZ and HCQ, and MTX, SSZ, and HCQ), biologic monotherapies (adalimumab, golimumab [SC], infliximab, certolizumab pegol, and 200 mg sarilumab), tofacitinib monotherapy, golimumab (IV) in combination with MTX, 150 mg and 200 mg sarilumab in combination with MTX, 4 mg baricitinib in combination with MTX, Anbainuo (biosimilar etanercept) in combination with MTX, and two biosimilar adalimumab drugs (SB5 and ABP501) in combination with MTX.

In terms of SAEs, abatacept (IV) in combination with MTX was the only treatment that had lower odds of SAEs when compared against MTX monotherapy. The Cochrane review by Hazlewood et al. reported no statistically significant results for treatments compared with MTX monotherapy;[267] our results indicated only abatacept (IV) in combination with MTX to have lower odds of SAEs compared with MTX monotherapy (odds ratio = 0.34; 95% CrI, 0.18 to 0.65). The difference in results may be due to the use of odds ratios in our report and rate ratios adjusted for treatment exposure in the Cochrane review. The remaining treatments from the NMA were shown to have no difference in the odds of SAEs compared with MTX monotherapy. However, tofacitinib in combination with MTX and 8 mg/kg tocilizumab in combination with MTX were trending toward having higher odds of SAEs compared with MTX monotherapy, without a statistically significant difference.

Abatacept (IV) in combination with MTX also demonstrated lower odds of SAEs versus etanercept monotherapy and combination therapy with MTX, tofacitinib in combination with MTX, adalimumab in combination with MTX, 4 mg/kg or 8 mg/kg tocilizumab monotherapy, 8 mg/kg tocilizumab in combination with MTX, golimumab (SC) in combination with MTX, certolizumab pegol in combination with MTX, HD203 (biosimilar etanercept) in combination with MTX, and SB4 (biosimilar etanercept) in combination with MTX.

There were higher odds of SAEs with 8 mg/kg tocilizumab in combination with MTX than with 4 mg/kg in combination with MTX, but these results should be interpreted with caution due to the very wide CrI (95% CrI, 1.34 to 247.30). A meta-analysis of five trials found 8 mg/kg tocilizumab monotherapy to have a lower risk of SAEs versus 8 mg/kg tocilizumab in combination with MTX (relative risk = 1.40; 95% CI, 1.03 to 1.92).[271] Our results indicated a trend toward significance for this same comparison. The difference in statistical significance is most likely due to the fact that the CrIs are generally wider than the CIs because the point estimates were almost the same (relative risk = 1.43 for our review versus 1.40 for their review). Infliximab in combination with MTX also had lower odds of SAEs than 8 mg/kg tocilizumab in combination with MTX, tofacitinib in combination with MTX, and golimumab (SC) in combination with MTX. SB2 (biosimilar infliximab) in combination with MTX also had lower odds of SAEs compared with 8 mg/kg tocilizumab in combination with MTX. Biosimilars are newer treatment options and may require more direct evidence to confirm the validity of this finding for SB2 in combination with MTX. There was insufficient evidence to detect a difference in SAEs among the other comparisons of biologics, biosimilars, and tsDMARDs against one another.

A 2011 Cochrane review by Singh et al. on the harms of biologics found one statistically significant result in the NMA for certolizumab pegol in comparison with adalimumab,[111] but this was not statistically significant in our NMA. These differences may be due to the new studies published since 2011 that were included for this review. To the authors' knowledge, there were no other NMAs that reported SAEs that had data available on head-to-head treatment comparisons to compare with our results.

### *Withdrawal Due to Adverse Events*

Most treatments were included in the NMA for WDAEs, except for: two double-csDMARD therapies (MTX with SSZ, and MTX with HCQ), adalimumab monotherapy, tofacitinib monotherapy, golimumab (SC) monotherapy, golimumab (IV) in combination with MTX, certolizumab pegol monotherapy, 200 mg sarilumab monotherapy, 150 mg and 200 mg sarilumab in combination with MTX, Anbainuo (biosimilar etanercept) in combination with MTX, and ZRC-3197 (biosimilar adalimumab) in combination with MTX.

