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Harmonization of Public Coverage Policies for Biologic Drugs in the Treatment of Rheumatoid Arthritis

Optimal Use 360 Report

CADTH

Authors: Chris Vannabouathong, Peter Dyrda

Acknowledgements: Tarry Ahuja, Christine Perras, Mina Tadrous, Mirhad Loncar, Jacob Karsh

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Abbreviations

bDMARD	biologic disease-modifying antirheumatic drug
CRA	Canadian Rheumatology Association
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DMARD	disease-modifying antirheumatic drug
ETN	etanercept
FPT	federal, provincial, and territorial
HCQ	hydroxychloroquine
LEF	leflunomide
MTX	methotrexate
RA	rheumatoid arthritis
SSZ	sulfasalazine
tsDMARD	targeted synthetic disease-modifying antirheumatic drug

Key Messages

- For rheumatoid arthritis (RA), treatment guidelines and clinical evidence support the combination (either dual or triple) of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) before accessing a biologic DMARD (bDMARD). Federal, provincial, and territorial (FPT) drug plans currently have different coverage criteria for bDMARD eligibility in RA. To align their criteria, these plans should consider the inclusion of at least 1 line of combination csDMARDs before a bDMARD:
  - For dual csDMARDs: Saskatchewan, Veterans Affairs Canada, and Canadian Armed Forces would need to change their current coverage criteria to include at least 1 line of dual csDMARDs before access to a bDMARD.
  - For triple csDMARDs: Alberta, Saskatchewan, Manitoba, Veterans Affairs Canada, and Canadian Armed Forces would need to alter their current coverage criteria because each of these FPT drug plans only consider csDMARD monotherapy or dual csDMARDs in their current coverage criteria.
- Most FPT drug plans require a failure of at least 2 lines to 3 lines of csDMARD therapy before a bDMARD, except British Columbia, Ontario, Newfoundland and Labrador, Veterans Affairs Canada, and Canadian Armed Forces, which offer an option to access bDMARDs after 1 line of combination csDMARDs. British Columbia, Ontario, the Atlantic provinces, Yukon, Correctional Service of Canada, and Non-Insured Health Benefits include triple csDMARDs in their coverage criteria. Alberta, Manitoba, Veterans Affairs Canada, and Canadian Armed Forces include dual, but not triple, csDMARDs in their criteria; however, Veterans Affairs Canada and Canadian Armed Forces do not require a trial of dual csDMARDs if 2 lines of csDMARD monotherapy have been attempted. Saskatchewan is the only jurisdiction that only requires csDMARD monotherapy. Canadian private insurers have also reached a consensus to implement a trial requirement of dual csDMARDs before a bDMARD across their formularies.
- Evidence-based guidelines, including the 2012 Canadian Rheumatology Association guidelines, recommend csDMARD monotherapy (methotrexate [MTX] is preferred unless contraindicated) as first-line treatment for RA, although a guideline published in 2018 by the Brazilian Society of Rheumatology stated that combination therapy with 2 or more csDMARDs may also be used as a first-line treatment. These guidelines generally recommend combination csDMARDs after csDMARD monotherapy is deemed ineffective.
- A network meta-analysis found that triple csDMARDs is more efficacious than dual csDMARDs, etanercept monotherapy, and 4 mg/kg tocilizumab monotherapy and comparable to other bDMARDs (alone or in combination with MTX), targeted synthetic DMARDs in combination with MTX, and biosimilars in combination with MTX. Additionally, economic evidence demonstrated that triple csDMARDs is more cost-effective than etanercept plus MTX combination therapy.
- Time to first bDMARD was, on average, longer in Alberta, British Columbia, and Ontario than in Saskatchewan, Manitoba, and the Atlantic provinces by approximately 4 months, which may be partially explained by differences in coverage criteria for the number of prior lines of csDMARD therapy required. Increasing the time to initiating a bDMARD could lead to budget savings without impacting clinical outcomes.

Executive Summary

Background: Treatment strategies for rheumatoid arthritis (RA) have evolved over time, leading to the development of various disease-modifying antirheumatic drugs (DMARDs). During the course of treatment, patients with RA will be exposed to 1 or more DMARDs, either alone or in combination. Two broad DMARD classifications are conventional synthetic DMARDs (csDMARDs) and biologic DMARDs (bDMARDs). The bDMARDs are more costly than csDMARDs and have led to increased drug spending. Given budgetary constraints, Canadian drug plans have implemented criteria for the use of pharmacotherapies for patients with RA; however, there has been continued variability in access to bDMARDs across the country. There is a need for improved and consistent access to RA medications across the country by harmonizing public coverage policies to ensure equity in the health care system and to support the optimal management of patients with RA.

Policy issues: A patient's access to bDMARDs depends on meeting drug plan eligibility and coverage criteria, which both differ across Canada. Before the pan-Canadian Pharmaceutical Alliance there was no formal process by which federal, provincial, and territorial (FPT) drug plans would discuss harmonized coverage criteria when listing new drugs. Treatment paradigms change over time with new evidence, as can coverage criteria. In 2015, a national standard for initiating bDMARDs was implemented for private drug plans, which prompted FPT drug plans to review harmonization of bDMARD coverage criteria among public drug plans.

Objective: The aim of this report is to combine insights from several recent CADTH publications to provide evidence for FPT payers to inform discussions to modernize and harmonize the coverage criteria for the initiation of bDMARD treatment in RA. The research questions were to determine the listing status and coverage criteria for the initiation of bDMARD therapy across FPT drug plans, treatment guideline recommendations regarding the use of csDMARDs before initiating therapy with bDMARDs in RA, what evidence supports the use of combination treatment with csDMARDs before initiating therapy with bDMARDs in RA, the utilization of csDMARDs and bDMARDs across FPT drug plans in RA (particularly the time to initiate the first bDMARD), and the budgetary impact if FPT drug plans harmonized to a comparable time to initiate the first bDMARD in RA.

Approach: This report provides a summary of insights from previously published CADTH reports. These reports aimed to answer the research questions within 4 domains: an Environmental Scan of listing status and coverage criteria, a summary and appraisal of clinical treatment guidelines, systematic reviews and critical appraisals of efficacy and cost-effectiveness outcomes, and technology reviews to assess utilization and budget impact.

Findings: Current coverage criteria are similar across jurisdictions: patients need to undergo prior treatment with csDMARDs before accessing a bDMARD. However, there are differences in the number of prior lines of csDMARD therapy required and whether these prior lines of treatment include monotherapy or combination therapy (i.e., dual or triple csDMARDs). Alberta and Yukon require failure of 3 lines of csDMARDs, while Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Prince Edward Island, Correctional Service of Canada, and Non-Insured Health Benefits require failure of 2 lines of csDMARDs. The remaining jurisdictions (i.e., British Columbia, Ontario, Newfoundland and Labrador, Veterans Affairs Canada, and Canadian Armed Forces) provide an option to access a bDMARD after failure of 1 line of combination csDMARDs. British Columbia, Ontario, the Atlantic provinces, Yukon,

Correctional Service of Canada, and Non-Insured Health Benefits include triple csDMARDs in their coverage criteria, while Alberta, Manitoba, Veterans Affairs Canada, and Canadian Armed Forces include dual, but not triple, csDMARDs in their criteria. Saskatchewan only includes csDMARD monotherapy in their criteria for bDMARD access.

Clinical treatment guidelines support the use of csDMARDs before bDMARDs. Canadian guidelines from 2012 recommend csDMARD monotherapy (methotrexate [MTX] is preferred unless contraindicated) as first-line treatment, although 1 guideline published in 2018 (Brazilian Society of Rheumatology) states that combination therapy with 2 or more csDMARDs may also be used as a first-line treatment. When csDMARD monotherapy is ineffective, combination therapy with 2 or more csDMARDs is generally recommended. Overall, these guidelines support the use of csDMARDs before initiating bDMARDs in patients with RA, generally recommending csDMARD monotherapy in the first-line and combination (dual or triple) csDMARDs in the second-line setting.

A network meta-analysis found that triple csDMARDs is more efficacious than dual csDMARDs, etanercept monotherapy, and 4 mg/kg tocilizumab monotherapy. Additionally, triple csDMARDs was found to be more cost-effective than etanercept plus MTX combination therapy in economic evaluations.

Time to first bDMARD was, on average, longer in Alberta, British Columbia, and Ontario than in Saskatchewan, Manitoba, and the Atlantic provinces by approximately 4 months, which may be partially explained by different coverage criteria in these jurisdictions for the number of lines of csDMARD therapy required before accessing bDMARDs. It is estimated that increasing the time to initiating a bDMARD by 4 months in Saskatchewan, Manitoba, and the Atlantic provinces could save approximately $9.6 million over a 3-year period.

Implications for policy-makers: Public payers should consider the inclusion of at least 1 line of combination (i.e., dual or triple) csDMARDs before a bDMARD, which is supported by evidence-based guidelines and clinical evidence. A mandatory trial of dual csDMARDs also would align with the national standard recently set by private insurers. Saskatchewan, Veterans Affairs Canada, and Canadian Armed Forces would need to alter their current coverage criteria to include at least 1 line of combination csDMARDs before access to a bDMARD. Public payers can also consider 1 line of triple csDMARDs for their coverage criteria for the initiation of bDMARD therapy, which is already required by some jurisdictions. Alberta, Saskatchewan, Manitoba, Veterans Affairs Canada, and Canadian Armed Forces would need to alter their current coverage criteria if all FPT drug plans agreed to implement the requirement of at least 1 line of triple csDMARDs before accessing a bDMARD. Implementing such policies may delay the time to first bDMARD use, which can reduce public spending without compromising patient outcomes.

