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Joint Estimation of Remission and Response for Methotrexate-Based DMARD Options in Rheumatoid Arthritis: A Bivariate Network Meta-Analysis

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Objective. To jointly estimate American College of Rheumatology (ACR50) response (a more commonly reported outcome) and remission (a more clinically relevant outcome) for methotrexate (MTX)-based treatment options in rheumatoid arthritis (RA).

Methods. We conducted a bivariate network meta-analysis (NMA) to compare MTX monotherapy and MTX-based conventional and biologic disease-modifying antirheumatic drug (DMARD) combinations for RA. The correlation between the outcomes was derived from an incident RA cohort study, whereas the treatment effects were derived from randomized trials in the network of evidence. The analyses were conducted separately for MTX-naïve and MTX–inadequate response (IR) populations in a Bayesian framework with uninformative priors.

Results. From the cohort study, the correlation between ACR50 response and Disease Activity Score 28 remission at 6 months was moderate (Pearson correlation coefficient = 0.58). In the bivariate NMA for MTX-naïve populations, most combinations of MTX with either biologic or tofacitinib were statistically superior to MTX alone for both ACR50 response and remission. Triple therapy (MTX + sulfasalazine + hydroxychloroquine) was the only nonbiologic DMARD statistically superior to MTX for either ACR50 response (odds ratio [OR] 95% credible interval: 2.1 [1.0, 4.3]) or remission (OR: 2.5 [1.0, 5.8]). In the MTX-IR analysis, all treatments except MTX + sulfasalazine were statistically superior to MTX alone. Compared to analyzing the outcomes separately, the bivariate model often resulted in more precise estimates and allowed remission to be estimated for all treatments.

Conclusion. Borrowing the strength of correlation between outcomes allowed us to demonstrate a statistically significant benefit for remission across most MTX-based DMARD combinations, including triple therapy.

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INTRODUCTION

Outcome evaluation in rheumatoid arthritis (RA) has evolved over time. In the 1980s, the American College of Rheumatology (ACR) Response Criteria was developed (1). The ACR20 response, which represents at least a 20% improvement in swollen and tender joint counts and three of five other measures (physician global, patient global, patient pain, function, inflammatory markers [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)]), quickly became the standard primary outcome measure in most clinical trials. Over time, it was recognized that this measure was not ideal for clinical practice as it reflected only a small improvement in disease activity. As such, more stringent definitions of response (ACR50/70/90) were increasingly reported. However, even these more stringent definitions do not match the treatment objective in contemporary rheumatology practice. Our goal with RA is not a "response" but rather adequate disease control, with remission being the ultimate goal of treatment (2). Although remission is now being measured more commonly in trials, it remains a less commonly considered outcome than ACR responses.

We have previously published a network meta-analysis (NMA) of methotrexate (MTX)-based nonbiologic and biologic treatment combinations for RA (3,4). One of the major findings from the review was that triple therapy (MTX, sulfasalazine, hydroxychloroquine) was similar to MTX plus biologic therapy and superior to MTX alone for ACR50 response, both as initial therapy and after an IR to MTX. In our NMA, it was not possible to evaluate remission for several of the treatments, including triple therapy and various biologic agents, as these data were not reported in the available trials. However, with advanced statistical methods, it is now possible to infer an unreported outcome because disease activity outcomes in RA, such as ACR50, and remission are correlated, and we can use information on the treatment effects for one outcome to infer another.

The objective of this article was to jointly estimate ACR50 and remission responses across common MTX-based treatment

options in RA. Our primary aim was to provide evidence on remission across all treatment comparisons given the importance of remission as an outcome in clinical practice. Secondarily, we were also interested in making comparisons with the univariate NMA to highlight differences in the approaches.

METHODS

We conducted a multivariate NMA to jointly estimate Disease Activity Score 28 (DAS28) remission and ACR50 response across MTX-based conventional synthetic and biologic DMARDs. To conduct our multivariate (bivariate) NMA, we first estimated the correlation between the ACR50 response and remission using data from an incident RA cohort. This then allowed us to jointly model the outcomes, with data on the treatment effects provided from the included randomized controls trials (RCTs).