Overall, there was insufficient evidence to detect a difference in the odds of WDAEs when comparing most biologics, tsDMARDs, and biosimilars with one another. The results for these head-to-head comparisons are consistent with those from the Cochrane NMA by Singh et al. from 2011.[111] In addition, an NMA comparing triple-csDMARD therapy versus TNF inhibitors found there was no statistically significant difference in terms of WDAEs.[264] This supports the findings from our WDAE analysis, in which none of the individual TNF inhibitors as monotherapy or in combination with MTX (etanercept, adalimumab, golimumab [SC], infliximab, or certolizumab pegol) were found to be different from triple-csDMARD therapy. Etanercept in combination with MTX, as well as one of its biosimilars (SB4 in combination with MTX), had lower odds of WDAEs compared with any csDMARD in combination with MTX and tofacitinib in combination with MTX.

There is some evidence to suggest that SB2 (biosimilar infliximab) and ABP501 (biosimilar adalimumab) in combination with MTX have higher odds of WDAEs compared with other treatments. In contrast, among the biosimilars investigated, SB4 (biosimilar etanercept) in combination with MTX and SB5 (biosimilar adalimumab) in combination with MTX had lower odds of WDAEs than a few treatments. There were no other NMAs assessing WDAEs that included biosimilars with which these results could be compared. More long-term data on WDAEs for tofacitinib, baricitinib, and the biosimilars are needed based on these results and due to their more recent entry into the market.

Additionally, several CrIs were very wide in this analysis, so caution should be used in drawing conclusions on these results.

## Conventional Synthetic DMARD as a Common Comparator

The following outcomes were assessed using NMAs: disease response (ACR 20, ACR 50, ACR 70), disease activity (DAS 28), disability (HAQ-DI), SAEs, and WDAEs. No evidence was available on double- or triple-csDMARD therapies in any of the outcomes.

### *Efficacy Outcomes*

Compared with csDMARD monotherapy, the following biologics in combination with a csDMARD had higher odds of achieving ACR 50: etanercept, adalimumab, 8 mg/kg tocilizumab, 100 mg sirukumab, and 50 mg sirukumab. However, the results for both doses of sirukumab should be interpreted with caution because the 95% CrIs were very wide. Of note, applications to regulatory agencies for sirukumab have been withdrawn globally since the time of analysis. Current practice as reported by the NICE and EULAR guidelines is to prescribe TNF inhibitors as the first biologic for patients with IR MTX.[19,262] These results indicate that if a patient is receiving concomitant treatment with any csDMARD (i.e., not necessarily MTX), two TNF inhibitors do demonstrate greater efficacy compared with csDMARD monotherapy. There is currently insufficient evidence to indicate a difference in treatment effect between etanercept, adalimumab, and tocilizumab in combination with a csDMARD. These results are similar to what was found overall for ACR 50 with MTX as the common comparator. In addition, several other NMAs have likewise concluded that there is no difference in disease response between biologics.[89,258,265,266]

There was insufficient evidence to detect a difference in benefit among treatments in terms of disease severity (DAS28) and disability (HAQ-DI). To the authors' knowledge, there were no other reviews using NMAs that compared only studies with csDMARD as the concomitant treatment in an NMA using the outcomes DAS28 or HAQ-DI; thus, it is not possible to compare the results.

An NMA could not be conducted for physical and mental HRQoL, pain, and fatigue, so it was not possible to assess head-to-head comparisons of treatments. As stated earlier, none of these patient-reported outcomes had any included studies with double- or triple-csDMARD therapy as one of the treatment arms.

### *Safety Outcomes*

#### Serious Adverse Events

Baricitinib at a dose of 4 mg in combination with a csDMARD had lower odds of SAEs compared with csDMARD in combination with adalimumab or etanercept. These results could indicate that treatment options (once biologics are the next choice for patients with IR MTX) should be broadened to allow tsDMARDs as one option versus strictly TNF inhibitors.[19,262] There were no other statistically significant comparisons of the biologics and tsDMARD (baricitinib) with one another. There was also no indication of a clinically important difference based on the comparisons of etanercept monotherapy with etanercept in combination with a csDMARD, 8 mg/kg tocilizumab in combination with a csDMARD, or 4 mg baricitinib in combination with csDMARD. To the authors' knowledge, there were no other reviews that considered the studies with csDMARD as a common comparator in separate NMAs. Only a few studies were included in the NMA for SAEs; hence, there is a possibility of type II error (i.e., considering there is no difference between treatments when there is a difference).

#### Withdrawal Due to Adverse Events

Treatments included in the NMA for WDAEs with a csDMARD as the common comparator were: etanercept monotherapy, etanercept in combination with a csDMARD, adalimumab in combination with a csDMARD, 8 mg/kg tocilizumab in combination with a csDMARD, certolizumab pegol in combination with a csDMARD, and 4 mg baricitinib in combination with a csDMARD.