Background

Disease and Treatments

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that causes inflammation of the synovial lining of the joints, tendons, and periarticular structures.[1-3] Clinically, a patient with RA usually presents with pain and swelling in the joints of hand

and feet, accompanied by morning stiffness that can last up to several hours.[4] Irreversible cartilage damage, seen as bony erosions and joint space narrowing on radiographs, also occurs with RA.[4,5] It is a debilitating disease: its symptoms compromise patients' physical functioning, work productivity, and health-related quality of life and it is associated with comorbid conditions (e.g., cardiovascular disease) and greater mortality risk.[4,6,7] Worldwide, RA is the most common chronic inflammatory joint disease, 1 of the leading causes of disability, and 1 of the most costly of all chronic diseases.[6,8] In Canada, it is estimated that 1.25% of individuals aged 16 years or older are living with RA, which has a yearly incidence of approximately 76 per 100,000 people.[9] RA can occur at any age but its incidence and prevalence increases with age —more than half of new cases are diagnosed in individuals between 40 years and 70 years of age. Early intervention is important to prevent or slow disease progression.[4,9-11] Treatment strategies for RA have evolved over time with the primary goal of treatment being a state of remission or low disease activity, This has led to the development of various disease-modifying antirheumatic drugs (DMARDs).[4,12,13]

Two broad DMARD classifications are conventional synthetic DMARDs (csDMARDs) and biologic DMARDs (bDMARDs).[4,12-15] Synthetic DMARDs are small molecules that are usually administered orally, whereas bDMARDs are large proteins that target specific components of the immune system and are administered parenterally.[2,4,12,13] According to the Canadian Rheumatology Association (CRA), DMARD therapy should be initiated as soon as possible after diagnosis, in the care of a rheumatologist or other health care professional trained and experienced in RA diagnosis, clinical assessment, and appropriate prescription of RA drug therapies.[13] Treatment decisions should be made between patients and physicians, considering the presence of poor prognostic factors or contraindications at baseline.[13] Patients should be monitored every 1 month to 3 months until the desired therapeutic target (i.e., remission or low disease activity) is achieved; however, if a patient does not respond to the initial course of therapy, the treatment regimen should be adjusted accordingly and regular follow-up should continue.[13] This approach to care, known as "treat-to-target" or "targeted care," is designed to minimize the time a patient spends in inadequate care and has resulted in better patient outcomes.[13,16-18] With this strategy, patients with RA will be exposed to 1 or more DMARDs, either alone or in combination.[13,14,17] The csDMARDs for RA include azathioprine, hydroxychloroquine (HCQ), leflunomide (LEF), methotrexate (MTX), and sulfasalazine (SSZ); bDMARDs include tumour necrosis factor inhibitors (i.e., adalimumab, certolizumab pegol, etanercept [ETN], golimumab, and infliximab), a T-cell co-stimulatory inhibitor (i.e., abatacept), an interleukin-1 receptor antagonist (i.e., anakinra), a B lymphocyte–depleting drug (i.e., rituximab), and interleukin-6 receptor antagonists (i.e., sarilumab and tocilizumab).[4,13,14]

Access to Medications

In 2017, the Conference Board of Canada conducted a pan-Canadian analysis on patients' access to arthritis medications.[19] This study identified differences between public and private coverage of these drugs, which highlights the need for improved and consistent access across the country, especially when treatment must be tailored to the individual patient. Specifically, public coverage of innovative therapies such as bDMARDs is more limited and less timely compared with private plans. Of all arthritis drugs prescribed in Canada and covered by private insurers, approximately 10% are not accessible through public plans.

In September 2015, the Ontario Rheumatology Association, with the Canadian Life and Health Insurance Association and CRA, announced the establishment of a national standard for access to biologic drugs for adult patients with RA who are privately insured.[20] This was

done to ensure that "the best clinical evidence is used to determine access and help create greater equity in access to needed biologics for Canadians" and that "all Canadians, no matter where they live or who they work for, can access their needed drugs in a more consistent and transparent manner." According to these criteria, a patient with RA must have had a minimum 12-week trial of MTX plus 1 other non-biologic DMARD before a biologic, unless combination therapy is not possible, then the prior use of 3 consecutive non-biologic DMARDs would be acceptable.

Policy Issue

A patient's access to bDMARDs is dependent on meeting drug plan eligibility and coverage criteria, which both differ across federal, provincial, and territorial (FPT) drug plans. Before the pan-Canadian Pharmaceutical Alliance, there was no formal process by which FPT drug plans would discuss harmonized coverage criteria when listing new drugs, although FPT drug plans can still ultimately decide to implement different coverage criteria depending on jurisdictional context. Treatment paradigms change over time with new evidence, as can coverage criteria. Over the past decade, new evidence has emerged related to the use of combination csDMARDs before initiating therapy with bDMARDs. Given the evolution of treatment and harmonization of criteria within private plans, there was rationale for FPT drug plans to evaluate coverage criteria within their drug plans.

Purpose of This Report

This report sought to combine insights from several recent CADTH reports to provide evidence for FPT payers to inform discussions to modernize and harmonize the coverage criteria for the initiation of bDMARD treatment in RA.

Methods

Research Questions

This report aimed to summarize insights for the following questions:

1. What is the listing status and coverage criteria for the initiation of bDMARD therapy across FPT drug plans?
2. What do treatment guidelines recommend for the use of csDMARDs before initiating therapy with bDMARDs in RA?
3. What evidence supports the use of combination treatment with csDMARDs before initiating therapy with bDMARDs in RA?
4. What is the utilization of csDMARDs and bDMARDs across FPT drug plans in RA, particularly the time to initiate the first bDMARD, and what is the budgetary impact if FPT drug plans were to harmonize to a comparable time to initiate the first bDMARD in RA?

Report Selection

This report provides a summary of insights extracted from previously published CADTH reports. These reports aimed to answer the research questions within 4 domains: an Environmental Scan of listing status and coverage criteria, a summary and appraisal of clinical treatment guidelines, systematic reviews and critical appraisals of efficacy and cost-effectiveness outcomes, and technology reviews to assess utilization and budget impact.

Within these domains, CADTH has previously published 7 reports, which are listed in Table 1 with links to the original reports for reference and for further details about methods and findings.

Consultations

The findings from this report and individual reports were shared with members of the CADTH Pharmaceutical Advisory Committee Formulary Working Group for Health Technology Assessments (FWG-HTA), which includes representatives from FPT health ministries and related health organizations. The information related to listing status and coverage criteria,[21] clinical treatment guidelines,[22] network meta-analysis,[24] and utilization analysis and budget impact assessment[26,27] are up-to-date as of July 9, 2020, April 5, 2021, March 1, 2017, and March 31, 2020, respectively.

Findings

Listing Status and Coverage Criteria for the Initiation of bDMARD Therapy Across FPT Drug Plans

Coverage criteria across Canadian public drug plans for bDMARD reimbursement is largely comparable in the medications covered, processes, dosing regimens, and prior therapy requirements (Appendix 1).[21] The differences between jurisdictions are the number of prior lines of csDMARD therapy required before accessing a bDMARD and whether these prior lines of treatment include monotherapy or combination therapy (i.e., dual or triple csDMARDs).

Most jurisdictions require a failure to respond to at least 2 lines to 3 lines of csDMARD monotherapy or combination therapy before bDMARD coverage, except British Columbia, Ontario, and Newfoundland and Labrador, which offer the shortest possible route to bDMARDs by providing an option to access them after 1 line of combination csDMARD therapy (Table 2). In contrast, Alberta and Yukon require trials of 3 lines of therapy, and Saskatchewan, Manitoba, New Brunswick, Nova Scotia, and Prince Edward Island require 2 lines of therapy. In terms of federal public plans, both Correctional Services of Canada and Non-Insured Health Benefits require 2 lines of prior therapy, while Veterans Affairs Canada and Canada Armed Forces provide an option to access bDMARDs after 1 line of combination csDMARD therapy.

As previously mentioned, British Columbia, Ontario, and Newfoundland and Labrador offer an option to access bDMARDs after 1 line of combination csDMARD therapy. In Ontario and Newfoundland and Labrador, only triple csDMARD therapy is accepted, whereas British Columbia accepts either dual or triple csDMARDs. Both Ontario and Newfoundland and Labrador also include prior csDMARD monotherapy in their coverage criteria but only if a

combination csDMARD regimen was also attempted, whereas British Columbia does not accept csDMARD monotherapy in their coverage criteria. Both Alberta and Manitoba require trials of csDMARD monotherapy and dual csDMARDs; Saskatchewan requires csDMARD monotherapy only; New Brunswick, Nova Scotia, and Prince Edward Island require a trial of csDMARD monotherapy or dual csDMARDs and a trial of triple csDMARDs; and Yukon requires a trial of csDMARD monotherapy and trials of dual or triple csDMARDs. For federal plans, Correctional Service of Canada accepts a trial of csDMARD monotherapy or dual csDMARDs and a trial of triple csDMARDs, Non-Insured Health Benefits requires both

Table 1: Summary of CADTH Reports on the Use of DMARDs in RA

Domain	Research question	CADTH report type	Year published	Report
Listing status and coverage criteria	What is the listing status and coverage criteria for the initiation of bDMARD therapy across FPT drug plans?	Environmental Scan	2020	Comparative Assessment of Coverage Criteria for Biologic Disease-Modifying Antirheumatic Drugs Across Canadian Public Drug Plans: An Environmental Scan[21]
Summary and appraisal of clinical treatment guidelines	What do treatment guidelines recommend for the use csDMARDs before initiating therapy with bDMARDs in RA?	Rapid Response: Summary and Critical Appraisal	2021	Conventional Disease-Modifying Antirheumatic Drugs for the Treatment of Rheumatoid Arthritis[22]
Systematic review and critical appraisals of efficacy and cost-effectiveness outcomes	What evidence supports the use of combination treatment with csDMARDs before initiating therapy with bDMARDs in RA?	Technology Review: Focused Critical Appraisal	2020	Efficacy and Safety of Combination Therapy with Conventional Synthetic Disease-Modifying Antirheumatic Drugs in Adult Patients with Moderate or Severe Rheumatoid Arthritis After Failure of, or Suboptimal Response to Methotrexate[23]
		Health Technology Assessment	2018	Drugs for the Management of Rheumatoid Arthritis: Clinical Evaluation[24]
		Rapid Response: Summary and Critical Appraisal	2019	Triple Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs for the Management of Rheumatoid Arthritis: A Review of Cost-Effectiveness[25]
Utilization and budget impact	What is the utilization of csDMARDs and bDMARDs across FPT drug plans in RA, particularly the time to initiate the first bDMARD?	Technology Review: Utilization Study	2021	Utilization Patterns of Disease-Modifying Antirheumatic Drugs for the Treatment of Rheumatoid Arthritis: Rationale for Improving the Harmonization of Coverage Criteria[26]
	What is the budgetary impact if FPT drug plans were to harmonize to a comparable time to initiate the first bDMARD in RA?	Technology Review: Budget Impact Analysis	2021	Initiation of Biologic Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis: A Budget Impact Analysis[27]

bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic disease-modifying antirheumatic drug; RA = rheumatoid arthritis; FPT = federal, provincial, and territorial.

csDMARD monotherapy and triple csDMARDs, and Veterans Affairs Canada and Canadian Armed Forces accept dual csDMARDs but also csDMARD monotherapy if another csDMARD monotherapy was also attempted (Table 2).