Deriving the correlation between treatment outcomes

To estimate the correlation between ACR50 response and DAS28 remission, we used data from the Canadian Early Arthritis Cohort (CATCH) (see Appendix A for list of investigators). CATCH is an ongoing observational cohort study of patients with early inflammatory arthritis followed prospectively since its inception in 2007 (5). Patients have been recruited from 22 centers across Canada. We included patients until March 2017 who were diagnosed with RA by either the 1987 or 2010 criteria (6,7), who were MTX-naïve or minimally exposed (less than 4 weeks), and who had started MTX either alone or in combination, within 3 months of entry into CATCH. Patients needed data for ACR response and DAS28 remission 6 months after starting MTX. Patients were allowed to receive other DMARDs or corticosteroids in addition to MTX.

From the CATCH data set, we calculated ACR50 response (1) and DAS28 remission outcomes at 6 months. Patients with missing data that prevented determination of their ACR50 response status were excluded. DAS28 remission was calculated using the four-variable ESR definition (DAS28-ESR < 2.6) or four-variable CRP definition (DAS28-CRP < 2.5) in patients with missing ESR values (8,9). We calculated the log-odds for each outcome (ACR50 response and DAS28 remission) from 10000 bootstrap samples, then the Pearson correlation coefficient between the log-odds of each outcome. We expected that the degree of correlation would vary based on the patient's baseline disease activity and so stratified these analyses according to baseline DAS28 score categories (low, moderate, and high). We used the correlation for patients with moderate or high disease

activity (DAS28-ESR ≥ 3.2, DAS28-CRP ≥ 2.9) (8,10) as the input for the multivariate NMA, to be consistent with randomized trials that formed the network of evidence (3,4).

Multivariate NMA

Inclusion criteria (Population, Intervention, Comparator, Outcomes: PICO). The multivariate NMA included RCTs from a previously published univariate network meta-analysis (3,4). The RCTs were identified from a comprehensive literature search in Medline and Embase and were supplemented with manual searches and screened by two reviewers, first by title and abstract, then by full text. The inclusion criteria for the NMA have been published in detail (3,4). Briefly, we included RCTs of at least 12 weeks duration at low or moderate risk of bias that evaluated MTX or an MTX-based DMARD combination in patients with RA. The comparator could be a placebo or any other DMARD if the trial provided direct or indirect evidence of the relative efficacy of the treatments of interest. No exclusion criteria were applied for disease activity, although all trials included patients with moderate or high disease activity. Similarly, the duration of follow-up in the trials varied, but the median follow-up duration was 6 months (3,4). The outcomes of interest were ACR50 response (1) (the primary outcome from our NMA) and DAS28 remission (11) (a secondary outcome from our NMA).

Analysis. As with the published univariate NMA (3,4), all analyses were conducted separately for MTX-naïve and MTX–inadequate response (IR) populations. The approach for the bivariate NMA was similar to a univariate NMA except that the outcomes

Table 1. Baseline demographics of patients in observational cohort (CATCH)

Characteristic	Value
Age, years; mean (SD)	55 (15)
Female, %	72
Symptom duration, days; mean (SD)	159 (89)
DAS28; mean (SD)	5.0 (1.0)
Seropositive (RF or ACPA), %	61
HAQ-DI; mean (SD)	1.0 (0.7)
Starting dose of methotrexate, mg/wk; mean (SD)	19 (4)
Methotrexate route, subcutaneous, %	43
Concurrent use of other DMARDs, %	57
Concurrent use of biologic therapy, %	1
Concurrent use of systemic glucocorticoids	
Oral, %	35
Intramuscular or intra-articular, %	34

Abbreviations: ACPA, anticitrullinated peptide antibody; DAS28, disease activity score-28; DMARD, disease-modifying antirheumatic drug; HAQ-DI, health assessment questionnaire – disability index; RF, rheumatoid factor; SD, standard deviation.

were modeled jointly. The model code has been published and is presented in Appendix B (12). Within each study, the outcomes were assumed to follow a bivariate normal distribution around the "true" joint distribution. The bivariate distribution was defined by the means and covariance matrix of the log-odds of the two outcomes, ACR50 response and DAS28 remission. The covariance matrix for each trial consisted of the calculated standard errors of the log-odds of the outcomes from the trial (diagonal elements), and the correlation between the log-odds of the outcomes, which was shared across studies and calculated using the CATCH data as described above (off-diagonal elements).