Only etanercept monotherapy was found to have lower odds of WDAEs compared with csDMARD monotherapy. This result is in line with what is recommended by the NICE and EULAR guidelines as the first option for treatment with a biologic after patients are IR MTX.[19,262] However, there was one study in which participants receiving etanercept monotherapy had more serious infections than those receiving csDMARD monotherapy; thus, it is important for clinicians and patients to discuss the benefits and harms of the available treatments to make a decision that fits with their treatment goals and tolerability. There were no statistically significant or clinically important comparisons of the biologics against one another based on the results. To the authors' knowledge, there were no other reviews that considered the studies with csDMARD as a common comparator in separate NMAs. Given the small number of studies included, there is a possibility of type II error.

#### Notable Harms

Among studies reporting on serious infections, one reported a higher number of participants developing a serious infection who were receiving etanercept monotherapy compared with participants receiving csDMARD monotherapy. Typically, patients are prescribed a TNF inhibitor in combination with a csDMARD, such as MTX, due to the synergy between the two treatments.[272] Taken together, for patients with moderate to severe RA who have an IR to MTX (and for whom MTX is not contraindicated), it may be better to avoid etanercept monotherapy in order to experience benefits and avoid potential side effects, such as serious infections.

There was insufficient evidence to identify any difference in the comparative harms of treatments with csDMARD concomitant therapy for the outcomes of mortality, TB, cancer, leukemia, lymphoma, congestive heart failure, MACEs, and herpes zoster. This is likely due to the small number of included studies that were in this NMA category (i.e., placebo + csDMARD as the common comparator), a situation that resulted in either a smaller NMA with weaker connections and lower power to detect any difference, or no NMA at all.

## Sensitivity Analyses

A priori sensitivity analyses included:

1) imputing standard errors for studies with no measure of dispersion (e.g., standard deviation, standard error) available (this was done by taking the median standard error from other studies included in the evidence network);
2) studies published before the year 2007;
3) studies published from the year 2007 onwards;
4) studies using end-of-treatment data from adaptive design trials;
5) only studies that explicitly mentioned that patients were IR MTX rather than inadequate responders to any csDMARD before study entry; and
6) only studies with overall low ROB.

It was not possible to conduct a sensitivity analysis removing studies that had low methodological quality because there were not enough studies to run the NMA models.

Post hoc sensitivity analyses included:

1) an analysis that included patients who were IR MTX and biologic-naive;
2) an analysis excluding studies that were conducted in Asian patients only;
3) an analysis of only studies that were conducted in Asian patients only;
4) a restricted time point analysis of end-of-treatment (or adaptive time point) data from week 12 to week 16; and
5) an analysis excluding triple-csDMARD therapy studies published before 2000.

### *Methotrexate as a Common Comparator*

**Disease Response (ACR 50)**

For ACR 50, there were no substantive differences between the reference case and the following sensitivity analyses: all treatment doses and a restricted time point analysis of results between week 12 and week 16.

In particular, the restricted time point analysis demonstrates that the choice to analyze end-of-treatment data from a wide range of time points from included studies did not have an important impact on the results, since a more homogeneous range of time points yielded comparable results in the sensitivity analysis. Therefore, results for the reference case were robust. In addition, use of the end-of-treatment data permits more studies to be included in the analysis rather than having to exclude a study that fits the eligibility criteria, but does not report data at the same time point. Studies are also designed with a treatment duration that

is appropriate for the patient population of interest. Thus, the reference case model is a good choice for analysis.

When the standard dose treatments were analyzed alongside lower and higher doses, the results were comparable to the reference case.

Seven sensitivity analyses did have some differences compared with the reference case. A larger proportion of these differences involved the reference case having statistical significance in favour of the treatment (or comparator, for outcomes where a lower value is better), and was no longer statistically significant in the sensitivity analysis. One methodological explanation for this is related to the sensitivity analysis having a reduced sample size for the evidence network, resulting in a loss of power to detect a difference.

Another difference between these sensitivity analyses and the reference case occurred when the reference case was not statistically significant, and the sensitivity analysis became statistically significant in favour of the treatment (or comparator, for outcomes where a lower value is better). These differences may have occurred because, in each sensitivity analysis, the included studies are more homogeneous than the reference case (e.g., we planned a sensitivity analysis to analyze only studies where patients were clearly IR MTX and not inadequate responders to another csDMARD). Due to the decrease in heterogeneity, there may be an increased likelihood of finding statistically significant results.