Table 2: Summary of Coverage Criteria for the Initiation of bDMARD Therapy Across FPT Drug Plans

FPT drug plan	Regimen(s) of csDMARD required before initiating a bDMARD
Provincial and territorial drug plans	
Alberta	**3 lines:** 2 lines of monotherapy AND 1 line of dual therapy
British Columbia	**1 line:** dual or triple therapy
Manitoba	**2 lines**: 1 line of monotherapy AND 1 line of dual therapy
New Brunswick	**2 lines:** 1 line of monotherapy or dual therapy AND 1 line of triple therapy
Newfoundland and Labrador	**1 line:** triple therapy OR **2 lines**: 1 line of monotherapy AND 1 line of triple therapy
Nova Scotia	**2 lines:** 1 line of monotherapy or dual therapy AND 1 line of triple therapy
Ontario	**1 line:** triple therapy OR **2 lines:** 1 line of monotherapy AND 1 line of dual therapy OR **3 lines:** 2 lines of monotherapy AND 1 line of dual therapy
Prince Edward Island	**2 lines:** 1 line of monotherapy or dual therapy AND 1 line of triple therapy
Saskatchewan	**2 lines**: 2 lines of monotherapy
Yukon	**3 lines:** 1 line of monotherapy AND 2 lines of dual or triple therapy
Federal drug plans	
Canadian Armed Forces	**1 line:** dual therapy OR **2 lines**: 2 lines of monotherapy
Correctional Service of Canada	**2 lines:** 1 line of monotherapy or dual therapy AND 1 line of triple therapy
Non-Insured Health Benefits	**2 lines**: 1 line of monotherapy AND 1 line of triple therapy
Veterans Affairs Canada	**1 line:** dual therapy OR **2 lines**: 2 lines of monotherapy

bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic disease-modifying antirheumatic drug; FPT = federal, provincial, and territorial; NA = not applicable.

Treatment Guideline Recommendations for the Use of csDMARDs Before Initiating Therapy With bDMARDs in RA

Nine evidence-based guidelines were identified that provide recommendations on the use of DMARDs in patients with RA (Appendix 2).[22] These guidelines were developed by rheumatology associations in different countries and regions in Europe, North America, Asia-Pacific, and Brazil; 1 guideline was published by the CRA in 2012. MTX monotherapy is the most commonly recommended first-line therapy and is endorsed in 7 of the included guidelines; of the remaining 2 guidelines, 1 recommends MTX, LEF, or SSZ monotherapy and the other considers MTX and SSZ as first-line treatments. Five guidelines recommend LEF, SSZ, or HCQ as alternative monotherapy options when MTX is not well-tolerated or does not reach targeted treatment results. One guideline states that, in addition to MTX monotherapy, combination therapy with 2 or more csDMARDs that include MTX may also be used as a first-line treatment; another recommends combination csDMARDs as first-line therapy for patients with poor prognostic factors, moderate-high disease activity, or recent-onset disease.

Eight guidelines recommend combination therapy with 2 or more csDMARDs if csDMARD monotherapy is ineffective; however, 2 of these guidelines also recommend bDMARDs and another recommends add-on bDMARD or targeted synthetic DMARD (tsDMARD) therapy for patients with adverse prognostic factors as second-line treatment options.

Overall, these guidelines support the use of csDMARDs before initiating bDMARDs in patients with RA and generally recommend csDMARD monotherapy (preferably MTX) in the first-line setting and combination (dual or triple) csDMARDs in the second-line setting.

Evidence That Supports the Use of Combination Treatment With csDMARDs Before Initiating Therapy With bDMARDs in RA

In a 2-year, randomized, double-blind, placebo-controlled trial (N = 102), adult patients with moderate or severe RA treated with triple csDMARD therapy (MTX-SSZ-HCQ) were compared with 2 groups treated with dual csDMARD therapy (MTX-HCQ or MTX-SSZ).[23,28] Two subgroups of patients were enrolled in this study based on prior MTX therapy: patients not previously treated with MTX and patients who responded suboptimally to MTX and entered the study with a baseline MTX dosage of 17.5 mg/week. The intention-to-treat analysis of this study revealed that patients who received triple csDMARDs had the best response to treatment and that this regimen was well-tolerated; similar efficacy results were seen within both subgroups.[28] The critical appraisal of this study concluded that it was a well-designed trial with standardized, valid, and reliable outcomes assessment, although there were some issues concerning its internal validity regarding the subgroup analysis and justification of the study sample size.[23]

The network meta-analysis evaluated the efficacy and safety of csDMARDs (alone or in combination), biologics (including biosimilars), and tsDMARDs in patients with moderate to severe RA who failed or were intolerant to MTX.[24] A total of 91 studies were included in the quantitative synthesis, which demonstrated a statistically significant improvement in the primary efficacy outcome (the American College of Rheumatology [ACR] 50 response) with triple csDMARDs compared with dual csDMARDs, ETN monotherapy, and tocilizumab 4 mg/kg monotherapy; treatment effects were similar when comparing triple csDMARDs to bDMARDs, tsDMARDs, and biosimilars in combination with MTX (Appendix 3). There were some limitations with the network meta-analysis because of differences between the included studies in study design, treatment doses, and background therapies.

The review of cost-effectiveness evidence on triple csDMARDs relative to other pharmacologic options in the management of RA in North America identified 2 economic evaluations, which both compared triple csDMARDs to ETN-MTX combination therapy.[25,29,30] One study included patients with MTX monotherapy–resistant RA, and the other included patients with early aggressive RA. Both studies concluded that ETN-MTX was not cost-effective relative to triple csDMARD therapy (Appendix 4). In the study on patients with MTX monotherapy–resistant RA, over a lifetime horizon of 50 years, the incremental cost-effectiveness ratio (ICER) for ETN-MTX combination therapy over triple csDMARDs was $521,520 (95% confidence interval [CI], $137,000 to dominated) per quality-adjusted life-year (QALY) gained. In the other study on patients with early aggressive RA, the ICER was $12.5 million (95% CI, $5.6 million to $14 million) per QALY gained.

Utilization of csDMARDs and bDMARDs Across FPT Drug Plans in RA Including the Time to Initiate the First bDMARD

The utilization patterns of csDMARDs were consistent across public drug plans, although there was variability in the use of SSZ and LEF across provinces (e.g., Manitoba had a greater use of SSZ, Saskatchewan had a greater use of LEF).[26] MTX was the most commonly used csDMARD both nationally and within each province; however, in Saskatchewan, both HCQ and LEF were reimbursed at a similar rate as MTX. In British Columbia, Manitoba, and the Atlantic provinces, HCQ and SSZ were the second-most and third-most, respectively, commonly used csDMARDs, whereas in Alberta, Saskatchewan, and Ontario, HCQ and LEF were the next most commonly prescribed csDMARDs after MTX. Azathioprine was the least prescribed csDMARD in all provinces except Manitoba, where LEF was the least used csDMARD. These differences may be explained by local prescribing patterns and coverage criteria for the initiation of a bDMARD within each FPT drug plan. The utilization patterns of bDMARDs were also consistent across public drug plans except for minor variations.

Regarding the number of unique csDMARDs reimbursed, findings were consistent between most jurisdictions, except for Manitoba and the Atlantic provinces. These drug plans had a lower proportion of 2-plus and 3-plus lines of csDMARDs reimbursed, demonstrating a more prevalent use of csDMARD monotherapy in these provinces compared with more frequent use of combination csDMARDs in the remaining jurisdictions. The average time to initiating the first bDMARD was longest in Alberta (792 days), followed by British Columbia (749 days) and Ontario (748 days); in Saskatchewan, Manitoba, and the Atlantic provinces, the average time to first bDMARD was earlier at 681, 668, and 664 days, respectively (the largest difference was between Alberta and the Atlantic provinces at 131 days or 4.3 months). These differences may be explained by coverage criteria in the number of lines of therapy required before accessing bDMARDs: just 2 lines of csDMARDs are required in Manitoba, Saskatchewan, and the Atlantic provinces (except Newfoundland and Labrador). Although Alberta, British Columbia, and Ontario have the longest average time to bDMARDs, there is variability between their coverage criteria for initiating a bDMARD; Alberta requires 3 lines of csDMARDs, British Columbia requires just 1 line of combination csDMARDs, and the criteria for Ontario ranges from 1 line to 3 lines of csDMARDs depending on the use of csDMARD monotherapy or combination csDMARDs.