From the modeled effects of each study, we fit a random effects bivariate NMA. The approach mirrored the univariate model, whereby the pooled mean was broken down into basic parameters relative to a reference treatment: a trial of treatment C versus B is modeled as the effect of C versus A (d_{AC}) minus the effect of B versus A (d_{AB}). The basic parameters were compared to estimate all pairwise treatment effects. Instead of modeling separate basic parameters for each treatment and outcome, in the bivariate model, the treatment effects for the two outcomes were assumed to be a sum of a treatment-specific effect and an outcome-specific effect. This approach borrows the strength across outcomes, reducing the number of parameters to be estimated (12).

Model fitting. We fitted the model within a hierarchical Bayesian framework, placing minimally informative prior probability distributions (priors) on all model parameters (Appendix B). We assumed the within-study correlation between the outcomes from our cohort study was one estimate taken from a sample of possible true values, drawn from a truncated normal distribution (truncated between –1 and 1 to reflect the lower and upper limits of possible correlation values). The mean of this distribution was the estimated correlation from the CATCH cohort. Because the standard deviation was unknown, it was sampled from a gamma distribution with a minimally informative prior ("hyper prior," *Gamma*(1,3)). All analyses were conducted in R statistical software running Just Another Gibbs Sampler (JAGS) (additional details in Appendix C).

Presentation of results. We summarized the results as the median and 95% credible interval (CrI) of the odds ratio (OR) for each pairwise comparison. We also converted the ORs into absolute responses by multiplying by the ORs relative to MTX by the baseline odds for MTX, which was calculated as the median from a Bayesian random effects model of the oral MTX arms.

In our prior univariate NMA, we had compared the direct and indirect evidence through node-splitting and found no evidence of inconsistency (statistical evidence that the direct and indirect evidence differ) (13). In a similar conceptual approach, we compared the posterior distributions of the bivariate and

Table 2. Correlation between ACR50 and DAS28 remission at 6 months

Baseline Disease Activity[a]	n	Outcome at 6 Months		Pearson Correlation
		ACR50	Remission	
High (DAS28-ESR > 5.1)	463	50%	30%	0.51
Moderate (3.2 ≤ DAS28-ESR ≤ 5.1)	297	37%	46%	0.58
Low or remission (DAS28-ESR < 3.2)	67	18%	66%	0.26

Abbreviation: CRP, C-reactive protein; DAS28, Disease Activity Score 28; ESR, erythrocyte sedimentation rate.
[a]Disease activity cut-points for DAS28 CRP: high > 4.6; low/remission < 2.9

univariate results, calculating the probability that they were the same. We considered a probability of less than 5% to be a statistically significant difference, which would indicate that statistical inconsistency was present between the univariate and bivariate models.

Sensitivity analyses. We subjected the priors for both the within-study and between-study correlation to sensitivity analyses. The specification of these priors is provided in Appendix D. Additionally, in the bivariate NMAs, for the main analysis, we assumed that the correlation between the outcomes was the same for the MTX-naïve and MTX-IR analyses. We therefore conducted sensitivity analyses for both (MTX-naïve and MTX-IR), in which we varied the within-study correlation from weak to strong (Pearson correlation 0.4 and 0.8, respectively) so as to cover the range of plausible values.