The post hoc sensitivity analysis that removed studies of triple-csDMARD published before 2000 had some small differences compared with the reference case. Two studies were excluded that involved double- and triple-csDMARD therapies that were weakly connected to the NMA. Since the weaker parts of the NMA were removed in this sensitivity analysis, it may have resulted in a more stable model and slightly different results than in the reference case. Thus, it may be useful to consider the results of the sensitivity analysis as well (Appendix 8, Table 56).

Our decision to analyze adaptive design trial data had minimal impact on the results since only a small proportion of results changed in the sensitivity analysis when analyzing end-of-treatment data for adaptive design trials. Furthermore, the method we chose (i.e., including the latest time point prior to adaptation in the analysis) made it possible to clearly identify which treatment was responsible for a particular treatment effect.

There were some small differences in the sensitivity analysis of studies published before 2007 versus the reference case, but none compared with the newer studies (2007 onward). One explanation may be that the reference case had a larger proportion of studies published from 2007 onwards, so the weight of the evidence is based on the results of the newer studies. Eligibility criteria for more recent trials may not be the same as for older trials because the patient characteristics that are likely to result in good treatment responses are more well known. Therefore, patients included in this review may have very particular sets of disease characteristics that are not applicable to all patients with RA, such as seropositivity or elevated levels of acute-phase reactants.

Differences in results for the sensitivity analysis of studies that enrolled participants who had an IR to MTX (not to another csDMARD) from the reference case were clustered within a few treatment nodes. Comparisons involving csDMARD in combination with MTX, abatacept (SC) in combination with MTX, and 4 mg/kg tocilizumab in combination with MTX may show differences due to their weak connection to the evidence network through one or two studies that could make them more sensitive to changes. For etanercept in combination with MTX

and 8 mg/kg tocilizumab in combination with MTX (for which there are more studies), the differences may be a result of an increase in homogeneity. Considering this clustering of changes to localized areas of the evidence network, more caution in interpreting results for comparisons involving the previously mentioned treatments may be warranted.

Similarly, the sensitivity analysis including only studies of patients who were IR MTX and biologic-naive had results that lost statistical significance compared with the reference case analysis; the changes were clustered on comparisons involving either SSZ in combination with MTX or a csDMARD in combination with MTX. These treatments had one and two studies contributing data to the evidence network for ACR 50, respectively. Therefore, the results for these treatments may have been more sensitive to change than the rest of the treatments for ACR 50. Interpretation around comparisons with these nodes should be made cautiously; however, overall, the model was fairly robust.

The sensitivity analysis excluding studies conducted in Asian patients only had a few results that lost statistical significance compared with the reference case, most likely due to a decrease in sample size for the sensitivity analysis. These were clustered in treatment comparisons involving: MTX in combination with SSZ, MTX in combination with HCQ, and 4 mg/kg and 8 mg/kg tocilizumab in combination with MTX. There were few studies (one or two) in the ACR 50 evidence network investigating these treatments, except for 8 mg/kg tocilizumab. Therefore, the effect estimates for comparisons with these treatments may have been more sensitive to change and should be interpreted more carefully. In addition, etanercept in combination with MTX was in the most treatment comparisons where a non-significant result from the reference case analysis became statistically significant, possibly because of the increase in homogeneity of the evidence network and the exclusion of head-to-head studies comparing etanercept in combination with MTX with a biosimilar etanercept for an Asian population. Similarly, for the sensitivity analysis of Asian-only studies, there was a decrease in heterogeneity between studies, but also a lower sample size that resulted in a loss of statistical significance for certain comparisons, particularly for comparisons involving csDMARD in combination with MTX. Analyzing studies conducted in Asian patients only also reduced the heterogeneity between studies and resulted in more comparisons with MTX monotherapy being statistically significant when they were not in the reference case.

Given that in the majority of comparisons, the sensitivity analysis results were comparable to the reference case, and that any differences were minor, the model for ACR 50 used for this report is fairly robust. However, it is important to carefully consider whether the results are applicable to specific patients with RA, such as Asian patients or patients with laboratory measures that would not fit the eligibility criteria of more recent studies. Additionally, it should be noted that comparisons from the ACR 50 evidence network involving double-csDMARD therapies (csDMARD in combination with MTX, MTX in combination with SSZ, or MTX in combination with HCQ), abatacept (SC) in combination with MTX, etanercept in combination with MTX, and 4 mg/kg and 8 mg/kg tocilizumab in combination with MTX were more sensitive to changes from the sensitivity analyses than comparisons of other treatments. Results should be interpreted with this uncertainty in mind.