Budgetary Impact if FPT Drug Plans Were to Harmonize to a Comparable Time to Initiate the First bDMARD in RA

The budget impact analysis showed that harmonizing the time to first bDMARD across jurisdictions may result in substantial savings.[27] It was estimated that, over a 3-year period, increasing the time to initiating a bDMARD by 4 months in the Atlantic provinces, Manitoba, and Saskatchewan would result in a savings of approximately $9.6 million. Conversely, decreasing the time to bDMARD initiation by 4 months in Ontario, Alberta, and British Columbia would result in an incremental cost to the drug plans of approximately $41.7 million over 3 years.

Implications for Policy-Making

Current coverage criteria for the initiation of bDMARD therapy for patients with RA is similar across jurisdictions in that patients need to have previously undergone treatment with csDMARDs; however, differences are seen in the number of prior lines of csDMARD therapy required, which ranges from 1 to 3, and whether csDMARDs are used as monotherapy or combination therapy (i.e., dual or triple csDMARDs). Clinical guidelines generally recommend combination csDMARD therapy if csDMARD monotherapy (MTX is preferred unless contraindicated) is ineffective. Clinical evidence indicates that dual csDMARDs results in more favourable outcomes than csDMARD monotherapy, and that triple csDMARDs is more efficacious than dual csDMARDs, ETN monotherapy, and tocilizumab 4 mg/kg monotherapy, and is comparable to bDMARDs, tsDMARDs, and biosimilars in combination with MTX. Additionally, economic evidence demonstrated that triple csDMARDs is more cost-effective than ETN-MTX combination therapy. The FPT drug plans that require more lines of csDMARD therapy before initiating a bDMARD tend to have longer delays to bDMARD use. This has a positive budgetary impact because of the high cost of bDMARDs and has no apparent impact on clinical outcomes (as measured by retention on therapy.

The insights gathered from these various CADTH reports demonstrate that harmonization and modernization of coverage criteria across Canadian public drug plans is warranted and there are clinical evidence and guidelines available to inform the optimal use of drugs for patients with RA. Based on these findings, public payers should consider the inclusion of at least 1 line of combination (i.e., dual or triple) csDMARDs before a bDMARD, which is supported by evidence-based guidelines and clinical evidence. Additionally, a mandatory trial of dual csDMARDs would align with the national standard recently set by private insurers. Not all jurisdictions currently require failure of 1 line of combination csDMARDs before bDMARD eligibility in RA (i.e., a bDMARD can be accessed after lines of csDMARD monotherapy only) and they would need to alter their coverage criteria if all FPT drug plans agree to align accordingly. Saskatchewan, Veterans Affairs Canada, and Canadian Armed Forces would need to amend their criteria to include at least 1 line of combination csDMARDs before access to a bDMARD. Public payers can also consider 1 line of triple csDMARDs in their coverage criteria for the initiation of bDMARD therapy. If all FPT drug plans agreed to implement this requirement, Alberta, Saskatchewan, Manitoba, Veterans Affairs Canada, and Canadian Armed Forces would need to alter their criteria. Implementing such policies may delay the time to first bDMARD use, which could reduce public spending without compromising patient outcomes; however, there is jurisdictional variability in bDMARD eligibility for RA and policy changes are required before such results can be evaluated.

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Appendix 1: Coverage Criteria for bDMARDs

Note this appendix has not been copy-edited.

Details on the requirements for prior therapy for each drug or group of drugs are summarized in the following table.

Table 3: Requirements for Failure of a Prior Line of Therapy Before bDMARD Eligibility for Patients With RA

Refractory,[a] intolerant,[a] or failure to respond to	Public drug plans	Notes
Prior to access to the following bDMARDs: abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, sarilumab, and tocilizumab		
• MTX + ≥ 1 of the following (not including HCQ): LEF, SSZ, azathioprine, tacrolimus, cyclosporine, gold, doxycycline, or • ≥ 1 DMARD combination	British Columbia	> 8 weeks trial of MTX (parenteral) ≥ 25 mg/week (≥ 15 mg/week if patient is ≥ 65 years of age) > 10 weeks trial of LEF, 20 mg/day > 3 months trial of SSZ, > 2 g/day > 3 months trial of azathioprine, 2 mg/kg/day to 3 mg/kg/day DMARD combination: > 4 months trial MTX-HCQ-SSZ (O'Dell protocol), > 10 weeks trial MTX-LEF Note: antimalarial in combination with 1 other DMARD is not acceptable Expectation for adequate dose/duration of DMARD trials; If a medication must be discontinued due to intolerance(s) before the expected duration of trial an alternate DMARD trial is required. Exceptions considered when additional DMARD trials cannot be attempted (supporting information must be provided for consideration).
• MTX, and • MTX + other DMARDs, and • LEF	Alberta[b]	> 12 weeks trial of MTX ≥ 20 mg/week (p.o., SC, or IM) (≥ 15 mg/week if patient is ≥ 65 years of age) > 4 months trial of MTX + other DMARDs. e.g., MTX with HCQ or MTX with SSZ. > 10 weeks trial of LEF 20 mg/day
• MTX, and • LEF	Saskatchewan	*For sarilumab and tocilizumab ONLY:* adequate trial of DMARDs
• ≥ 3 DMARDs (1 of which is MTX and/or LEF), and • 1 combination of DMARDs	Manitoba	Unless intolerance or contraindications to these agents is documented.

Refractory,[a] intolerant,[a] or failure to respond to	Public drug plans	Notes
Option 1: • MTX, and • LEF, and • ≥ 1 DMARD combination **Option 2:** • MTX, AND • MTX + LEF **Option 3:** • MTX, SSZ, and HCQ	Ontario[c]	> 3 months trial of each therapy. MTX (20 mg/week), LEF (20 mg/day), SSZ (2 g/day) and HCQ (400 mg/day, based by weight up to 400 mg per day). If the patient could not receive adequate trial(s) of MTX and/or LEF due to contraindication(s) or intolerance(s), the nature of contraindication(s) or intolerance(s) must be provided along with details of trials of other DMARDs or clear rationale why other DMARDs cannot be considered. If the patient could not receive an adequate trial of MTX, SSZ, and HCQ due to intolerance, then the DMARD trial criteria must be met.
• MTX or MTX + DMARD, and • MTX + ≥ 2 DMARDs	New Brunswick[b], Nova Scotia[b], Prince Edward Island[b] CSC[b]	**New Brunswick, Nova Scotia, Prince Edward Island** > 12 weeks trial of MTX ≥ 20 mg/week (p.o., SC, or IM) (≥ 15 mg if patient is ≥ 65 years of age). > 3 months trial of MTX + other DMARDs e.g., MTX with HCQ and SSZ Optimal treatment response to DMARDs may take up to 24 weeks, however coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. If patient factors (e.g., intolerance) prevent the use of triple DMARD therapy, these must be described and dual therapy with DMARDs must be tried. **CSC** If patient could not receive an adequate trial of MTX, SSZ, HCQ due to contraindication(s) or intolerance(s), the nature must be provided along with the details of trial of other DMARDs or clear rationale why other DMARDs cannot be considered **FOR abatacept and infliximab ONLY**: Failure or intolerance with a SC biologic (e.g., adalimumab) should be assessed before starting an IV biologic (e.g., infliximab, abatacept, tocilizumab). **FOR tocilizumab ONLY:** An adequate trial has documented intolerance to or a contraindication to both DMARDs and anti-TNF agents. Failure or intolerance with a SC biologic (e.g., adalimumab) should be assessed before starting an IV biologic (e.g., infliximab, abatacept, tocilizumab).
Option 1: • MTX, and • MTX + ≥ 2 DMARDs **Option 2:** • MTX + ≥ 2 DMARDs	Newfoundland and Labrador[b]	> 12 weeks trial of MTX ≥ 20 mg/week (p.o., SC, or IM) (≥ 15 mg if patient is ≥ 65 years of age). > 3 months trial of MTX + other DMARDs e.g., MTX with HCQ and SSZ Optimal treatment response to DMARDs may take up to 24 weeks, however coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. If patient factors (e.g., intolerance) prevent the use of triple DMARD therapy, these must be described and dual therapy with DMARDs must be tried.
• Parenteral MTX, and • ≥ 2 of the following: LEF, SSZ, azathioprine; and • ≥ 1 DMARD combination	Yukon	> 12 weeks trial for each course of therapy. DMARD combination e.g., MTX with cyclosporine, MTX with HCQ and SSZ, MTX with LEF **FOR abatacept ONLY**: Must have failed adequate trial of an anti-TNF agent

Refractory,[a] intolerant,[a] or failure to respond to	Public drug plans	Notes
Option 1: • MTX, and • MTX + ≥ 2 DMARDs (SSZ and HCQ) **Option 2:** • ≥ 2 DMARDs combination (SSZ, HCQ, azathioprine, LEF, cyclosporine); if the patient has a contraindication, failure, or intolerance to MTX	NIHB[b]	**NIHB** > 12 weeks trial for each course of therapy. MTX ≥ 20 mg/week (p.o., SC, or IM) (≥ 15 mg if patient is ≥ 65 years of age). **FOR abatacept IV ONLY**: Must have failed (FOR IV FORMULATION ONLY): > 12 weeks trial of etanercept (SC) OR adalimumab (SC) OR golimumab (SC) OR certolizumab pegol (SC) OR abatacept (SC) OR tocilizumab OR tofacitinib (p.o.) or infliximab biosimilars (IV)
• ≥ 2 DMARDs used as monotherapy or as combination therapy (must include MTX unless contraindicated or not tolerated)	VAC, CAF[b]	**VAC** > 12 weeks trial for each course of therapy **CAF** > 12 weeks trial of MTX ≥ 20 mg/week (p.o., SC, or IM); 10 weeks trial of LEF 20 mg daily; 20 weeks trial of gold weekly injections; 3 months trial of SSZ ≥ 2 g daily; 3-month trial of azathioprine 2 mg/kg/day to 3 mg/kg/day **FOR tocilizumab ONLY**: An adequate trial, have documented intolerance to or a contraindication to both DMARDs and anti-TNF agents.
Prior to access to rituximab		
Adequate trial of ≥ 1 anti-TNF agent	British Columbia, Alberta, Ontario, Saskatchewan, Manitoba, Nova Scotia, Newfoundland and Labrador, Prince Edward Island, Yukon, NIHB, CSC, VAC, CAF	**British Columbia, Ontario, VAC** Including intolerance/contraindication to anti-TNF agent **Alberta** > 12 weeks trial of 1 anti-TNF agent

ACR = American College of Rheumatology; CAF = Canadian Armed Forces; CSC = Correctional Services of Canada; DAS = disease activity score; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; HCQ = hydroxychloroquine IM = intramuscular; LEF = leflunomide; MTX = methotrexate; NIHB = Non-Insured Health Benefit; p.o. = orally; RA = rheumatoid arthritis; SC = subcutaneous; SSZ = sulfasalazine; TNF = tumour necrosis factor; VAC = Veterans Affairs Canada.