**Continuous Outcomes**

There were no substantive differences between the sensitivity analysis imputing missing standard errors and the reference case for DAS28, pain, fatigue, and HRQoL (SF-36 PCS and MCS). Therefore, our decision to exclude studies from the reference case that had no measure of dispersion (e.g., standard deviation, standard error) reported anywhere in the study is unlikely to have changed the results. Pain and HAQ-DI had some non-statistically

significant results in the sensitivity analysis that were statistically significant in favour of the treatment in the reference case. However, the CrIs were both close to the line of non-significance, and only a small shift resulted in the change. For example, certain effect estimates were slightly statistically significant in the reference case and became slightly non-statistically significant in the sensitivity analysis; or slightly non-statistically significant effect estimates in the reference case became slightly statistically significant in the sensitivity analysis. Therefore, we find the reference case is still a good choice for reporting the results of HAQ-DI and pain.

Results between the reference case and sensitivity analysis of end-of-treatment data from adaptive design trials for radiographic progression differed for two main reasons. First, the reference case analysis compared individual drugs with one another, while the sensitivity analysis compared a mixture of some individual drugs and some treatment strategies because it involved adaptive design trial data after early escape, rescue therapy, or treatment switches. Secondly, the sensitivity analysis yielded very wide CrIs and nonsensical point estimates for the treatment effect. This is likely because: 1) the evidence network was sparse, with only 17 treatment nodes, 11 of which were connected by data from only one study; and 2) there was heterogeneity in the evidence network, especially because six studies followed a strict protocol where participants were randomized to receive an individual drug and 11 studies followed an adaptive design that could involve early escape, rescue therapy, switching treatment arms, or a combination of these. This source of heterogeneity is important because adaptive design trials present results on treatment strategies (e.g., strategy A, B, etc.), whereas typical parallel RCTs assess individual drugs (e.g., drug A, B, etc.). Given these results and the objective of this review to compare the efficacy and safety of individual drugs, the reference case analysis was retained and reported in the main results.

**Withdrawal Due to Adverse Events**

For all sensitivity analyses conducted with the WDAE, there were no substantive differences in the results between the reference case and the sensitivity analysis. In particular, there were no cases where a statistically significant result in the reference case favouring the treatment was then statistically significant in the sensitivity analysis favouring the control. There were also no cases where a statistically significant result in the reference case favouring the control was then statistically significant in the sensitivity analysis favouring the treatment. This demonstrates that the reference case model for WDAEs was robust across all sensitivity analyses, indicating that the results are likely to be reliable. That said, results in the reference case with wide CrIs for this outcome should be considered with caution.

**Conventional Synthetic DMARD as a Common Comparator**

There were no substantive changes for any of the sensitivity analyses for ACR 50, DAS 28, HAQ-DI, or WDAE when compared with the reference case. Therefore, the models for these outcomes were robust.

## Strengths and Limitations

Our review has several strengths. First, the use of an NMA allowed for a comprehensive assessment of the comparative benefits and harms of double- and triple-csDMARD therapies, biologics, biosimilars, and tsDMARDs that would not have been possible with pairwise MAs alone. In addition, the validity of the NMAs was assessed by testing the assumptions of homogeneity, consistency, and similarity. Second, the literature search also

followed comprehensive methods and was executed in accordance with the protocol that was specified a priori*;* it also included grey literature to reduce the impact of publication bias. We also accounted for adaptive design trials by analyzing their data at the time of adaptation and conducted a sensitivity analysis using end-of-treatment results to test the robustness of the reference case; we found no major difference. The publication dates of included studies were also considered through a sensitivity analysis to determine if older and more recent studies differed in their results. In addition, the impact of differences in patients' characteristics was explored in planned and post hoc sensitivity analyses. The restriction of the scope to patients with moderate to severe RA and an IR to MTX allowed for more homogeneity in the included studies. Analyses were conducted separately for evidence networks in which the common comparator was MTX monotherapy and evidence networks in which the common comparator was any csDMARD. This was to ensure that results could be more clinically relevant, since many physicians and patients would be interested in knowing the treatment effects when MTX is used as background therapy because it is the most commonly used csDMARD.[263] Furthermore, the results of the NMAs with csDMARD as a common comparator permitted the investigation of the benefits and harms of treatments that patients with intolerance to MTX could receive.

A few limitations were present in this review. In terms of included studies, due to the use of adaptive design trials in about one-third of included studies, it was not possible to use data from the full length of these studies because of dose modifications or changes to treatments. Thus, the results for this review reflect mostly short-term efficacy and safety findings rather than the durability of response to the treatments in the longer-term. Another limitation is that the majority of included studies that permitted patients to take MTX either did not clearly report which route of administration was permitted (57 studies) or allowed participants to receive oral or SC MTX (14 studies). In addition, the doses of MTX permitted were not the same for all studies. There were also 14 studies that permitted concomitant treatment with any csDMARD without specifying which one. While analyzing these studies in a separate NMA (i.e., MTX as a common comparator and csDMARD as a common comparator) may have reduced the power of the NMAs to detect a difference between treatments, we felt it was important to maintain homogeneity. Risk of bias was unclear for half of the studies due to insufficient details on random sequence generation, allocation concealment, and blinding of subjective outcomes. The planned sensitivity analysis excluding unclear studies or those with a high ROB was not possible, as only 10 studies were considered to have low ROB overall; thus, results should be interpreted with caution. Most of the patients in the included studies were Caucasian women, though less than a quarter of studies were conducted in Asian patients only; this limits the generalizability of the results to other races, particularly in a multicultural country such as Canada.

An additional limitation in the included studies involves the choice of outcome measures. DAS28 was selected to report disease activity because it is the most commonly used scale and is reported in a majority of trials[273] (particularly those from before the ACR/EULAR criteria were developed). However, the DAS 28 has been criticized because the development and validation of the scale were suboptimal.[273] Furthermore, clinical remission does not equate with a pain-free state; in fact, many patients in remission still experience pain, which is a key patient-reported outcome. Our review attempted to address the issue of clinical outcome measures that do not adequately address what is most important to patients by also including patient-reported outcomes (pain, fatigue, HRQoL); however, many of the included studies did not report on these. In addition, certain outcomes commonly reported in RA trials are generic, such as the HAQ-DI for disability and the SF-36 for HRQoL, which are less responsive to clinically relevant changes than disease-specific

outcome measures. Furthermore, not all included studies reported results on all of the outcomes of interest for this review, which means that certain treatments are underrepresented in the NMAs, such as double- and triple-csDMARD therapies and certain biologic monotherapies. As a result, it was necessary to interpret the relative benefits and harms of treatments by outcome rather than across several outcomes as once. It should also be noted that the studies used different end-of-treatment time points, ranging from 12 weeks to three years. Due to our analysis focusing on end-of-treatment data, these shorter and longer durations of treatments may limit the ability to compare treatment effects and safety over the same treatment durations.

Analysis of included studies was restricted to the standard approved doses; for baricitinib, a dose approved in Europe was selected, and for sirukumab, the phase III trial doses were selected, as these were up for review with the FDA at the time of analysis (before all applications for approval were withdrawn by the company). In the case of tocilizumab, there are two approved doses (4 mg/kg and 8 mg/kg), which were both included. As a result, eligible studies with treatment arms involving lower or higher doses of drugs were excluded from analysis; at times, an entire study was excluded because it was reduced to one or no eligible treatment arms. Moreover, this limits the generalizability of the results to clinical practice, since the standard dose is not always what is actually prescribed and used by patients with RA. To address this limitation, a sensitivity analysis including the lower and higher doses of treatments was performed; this indicated the results of the report based on standard doses alone are robust. Another limitation was for treatments that had a small number of participants (e.g., due to only one or two included studies contributing to the treatment node) or low event rates. The results for these treatments may not be as reliable, as evidenced by very wide CrIs for some treatment comparisons in ACR 20, ACR 50, ACR 70, WDAEs, and SAEs. Therefore, the level of confidence based on results with wide CrIs is low.

Patients in RCTs must meet strict eligibility criteria (e.g., no comorbidities, no current pregnancies, strict treatment doses); thus, they may not represent all patients in clinical practice. RCTs are also conducted in a highly controlled manner that may not reflect typical patient behaviour (e.g., higher than normal adherence). Moreover, as the publication date of the studies ranged from 1995 to 2017, it is possible that the patients included in the oldest studies were different in terms of baseline characteristics from those in the newest studies; however, our sensitivity analysis of older versus newer publication dates did not demonstrate any important differences in the results. Considering all of this, results from this review may not be generalizable to all patients. No adjustment for baseline covariates was attempted in this review, as it was not identified as an important consideration based on the input received during the external review or by the clinical experts. However, there were some differences in patient characteristics across the studies that may represent a potential source of bias that could be investigated in future reviews.