Note: Certolizumab pegol was not eligible for reimbursement by CSC, VAC, CAF. Renflexis, an infliximab biosimilar, was not eligible for reimbursement by Yukon. Sarilumab was not eligible for reimbursement by Nova Scotia, Yukon, and CSC. Truxima, a rituximab biosimilar, was only eligible for reimbursement by Alberta, Ontario, and Yukon. Coverage for etanercept and infliximab biosimilars may be provided in exceptional cases by VAC while the drugs are under review.

[a]*Refractory* is defined as lack of effect at the recommended doses and for duration of treatments specified above. *Intolerant* is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs.

[b]Patients who do not exhibit a clinical response or experience gastrointestinal intolerance to p.o. MTX may have a trial of parenteral MTX before being accepted as refractory.

[c]Actemra (tocilizumab), Brenzys (etanercept), Cimzia (certolizumab pegol), Erelzi (etanercept), Inflectra (infliximab), Kevzara (sarilumab), Orencia (abatacept), Renflexis (infliximab), Simponi (golimumab), Xeljanz (tofacitinib).

Source: Canadian public drug plan formularies.[31-48]

Appendix 2: Treatment Guidelines on DMARDs for RA

Note this appendix has not been copy-edited.

Main study findings and authors' conclusions from 9 evidence-based guidelines are summarized in the following table.

Table 4: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
EULAR (2020)[49]	
Recommendation "Methotrexate (MTX) should be part of the first treatment strategy (p. 690)."[49] Evidence informing this recommendation was not provided.	**LoE**: 1a (SR of RCTs) **SoR**: A (consistent level 1 studies[a])
Recommendation "In patients with contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy (p. 690)."[49] Evidence informing this recommendation was not provided.	**LoE**: 1a (SR of RCTs) **SoR**: A (consistent level 1 studies)
Recommendation "Short-term GC should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible (p. 692)."[49] Three clinical trials suggested that MTX-GC showed similar effectiveness when compared to MTX-bDMARDs.	**LoE**: 1a (SR of RCTs) **SoR**: A (consistent level 1 studies)
Recommendation "If the treatment target is not achieved with the first csDMARDs strategy, in the absence of poor prognostic factors, other csDMARDs should be considered (p. 692)."[49] Evidence informing this recommendation was not provided.	**LoE:** 5 (expert opinion without explicit critical appraisal) **SoR**: D (level 5 evidence[b] or troublingly inconsistent or inconclusive studies of any level)
APLAR (2019)[58]	
Recommendation "Starting treatment with csDMARD monotherapy, preferably MTX, is recommended as soon as the diagnosis of RA is made (p. 359)."[58] Evidence for the use csDMARDs, particularly MTX, as first-line therapy for patients diagnosed with RA was presented in previous 2016 EULAR[51] and 2015 ACR[52] treatment guidelines. The efficacy of using MTX monotherapy as first-line treatment for patients with RA was outlined in a 2014 SR and moderate-quality evidence from individual studies. The previous recommendation found in the 2015 version of this guideline presented 2 strong recommendations on csDMARDs as first-line RA treatment, and that MTX is the preferred csDMARD. Based on current and past moderate-quality evidence, the previous 2 statements were integrated into 1 recommendation.	**Quality of Evidence:** Moderate (moderately confident in the effect estimate) **Strength of Recommendation:** NR

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
Recommendation "Patients who cannot tolerate MTX may receive other csDMARDs such as LEF or SSZ as first-line treatment. HCQ, iguratimod, bucillamine, cyclosporine, intramuscular gold or tacrolimus may also be considered depending on availability (p. 361)."[58] This recommendation is consistent with the previous recommendation in the 2015 version and is consistent with the 2016 EULAR[51] treatment guideline. Three SRs and 1 RCT provided evidence for the efficacy of LEF compared with MTX. One SR and 2 RCTs support SSZ as an alternative to MTX. There were limited data on the efficacy of the other mentioned csDMARDs.	**Quality of Evidence:** Moderate (moderately confident in the effect estimate) **Strength of Recommendation:** NR
Recommendation "In patients with high disease activity, combination csDMARD therapy should be considered, with close monitoring of therapy-related toxicities (p. 361)."[58] This recommendation was based on RCTs in which patients with active RA were provided combination therapy. Four RCTs showed that triple therapy was more efficacious than monotherapy but was accompanied with higher hepatotoxicity. An additional 7 RCTs that looked at double or triple therapy vs. monotherapy had similar findings. A previous Cochrane review from 2002 also showed higher efficacy in combination therapy compared to monotherapy.	**Quality of Evidence:** Low (confidence in the effect estimate is limited) **Strength of Recommendation:** NR
French Society for Rheumatology (2019)[53]	
Recommendation "Methotrexate is the first-line DMARD in patients with active RA, starting at a dosage of at least 10 mg/week then reaching the optimal dosage within no more than 4–8 weeks (p. 141)."[53] Evidence informing this recommendation was not provided.	**LoE:** 1a (SR of RCTs) **SoR:** A (consistent level 1 studies)
Recommendation "In DMARD-naive patients who have contraindications or early intolerance to methotrexate, leflunomide and sulfasalazine are good alternatives (p. 141)."[53] Evidence informing this recommendation was not provided.	**LoE:** 1a (SR of RCTs) **SoR:** A (consistent level 1 studies)
Recommendation "While awaiting the effects of csDMARD therapy, oral or parenteral glucocorticoid therapy can be considered, in a low cumulative dosage, if possible for no longer than 6 months. The glucocorticoid dose should be tapered to nothing as promptly as possible (p. 141)."[53] Evidence informing this recommendation was not provided.	**LoE:** 1a (SR of RCTs) **SoR:** B (consistent level 2[c] or 3 studies[d] or extrapolations from level 1 studies)

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
Recommendation "In patients with an inadequate response or intolerance to methotrexate, the treatment must be optimized. In patients with adverse prognostic factors, add-on bDMARD or tsDMARD therapy can be considered, using a TNFα antagonist, abatacept, an IL-6 pathway antagonist, a JAK inhibitor, or, under specific circumstances, rituximab. In patients without adverse prognostic factors, a switch to another csDMARD (leflunomide, sulfasalazine) or the combination of several csDMARDs can be considered; if this strategy fails or is contraindicated, targeted therapy (with a bDMARD or tsDMARD) should be considered (p.141)."[53] Evidence informing this recommendation was not provided.	**LoE:** 1b (individual RCT) **SoR:** #A (consistent level 1 studies)
Brazilian Society of Rheumatology (2018)[50]	
Recommendation "The first line of treatment should be a csDMARD started as soon as the diagnosis of RA is established (p. 4)."[50] Evidence for this recommendation was described as low to moderate.	**LoA:** 9.93 (mean score out of 10) Quality of evidence was described as low to moderate **Strength of Recommendation:** NR
Recommendation "Methotrexate is the first-choice csDMARD (p. 6)."[50] Moderate-quality evidence suggested that there was no significant difference in the efficacy of csDMARDs for most relevant outcomes including number of painful and swollen joints, disease activity, pain, and functional capacity. High evidence suggested there were more adverse events with LEF compared to MTX; however, low to very low evidence suggested that MTX had the highest risk of hepatic pulmonary adverse events.	**LoA:** 10 Quality of evidence was described as very low to high **Strength of Recommendation:** NR
Recommendation "Combination of two or more csDMARDs, including MTX, may be used as the first line of treatment (p. 6)."[50] High to moderate evidence suggested that triple therapy with MTX-SSZ-HCQ and MTX-LEF compared with MTX monotherapy showed an improved response. Moderate to low evidence suggests that there was no clinically significant difference in MTX alone or in combination in other disease activities, radiographic progression, and therapeutic safety.	**LoA:** 9.62 Quality of evidence was described as low to high **Strength of Recommendation:** NR
Recommendation "After failure of first-line therapy with MTX, therapeutic strategies include combining MTX with another csDMARD (leflunomide), with two csDMARDs (hydroxychloroquine and sulfasalazine), or switching MTX for another csDMARD (leflunomide or sulfasalazine) alone (p. 6)."[50] Moderate to low evidence suggested combination therapies with MTX may provide a better response, with no significant difference in radiographic progression or adverse events from discontinuation.	**LoA:** 9.12 Quality of evidence was described as low to moderate **Strength of Recommendation:** NR

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
NICE (2018)[54]	
Recommendation "For adults with newly diagnosed active RA: • Offer first-line treatment with cDMARD monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms. • Consider hydroxychloroquine for first-line treatment as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease. • Escalate does as tolerated (p. 8-9)."[54] "Consider short-term bridging treatment with glucocorticoids (oral, intramuscular or intra-articular) when starting new cDMARD (p. 9)."[54] Overall evidence suggested that starting treatment with more than 1 csDMARD was no more effective than starting with a monotherapy csDMARD approach. Additionally, evidence from RCTs in DMARD-naive patients showed no difference in the effectiveness of MTX, LEF, and SSZ as monotherapies. The committee agreed that any of these csDMARDs may be used as first-line therapies.	Quality of evidence and strength of recommendations were NR
Recommendation "Offer additional cDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation (p. 9)."[54] Evidence from RCTs was limited regarding the use of glucocorticoids for symptom relief in patients starting new DMARD therapy, and no evidence was found regarding the effectiveness of glucocorticoids in terms of disease activity, QoL, or function. The committee agreed that the use of glucocorticoids may be considered on a case-by-case basis.	Quality of evidence and strength of recommendations were NR
ACR (2016)[e 52]	
Recommendations for patients with symptomatic early RA: **Recommendation** "If the disease activity is moderate or high, in patients who have never taken DMARD: • Use DMARD monotherapy over double therapy • Use DMARD monotherapy over triple therapy (p. 8)."[52] Overall, 7 RCTs informed this recommendation. The strength for this recommendation is conditional due to low-quality evidence. Additionally, the evidence for this recommendation was shown to be imprecise. It was suggested that there was little difference in the benefit of double therapy over monotherapy, and triple therapy may be desired by some patients.	**SoR:** Conditional (uncertainty of harms and benefits due to low-quality evidence) **LoE:** Moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate) **LoE:** High (further research is very unlikely to change our confidence in the estimate of effect)

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
Recommendation "If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDs or a TNFi or a non-TNF biologic (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (p. 8)."[52] One RCT provided low-quality evidence that suggested that when DMARD monotherapy was failing, adding treatment options is supported and recommending no additional treatment is not an option.	**SoR:** Strong (the benefits outweigh the harms) **LoE:** Low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate)
Recommendations for patients with established RA: **Recommendation** "If disease activity is moderate or high, in patients who have never taken DMARD: • Use DMARD monotherapy (MTX preferred) over tofacitinib • Use DMARD monotherapy (MTX preferred) over combination DMARD therapy (p. 11)."[52] Overall, 8 RCTs informed this recommendation. This recommendation is conditional because despite positive evidence for tofacitinib, conflicting evidence suggested benefit, risk, and cost favoured MTX monotherapy. The evidence for DMARD monotherapy over combination DMARD therapy was low-quality because evidence supporting the benefit of double therapy over monotherapy was indirect and imprecise.	**SoR:** Conditional (uncertainty of harms and benefits due to low-quality evidence) **LoE:** High (further research is very unlikely to change our confidence in the estimate of effect) **LoE:** High (further research is very unlikely to change our confidence in the estimate of effect)
Recommendation "If disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDs or add a TNFi or a non-TNF biologic or tofacitinib (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (p. 11)."[52] Overall, 14 RCTs informed this recommendation. This recommendation is strong because clinical experience supported adding treatment options when DMARD monotherapy is failing. Additionally, voting supported bDMARD therapy using in combination with MTX due to evidence of efficacy compared with bDMARD monotherapy.	**SoR:** Strong (the benefits outweigh the harms) **LoE:** Moderate to very low (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; We are very uncertain about the estimate)
Todoerti et al. (2013)[55]	
Recommendation "MTX must be considered the DMARD of first choice in RA patients both alone and in combination (with low dosage glucocorticoid and/or other DMARDs) (p. 209)."[55] One meta-analysis and 1 RCT suggested that MTX-based treatment with the addition of a low-dose steroid (such as a glucocorticoid) improved outcomes related to radiographic progression and lower disease activity.	**LoE:** 2b (individual cohort study) **SoR:** B (consistent level 2 or 3 studies or extrapolations from level 1 studies)

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
Recommendation "In patients that are non-responders to MTX at the maximum tolerated dosage, combination therapy can be started with DMARD or a biological agent (p. 209)."[55] One Cochrane review suggested that combining MTX with other DMARDs compared with MTX alone had no significant advantage in DMARD-naive or non-respondent patients, except for the combination of MTX-HCQ-SSZ (known as the O'Dell protocol). Additional evidence compared the efficacy of triple therapy to adding a bDMARD to therapy and suggested that the addition of the bDMARD improved clinical and radiographical outcomes.	**LoE:** 1b (individual RCT) **SoR:** B (consistent level 2 or 3 studies or extrapolations from level 1 studies)
CRA (2012)[56]	
Recommendation "Glucocorticoids (GC; oral, intramuscular, or intraarticular) can be added to DMARD therapy as part of the initial treatment strategy of patients with RA (I), and may be an option for managing flares, as bridge therapy while waiting for DMARD to take effect, or for symptom control if no other options exist (IV). GC should be used in the lowest possible dose and tapered as rapidly as clinically feasible (IV) (p. 1569)."[56] One SR of RCTs that informed the EULAR 2010 guidelines suggested that short-term treatment with GC was beneficial for symptom control and inhibiting radiographic progression when added to DMARD monotherapy of combination therapy. Other evidence informing the NICE 2009 guidelines showed there was a discordance between strong evidence for the use of GC and paucity of other research studies. Additional evidence from the EULAR 2007 guidelines suggested there was a risk of adverse events depending on the dosage of GC used.	**LoE:** I (meta-analyses, SRs of RCTs, or individual RCTs), IV (expert opinion) **SoR:** A (strong recommendation)/D (consensus recommendation)
Recommendation "Methotrexate is the preferred DMARD with respect to efficacy and safety and should be the first DMARD used in patients with RA unless contraindicated (p.1569)."[56] RCT and observational evidence from the EULAR 2010 guidelines suggested that MTX was effective in DMARD-naive patients with early moderate to severe RA. Additionally, no other csDMARD or bDMARD monotherapies were shown to have better clinical efficacy compared to MTX. One SR supported the beneficial safety of long-term MTX.	**LoE:** I (meta-analyses, SRs of RCTs, or individual RCTs) **SoR:** A (strong recommendation)

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
Recommendation "Initial combination therapy with traditional DMARD should be considered, particularly in patients with poor prognostic features, moderate-high disease activity, and in patients with recent-onset disease. Combination therapy should also be considered in patients who have an inadequate response to monotherapy (p. 1571)."[56] RCT evidence informing the ACR 2008 guidelines suggested there was efficacy in DMARD combinations in different clinical situations. An SR of RCT and observational studies informing the NICE 2009 guidelines suggested that several combinations (including GC) was superior to DMARD monotherapy. An SR of RCTs informing the EULAR 2010 guidelines found low-quality evidence in trials comparing combination therapy to monotherapy.	**LoE:** I (meta-analyses, SRs of RCTs, or individual RCTs) **SoR:** B (moderate recommendation)
Recommendation "When treating with combination therapy, methotrexate (MTX) should be used as the anchor drug unless contraindicated. Combinations not including MTX can be considered on a case-by-case basis (p. 1571)."[56] Evidence informing the NICE 2009 guideline and ACR 2008 guideline provided details for combination therapy in RA. At least 1 RCT showed increased efficacy for a number of combination therapies over monotherapy.	**LoE:** I (meta-analyses, SRs of RCTs, or individual RCTs) **SoR:** A (strong recommendation)
Recommendation "Combination therapy with leflunomide (LEF) and methotrexate (MTX) should be used with caution as it is associated with higher toxicity (GI and liver) (I) and has no added benefit relative to other DMARD combinations (IV) (p. 1572)."[56] Evidence from 1 RCT suggested combination therapy with MTX-LEF had better efficacy compared to MTX-placebo in patients with high disease activity. It should be noted that LEF was associated with risk of severe liver injury. Additionally, several Canadian provincial formularies require patients to fail LEF or MTX-LEF before accessing bDMARD therapy.	**LoE:** I (meta-analyses, SRs of RCTs, or individual RCTs), IV (expert opinion) **SoR:** A (strong recommendation)
SIGN (2011)[57]	
Recommendation "Low-dose oral corticosteroids can be used in combination with DMARD therapy for short term relief of signs and symptoms, and in the medium to long term to minimize radiological damage (p. 9)."[57] A Cochrane review of RCTs suggested that low-dose corticosteroids were effective in short-term relief of symptoms compared with NSAIDs and minimized radiographical damage in the medium to long term. An additional Cochrane review found that corticosteroids in combination with DMARDs reduced the rate of progression for RA.	**Quality of Evidence:** A

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
Recommendation "Methotrexate and sulfasalazine are the DMARDs of choice due to their more favourable efficacy and toxicity profiles (p. 10)."[57] "DMARD therapy should be sustained in patients with early RA to control the signs and symptoms of disease (p. 10)."[57] Evidence from an SR suggested that the efficacy of MTX was similar to other common csDMARDs including LEF and SSZ, but HCQ was less effective. Additional evidence from 2 RCTs suggested sustained use of DMARD therapy was necessary due to relapse symptoms and signs occurring with therapy withdrawal.	**Quality of Evidence:** A **Quality of Evidence:** B
Recommendation "A combination DMARD strategy, rather than sequential monotherapy, should be considered in patients with an inadequate response to initial DMARD therapy (p. 11)."[57] An SR of 3 RCTs suggested that combination therapy was more effective than sequential monotherapy in overall RA improvement and reduction in progression. MTX was the most common DMARD in combination therapy.	**Quality of Evidence:** A

ACR = American College of Rheumatology; APLAR = Asia-Pacific League of Associations for Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism; GC = glucocorticoids; HCQ = hydroxychloroquine; JAK = Janus Kinase; LEF = leflunomide; LoA = level of agreement; LoE = level of evidence; MTX = methotrexate; NICE = National Institute for Health and Care Excellence; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; QoL = quality of life; RA = rheumatoid arthritis; RCT = randomized controlled trial; SoR = strength of recommendation; SR = systematic review; SSZ = sulfasalazine; TNF = tumour necrosis factor; TNFi = tumour necrosis factor inhibitor; tsDMARD = targeted synthetic disease-modifying antirheumatic drug; vs. = versus.