Median and range or interquartile range data were converted into the mean and standard error, which could lead to bias. While this is a commonly used practice in conducting systematic reviews, it is possible that the results are biased in favour of a biologic when the true effect is additive based on, for example, the combination of MTX and a biologic.

Lastly, when no measure of dispersion was reported, the baseline value was used to impute the standard error for the mean change from baseline. It was assumed that the variance does not change significantly from baseline to the end of the study, as it is a representation of the patient population. Since the imputation was within the same study, it is likely that any

resulting error from these assumptions is low because the patient population is the same. However, in the event that there were no baseline data available, the study was excluded from the reference case because imputation of the standard error from other studies was considered to be more biased.

## Conclusion

The patient groups who provided input into this review indicated that the ultimate goal of therapy should be disease remission or achieving low disease activity. Improved fatigue and decreased pain were also important to them. The outcomes most often evaluated in the studies included disease response (measured with ACR 20, ACR 50, and ACR 70), disease activity (measured with DAS 28), function (measured with HAQ-DI), and remission, as well as the safety outcomes of WDAEs and SAEs. There were fewer data to inform the outcomes of pain, fatigue, and HRQoL. Mortality, serious infections, cancer, TB, and herpes zoster could not be assessed in NMAs due to many all-arm, zero-event studies; very few data were available on leukemia, lymphoma, congestive heart failure, and MACEs.

In general, most treatments were shown to result in greater benefits compared with MTX, but there was often insufficient evidence to detect a difference between csDMARD monotherapy and the other treatments (in NMAs with csDMARD as the common comparator). Results for sirukumab in this review may no longer be relevant due to the company's recent withdrawal of applications to regulatory agencies globally.[57]

Since the included studies often permitted the participation of both patients in whom MTX had failed as well as patients who had an intolerance to MTX, it is not possible to draw definitive conclusions on the best treatment options for these two types of patients separately. This is because the observed effect for a treatment cannot be clearly attributed to one type of patient or the other.

Triple-csDMARD therapy was one of several treatments that offered statistically significantly greater benefit than double-csDMARD therapy for disease response (measured with ACR 50). However, triple-csDMARD therapy had similar efficacy versus double-csDMARD therapy for function (measured with HAQ-DI). Triple-csDMARD therapy is also likely to have a comparable disease response (ACR 50) to biologics in combination with MTX. There were no included studies of double- or triple-csDMARD therapy with data for the outcomes of disability (HAQ-DI), remission, fatigue, serious infections, TB, cancer (including leukemia and lymphoma as separate outcomes), and MACE.

Combining MTX with a biologic, biosimilar, or tsDMARD is another good treatment option because it demonstrated greater benefits compared with monotherapy with a biologic or tsDMARD. In terms of which biologic, biosimilar, or tsDMARD to use in combination with MTX, the evidence from this review does not indicate that one treatment stands out as having greater benefits than the others because 1) not all treatments had data available for each of the outcomes; and 2) there were often no important differences in the head-to-head comparison results of these treatments. However, if safety is a concern for patients, there is some evidence to indicate that abatacept (IV) in combination with MTX has lower harms than other treatments, based on SAE data. Clinicians should talk to patients about their treatment goals and tolerance for side effects (as well as the risks of side effects) to identify an appropriate treatment strategy. Other important factors to consider are the cost of the treatment, the accessibility of the treatment (e.g., whether it is necessary to travel to a clinic to receive it), and the route of administration (i.e., IV, SC, or oral).

In terms of biologic monotherapy, the evidence indicates that monotherapy with TNF inhibitors may not be the preferred option due to lower benefits compared with TNF inhibitors in combination with MTX. Tocilizumab monotherapy at a dose of 8 mg/kg demonstrated benefits compared with a few other treatments (i.e., for ACR 50, any csDMARD in combination with MTX as well as adalimumab monotherapy [though the CrIs were wide]; for remission, etanercept monotherapy and etanercept in combination with MTX). When there were no statistically significant differences for comparisons of 8 mg/kg tocilizumab with other treatments for ACR 50 and remission, as well as for DAS28 and HAQ-DI (no data were available for HRQoL, pain, fatigue, or radiographic progression), 8 mg/kg tocilizumab had a favourable point estimate compared with biologic monotherapies and biologics in combination with MTX.