[a]Level 1 studies refer to SR of RCTs, individual RCTs, and "all or none" studies.

[b]Level 5 evidence refers to expert opinion without explicit critical appraisal.

[c]Level 2 studies refer to SR of cohort studies, individual cohort studies, or "outcomes" research and ecological studies.

[d]Level 3 studies refer to SR of case-control studies, and individual case-control studies.

[e]The American College of Rheumatology uses the term "DMARD" to describe conventional synthetic DMARD therapy.

Appendix 3: Network Meta-Analysis of Drugs for the Management of RA

Note this appendix has not been copy-edited.

Primary efficacy outcome (ACR 50 response) results from the network meta-analysis are presented in the following table.

Table 5: Comparative Effects Between Treatments for RA — Random-Effects Model

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
Comparator: Placebo-MTX			
csDMARD-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)[a]	4.39 (1.28 to 7.57)[a]	0.39 (0.03 to 0.75)[a]
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)[a]	4.63 (2.19 to 7.15)[a]	0.42 (0.14 to 0.70)[a]
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)[a]	2.94 (1.98 to 4.34)[a]	0.22 (0.12 to 0.38)[a]
ABA_STD (IV)-MTX	4.12 (2.59 to 6.75)[a]	3.03 (2.18 to 4.10)[a]	0.23 (0.14 to 0.35)[a]
ABA_STD (SC)-MTX	3.68 (1.51 to 8.88)[a]	2.81 (1.43 to 4.69)[a]	0.21 (0.05 to 0.42)[a]
ADA_STD-MTX	3.99 (2.84 to 5.62)[a]	2.96 (2.33 to 3.72)[a]	0.23 (0.16 to 0.30)[a]
TOF_STD-MTX	5.83 (3.45 to 9.79)[a]	3.73 (2.68 to 4.93)[a]	0.32 (0.20 to 0.44)[a]
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)[a]	2.87 (1.87 to 4.14)[a]	0.22 (0.10 to 0.36)[a]
TOC_4 (IV)-MTX	2.71 (1.43 to 5.09)[a]	2.26 (1.37 to 3.47)[a]	0.15 (0.04 to 0.28)[a]
TOC_8 (IV)-MTX	4.31 (2.62 to 7.20)[a]	3.11 (2.21 to 4.23)[a]	0.25 (0.14 to 0.37)[a]
GOL_STD (SC)-MTX	6.00 (3.27 to 11.35)[a]	3.80 (2.58 to 5.27)[a]	0.32 (0.19 to 0.48)[a]
GOL_STD (IV)-MTX	2.90 (1.21 to 7.12)[a]	2.38 (1.19 to 4.19)[a]	0.16 (0.02 to 0.37)[a]
INF_STD-MTX	3.00 (1.78 to 5.08)[a]	2.44 (1.63 to 3.48)[a]	0.17 (0.07 to 0.28)[a]
CERTO_STD-MTX	5.35 (3.42 to 8.67)[a]	3.56 (2.66 to 4.67)[a]	0.30 (0.20 to 0.41)[a]
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)[a]	3.63 (1.39 to 6.60)[a]	0.30 (0.05 to 0.63)[a]
BAR_4-MTX	5.44 (3.16 to 9.69)[a]	3.59 (2.52 to 4.91)[a]	0.30 (0.18 to 0.44)[a]
HD203-MTX	7.11 (2.46 to 23.00)[a]	4.16 (2.10 to 6.59)[a]	0.37 (0.13 to 0.63)[a]
SB4-MTX	4.65 (1.78 to 13.60)[a]	3.27 (1.64 to 5.61)[a]	0.26 (0.07 to 0.52)[a]
ANBAI-MTX	8.76 (3.02 to 26.39)[a]	4.61 (2.44 to 6.82)[a]	0.42 (0.17 to 0.66)[a]
CT-P13–MTX	4.13 (1.82 to 9.95)[a]	3.03 (1.66 to 4.93)[a]	0.24 (0.08 to 0.45)[a]
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)[a]	2.84 (1.41 to 4.79)[a]	0.21 (0.05 to 0.43)[a]

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
ZRC-3197–MTX	3.87 (1.29 to 11.77)[a]	2.90 (1.25 to 5.28)[a]	0.22 (0.03 to 0.49)[a]
ABP501-MTX	3.59 (1.45 to 8.79)[a]	2.76 (1.38 to 4.67)[a]	0.20 (0.04 to 0.42)[a]
Comparator: csDMARD-MTX			
MTX-SSZ	1.70 (0.19 to 13.51)	1.56 (0.22 to 6.20)	0.07 (−0.14 to 0.50)
MTX-HCQ	7.41 (1.03 to 50.72)[a]	4.01 (1.02 to 10.34)[a]	0.38 (0.004 to 0.74)[a]
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)[a]	4.29 (1.62 to 10.10)[a]	0.41 (0.11 to 0.69)[a]
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)[a]	2.78 (1.61 to 4.98)[a]	0.21 (0.12 to 0.32)[a]
ABA_STD (IV)-MTX	3.90 (1.38 to 10.08)[a]	2.87 (1.26 to 6.42)[a]	0.23 (0.06 to 0.36)[a]
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)[a]	2.82 (1.27 to 6.16)[a]	0.22 (0.06 to 0.32)[a]
TOF_STD-MTX	5.49 (1.87 to 14.52)[a]	3.53 (1.55 to 7.90)[a]	0.31 (0.13 to 0.45)[a]
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)[a]	2.71 (1.14 to 6.26)[a]	0.21 (0.03 to 0.36)[a]
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)[a]	2.95 (1.29 to 6.63)[a]	0.24 (0.07 to 0.38)[a]
GOL_STD (SC)-MTX	5.67 (1.88 to 15.77)[a]	3.59 (1.55 to 8.13)[a]	0.31 (0.12 to 0.48)[a]
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)[a]	3.37 (1.51 to 7.46)[a]	0.29 (0.12 to 0.42)[a]
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)[a]	3.38 (1.01 to 9.05)[a]	0.29 (0.002 to 0.63)[a]
BAR_4-MTX	5.14 (1.77 to 13.79)[a]	3.39 (1.49 to 7.61)[a]	0.29 (0.11 to 0.45)[a]
HD203-MTX	6.70 (2.15 to 20.61)[a]	3.85 (1.75 to 8.14)[a]	0.35 (0.12 to 0.60)[a]
SB4-MTX	4.40 (1.55 to 12.45)[a]	3.05 (1.40 to 6.43)[a]	0.25 (0.07 to 0.48)[a]
ANBAI-MTX	8.25 (1.95 to 32.91)[a]	4.30 (1.61 to 10.22)[a]	0.40 (0.12 to 0.66)[a]
CT-P13–MTX	3.90 (1.13 to 12.64)[a]	2.86 (1.10 to 6.97)[a]	0.22 (0.02 to 0.44)[a]
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)
Comparator: MTX+SSZ			
MTX-HCQ	4.33 (1.00 to 21.90)	2.46 (1.00 to 10.24)	0.27 (−0.0004 to 0.58)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)[a]	2.70 (1.05 to 12.68)[a]	0.31 (0.02 to 0.56)[a]
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)
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)
Comparator: MTX-HCQ			
SSZ-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)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)
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)
Comparator: SSZ-HCQ			
MTX-SSZ-HCQ	4.36 (1.27 to 15.97)[a]	2.50 (1.18 to 4.96)[a]	0.32 (0.05 to 0.59)[a]
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)[a]	2.06 (1.04 to 4.27)[a]	0.22 (0.01 to 0.39)[a]
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)[a]	2.09 (1.04 to 4.41)[a]	0.23 (0.01 to 0.42)[a]