Additionally, there was insufficient evidence for SAEs and WDAEs to indicate that 8 mg/kg tocilizumab was worse than other treatments, including the comparator MTX monotherapy. There was also insufficient evidence to detect a difference between 8 mg/kg tocilizumab monotherapy and other treatments in terms of notable harms, with data available for tocilizumab, namely serious infections and TB. IL-6 inhibitors, such as tocilizumab, interfere with acute-phase reactants; hence, for outcomes that measure levels of acute-phase reactants, such as ACR response and remission (using DAS28 score < 2.6), drugs such as tocilizumab may demonstrate greater efficacy compared with others.[19] Therefore, it is unclear whether 8 mg/kg tocilizumab monotherapy is preferable to other treatments because there is insufficient evidence to detect a difference between it and other treatments for the remaining efficacy outcomes in this review.

Based on results for the NMAs with csDMARD as the common comparator, there was no clinical difference found between the TNF inhibitors etanercept, adalimumab, and certolizumab pegol and the IL-6 inhibitor tocilizumab (8 mg/kg) in combination with a csDMARD for achieving disease response (ACR 50). However, in terms of safety, 4 mg baricitinib in combination with a csDMARD did demonstrate lower odds of SAEs compared with a csDMARD in combination with either etanercept or adalimumab.

While many studies have been conducted in patients who are IR MTX with moderate to severe disease activity, there are still unanswered questions regarding the comparative benefits and harms of treatments used for this patient population:

- There were insufficient data to support conclusions regarding the benefits and harms of the combination of a csDMARD (MTX or another) with a biologic, biosimilar, or tsDMARD compared with csDMARD monotherapy and with other biologics, biosimilars, or tsDMARDs in combination with a csDMARD.
- There was insufficient evidence to detect a difference between treatments for radiographic progression for any comparisons. This may have been due in part to the limited quantity of studies with longer-term data in the analysis, since many studies involved an adaptive design as early as 12 weeks or 16 weeks.
- There was limited evidence available to compare the benefits and harms of double- and triple-csDMARD therapies against one another and against biologics, biosimilars, and tsDMARDs. The outcomes of HAQ-DI, remission, HRQoL, fatigue, serious infections, cancer (including leukemia and lymphoma as separate outcomes), and MACEs did not include data from any studies of double- or triple-csDMARD therapies as they did not report on these outcomes. With csDMARD as a common comparator, there were no studies of double- and triple-csDMARD therapies available.

- There was limited evidence to determine which biologic or biosimilar (combined with MTX) was the most effective compared with another biologic or biosimilar (combined with MTX). This may be due to either a lack of power or too short a treatment duration to detect a difference, or simply that there is no important difference in the benefits of biologics, biosimilars, and tsDMARDs.

The results of this review must be interpreted in light of the limitations of the data. Namely, one-third of the studies used an adaptive design, which meant that only the data before the adaptation could be used in the analyses. In addition, the inclusion of RCTs and controlled clinical trials, as well as the method of analyzing data from adaptive design trials before the time of adaptation, signifies that the efficacy and safety results are limited to the short term. Hence, the long-term benefits and harms as well as the durability of the interventions were not captured in the reference case analysis, but it is important that patients and clinicians also consider evidence from long-term treatment in their decision-making. Furthermore, some of the results yielded wide CrIs, which means those treatment comparisons are less reliable. Results from the sensitivity analyses indicated that the findings in this review may not be generalizable to Asian patients. They also indicated that the models remained robust when compared with another sensitivity analysis of studies including a variety of races. Results also may not be generalizable to patients at all socioeconomic levels, literacy levels, or health literacy levels, as these factors could not be investigated in this review. Many included studies had unclear or high ROB overall; thus, the findings from this review should be interpreted with caution until more research is available. Moreover, real-world evidence from observational studies should be considered to provide further context into the applicability of the findings from this review.

Finally, in answer to the original policy question regarding what the optimal treatment is for patients with moderate to severe RA who have had an IR to MTX, various treatment strategies were found to be effective for different outcomes, but there was inconclusive evidence on the comparative efficacy and safety of the treatments versus one another. It is important to recall that the majority of included studies had a high or unclear ROB. Therefore, the results from this report should be interpreted with caution. Whether one treatment is prescribed over another will depend on therapy goals and how the patient tolerates the treatment; decisions should take into consideration treatment accessibility and affordability as well as individual patient preference with regards to the balance between benefits and harms. A decision on the next treatment option should be made after the patient and physician have discussed these important factors.

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