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)[a]	1.96 (1.03 to 4.07)[a]	0.20 (0.01 to 0.36)[a]
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)[a]	2.26 (1.07 to 4.74)[a]	0.27 (0.02 to 0.53)[a]
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)[a]	2.51 (1.06 to 5.57)[a]	0.32 (0.02 to 0.59)[a]
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)
Comparator: MTX-SSZ-HCQ			
ETN_STD	0.20 (0.05 to 0.77)[b]	0.36 (0.18 to 0.83)[b]	−0.34 (−0.63 to −0.05)[b]
ETN_STD-MTX	0.45 (0.12 to 1.66)	0.64 (0.37 to 1.39)	−0.19 (−0.48 to 0.11)
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)[b]	0.32 (0.12 to 0.86)[b]	−0.36 (−0.66 to −0.04)[b]
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)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)
Comparator: ETN_STD			
ETN_STD-MTX	2.24 (1.37 to 3.82)[a]	1.81 (1.25 to 2.77)[a]	0.15 (0.06 to 0.26)[a]
ABA_STD (IV)-MTX	2.34 (1.01 to 5.26)[a]	1.87 (1.01 to 3.49)[a]	0.16 (0.003 to 0.31)[a]
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)[a]	1.83 (1.03 to 3.29)[a]	0.16 (0.01 to 0.27)[a]
TOF_STD-MTX	3.31 (1.37 to 7.42)[a]	2.30 (1.24 to 4.22)[a]	0.24 (0.07 to 0.39)[a]
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)[a]	1.93 (1.03 to 3.59)[a]	0.17 (0.01 to 0.32)[a]
GOL_STD (SC)-MTX	3.41 (1.35 to 8.29)[a]	2.34 (1.22 to 4.40)[a]	0.25 (0.06 to 0.42)[a]
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)[a]	2.19 (1.22 to 4.01)[a]	0.22 (0.06 to 0.37)[a]
RIT_STD	2.02 (0.43 to 9.91)	1.69 (0.50 to 4.35)	0.13 (−0.12 to 0.48)
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)[a]	2.21 (1.19 to 4.13)[a]	0.23 (0.05 to 0.39)[a]
HD203-MTX	4.04 (1.41 to 12.12)[a]	2.53 (1.28 to 4.61)[a]	0.29 (0.06 to 0.53)[a]
SB4-MTX	2.65 (1.02 to 7.18)[a]	2.01 (1.02 to 3.69)[a]	0.19 (0.003 to 0.42)[a]
ANBAI-MTX	4.98 (1.37 to 17.77)[a]	2.81 (1.25 to 5.56)[a]	0.34 (0.06 to 0.60)[a]
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)
Comparator: ETN_STD-MTX			
ABP501-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)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)
Comparator: ABA_STD (IV)-MTX			
ABA_STD (SC)-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)
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)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)
Comparator: ABA_STD (SC)-MTX			
ADA_STD-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)
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)
Comparator: ADA_STD-MTX			
TOF_STD-MTX	1.46 (0.82 to 2.58)	1.26 (0.88 to 1.74)	0.09 (−0.04 to 0.23)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)
Comparator: TOF_STD-MTX			
TOC_4 (IV)	0.26 (0.09 to 0.77)[b]	0.39 (0.16 to 0.85)[b]	−0.26 (−0.43 to −0.06)[b]
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)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
CT-P13–MTX	0.71 (0.27 to 1.98)	0.81 (0.42 to 1.45)	−0.08 (−0.29 to 0.17)
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)
Comparator: TOC_4 (IV)			
TOC_8 (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)[a]	2.15 (1.07 to 4.92)[a]	0.19 (0.02 to 0.33)[a]
GOL_STD (SC)-MTX	3.93 (1.27 to 12.39)[a]	2.62 (1.17 to 6.60)[a]	0.27 (0.05 to 0.46)[a]
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)[a]	2.46 (1.15 to 6.12)[a]	0.24 (0.05 to 0.40)[a]
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)[a]	2.48 (1.12 to 6.30)[a]	0.25 (0.04 to 0.42)[a]
HD203-MTX	4.66 (1.11 to 21.40)[a]	2.84 (1.08 to 7.72)[a]	0.31 (0.02 to 0.60)[a]
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)[a]	3.13 (1.22 to 8.27)[a]	0.36 (0.06 to 0.63)[a]
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)
Comparator: TOC_8 (IV)			
TOC_4 (IV)-MTX	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)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)
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)
Comparator: TOC_4 (IV)-MTX			
TOC_8 (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)
Comparator: TOC_8 (IV)-MTX			
GOL_STD (SC)-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)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)
Comparator: GOL_STD (SC)-MTX			
GOL_STD (IV)-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)
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)
Comparator: GOL_STD (IV)-MTX			
ABP501-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)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)
Comparator: INF_STD-MTX			
CERTO_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)
Comparator: CERTO_STD-MTX			
RIT_STD	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)
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)
Comparator: RIT_STD			
RIT_STD-MTX	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)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)
Comparator: RIT_STD-MTX			
BAR_4-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)
Comparator: BAR_4-MTX			
HD203-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)
Comparator: HD203-MTX			
SB4-MTX	0.66 (0.19 to 2.27)	0.79 (0.39 to 1.61)	−0.10 (−0.38 to 0.19)
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)
Comparator: SB4-MTX			
ANBAI-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)

Treatment	OR (95% CrI)	RR (95% CrI)	RD (95% CrI)
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)
Comparator: ANBAI-MTX			
CT-P13–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)
Comparator: CT-P13–MTX			
SB2-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)
Comparator: SB2-MTX			
SB5-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)
Comparator: SB5-MTX			
ZRC-3197–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)
Comparator: ZRC-3197–MTX			
ABP501-MTX	0.92 (0.24 to 3.50)	0.95 (0.40 to 2.40)	−0.02 (−0.32 to 0.26)

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; MTX = methotrexate; OR = odds ratio; RD = risk difference; RIT = rituximab; RR = relative risk; SAR_200 = 200 mg sarilumab; SB2 = biosimilar infliximab 3 mg/kg; SB4 = biosimilar etanercept 50 mg; SB5 = biosimilar adalimumab; SC = subcutaneous; SSZ = sulfasalazine; STD = standard dose; TOC_4 = tocilizumab 4 mg/kg; TOC_8 = 8 mg/kg tocilizumab; TOF = tofacitinib; ZRC-3197 = biosimilar of adalimumab.

[a]Results are statistically significant and favour the treatment.

[b]Results are statistically significant and favour the comparator.

Appendix 4: Cost-Effectiveness of Triple csDMARDs for RA

Note this appendix has not been copy-edited.

Main study findings and authors' conclusions from the included economic evaluations are summarized in the following table.

Table 6: Summary of Findings of Included Economic Evaluations

Main study findings	Authors' conclusion
Bansback et al. (2017)[30]	
Within-trial analysis (base case) • ETN-MTX (n = 163) vs. triple therapy (n = 171) at 24 weeks (following ≥ 12 weeks of MTX monotherapy) • Cost of drugs ($): 11,295 vs. 343 • Total costs ($): 12,002 ± 2,656 vs. 1,225 ± 2,558[a] • Increase in total costs ($): 10,786 (95% CI, 10,163 to 11,353)[b] • Change in EQ-5D (QALY): 0.358 ± 0.075 vs. 0.353 ± 0.075 • QALYs gained: 0.004 (95% CI, −0.004 to 0.012) • ICER ($/QALYs gained): 2.67 million (95% CI, 0.87 to infinity);[c] suggesting that ETN-MTX is clinically superior to triple therapy, but the clinical gains come at a high cost. ETN-MTX is not cost-effective at a WTP threshold of $100,000 per QALY gained. • ETN-MTX (n = 163) vs. triple therapy (n = 161) at 48 weeks (following ≥ 12 weeks of MTX monotherapy) • Cost of drugs ($): 19,634 vs. 3,680 • Total costs ($): 21,611 ± 6,756 vs. 6,328 ± 14,108[a] • Increase in total costs ($): 15,233 (95% CI, 12,204 to 17,275)[b] • [Increase in other health care and productivity costs ($): < 800] • Change in EQ-5D (QALY): 0.743 ± 0.147 vs. 0.726 ± 0.145 • QALYs gained: 0.016 (95% CI, −0.007 to 0.039) • ICER ($/QALYs gained): 0.978 million (95% CI, 0.39 to infinity);[c] suggesting that ETN-MTX provides clinical benefits at a high cost **Lifetime analysis (base case) over 50 years** • ETN-MTX (n = 163) vs. triple therapy (n = 161) over a lifetime of 50 years (following ≥ 12 weeks of MTX monotherapy) • Total costs ($): NR • Increase in total costs ($):77,290 • Change in HAQ scores (QALY): NR • QALYs gained: 0.148 (95% CI, 0.01 to 0.31) • ICER ($/QALYs gained): 521,520 (95% CI, 137,000 to dominated) **Sensitivity and scenario analysis** • Best possible ICER ($/QALYs gained): 350,000 with worst possible radiographic progression and change in HAQ in the triple therapy group • For the ICER to fall below 100,000 $/QALY gained, the price of biologics would have to fall by two-thirds.	"…in patients who have RA not adequately controlled by methotrexate alone, we found that the additional costs associated with using ETN–MTX before triple therapy do not provide good value. Even from a long-term perspective, under optimistic scenarios, first-line therapy with ETN–MTX or other biologics likely is not a cost-effective use of resources compared with using triple therapy first." (p 14)

Main study findings	Authors' conclusion
Jalal et al. (2016)[29]	
Lifetime analysis (base case)[d] • Immediate ETN-MTX vs. immediate triple therapy over a 5-year time horizon[e] • Total costs ($): 148,800 vs. 52,600 • Increase in total costs ($): 96,200 • Change in HAQ scores (QALY): 3.4831 vs. 3.4755 • QALYs gained: 0.0076 • ICER ($/QALYs gained): 12.5 million; suggesting that although immediate ETN-MTX is marginally more clinically effective than immediate triple therapy, that benefit comes at a cost so high that the therapy is not cost-effective relative to triple therapy • Step-up triple therapy and step-up ETN-MTX resulted in lower QALYs at higher costs and as such were not cost-effective relative to immediate triple therapy **Deterministic sensitivity analysis[f]** • ICER range ($/QALY gained): 5.6 million to 14 million for ETN-MTX over triple therapy, as annual ETN cost changes from $12,000 to $30,000 • Other modifiable parameters included utility function converting HAQ to QoL, annual discontinuation rates, cost of triple therapy, direct and indirect cost factors, discount rate, and annual wage. **Probabilistic sensitivity analysis** • Immediate triple therapy is likely to be the most CE strategy and the dominant strategy at WTP thresholds < $6 million/QALY gained • Between $6 million/QALY gained and $12.5 million/QALY gained, the probability of first-line triple therapy being the most CE strategy is < 50% but it remains the optimal strategy • Step-up triple therapy is less CE than immediate triple therapy at all WTP thresholds examined • Step-up ETN-MTX is dominated by other strategies at all WTP thresholds examined	"…[immediate triple therapy] is highly CE in early aggressive RA in the first 5 years of disease, and a substantial reduction in biologic agent cost is required for it to be cost-effective at these WTP thresholds." (p. 1755)

CE = cost-effective; CI = confidence interval; ETN = etanercept; HAQ = health assessment questionnaire; ICER = incremental cost-effectiveness ratio; MTX = methotrexate; NR = not reported; QALY = quality-adjusted life-year; WTP = willingness to pay; vs. = versus.

[a]Based on multiple imputation results.

[b]Adjusted for baseline HAQ score and sex.

[c]Adjusted for baseline EQ-5D score.

[d]ICERs at year 1 and 2 are not reported in this review.

[e]Results from 1-year and 2-year time horizons are not reported in this review.

[f]Results from the value of information analysis are not reported in this review.