RESULTS

Correlation of ACR50 response and remission

From the overall CATCH cohort, 1072 patients were eligible for this analysis and 827 had complete outcome data for both ACR50 and DAS28 remission (see Appendix E for detailed study
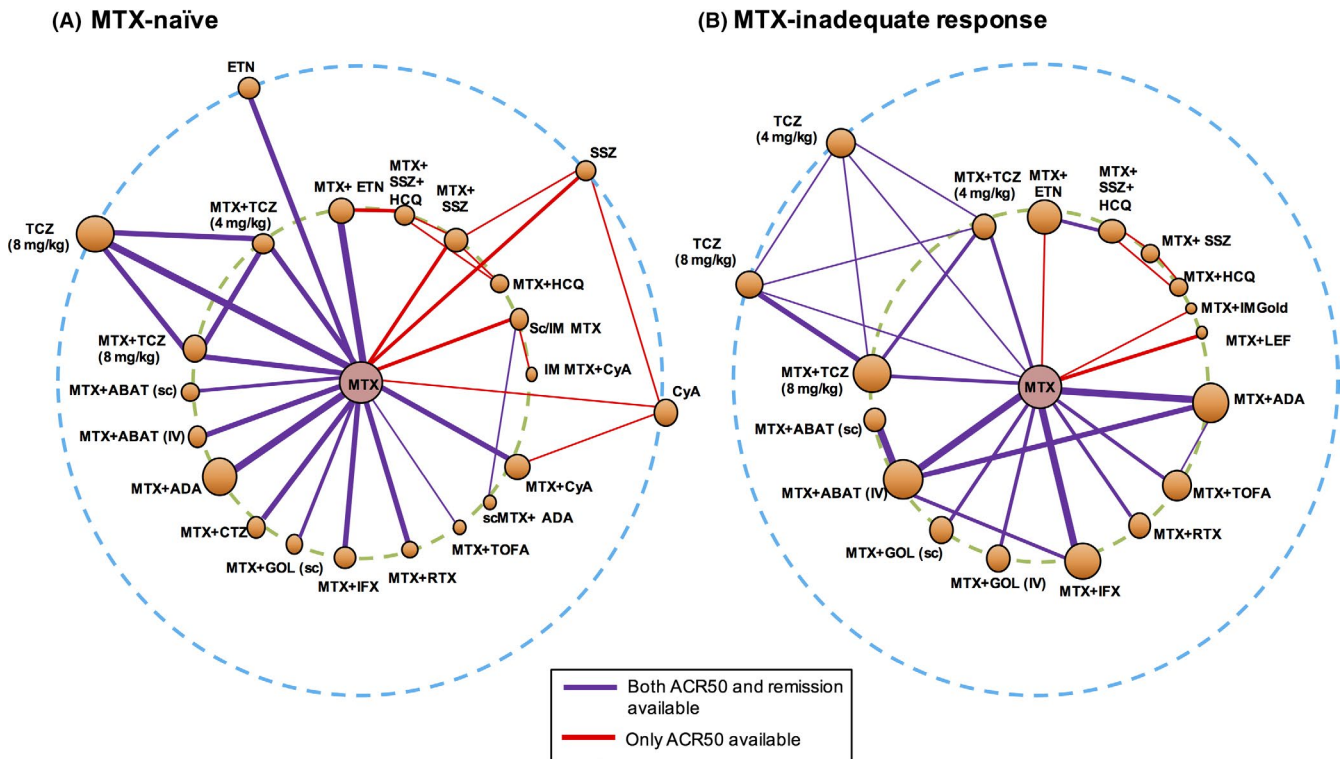
Figure 1. Networks of included studies for methotrexate (MTX) naïve (**A**) and MTX inadequate response populations (**B**). Each line represents direct comparison between two treatments, with the color of the line indicating if there was at least one trial available with data on the outcomes of interest. Treatments on the innermost circle (green dashed line) are the treatments of interest, whereas treatments on the outermost circle (blue dashed line) are other treatments that formed links between treatments of interest. Abbreviations: ABAT, abatacept; ADA, adalimumab; CTZ, certolizumab; CyA, ciclosporin; ETN, etanercept; GOL, golimumab; HCQ, hydroxychloroquine; IFX, infliximab; IM, intramuscular; IV, intravenous; LEF, leflunomide; RTX, rituximab; sc, subcutaneous; SSZ, sulfasalazine; TOFA, tofacitinib; TCZ, tocilizumab.

flowchart). The within-patient correlation between ACR50 response and remission was estimated from the 827 eligible patients in the CATCH data set. The baseline characteristics of these patients (Table 1) were similar to those of the overall CATCH cohort (14). The mean age was 55, 72% were female, 61% were seropositive, and the baseline disease activity and functional disability was high (mean DAS28 = 5.0, Health Assessment Questionnaire – Disability Index [HAQ-DI] = 1.0). The mean dose of MTX was 19 mg/wk, and it was often administered subcutaneously (43%) and in combination with other conventional synthetic DMARDs (57%) and glucocorticoids (35% oral, 35% intra-articular or intramuscular).

The correlation between ACR50 response and remission at 6 months varied according to the baseline DAS28 scores (Table 2). As expected, as the baseline disease activity increased, patients were less likely to achieve remission but more likely to achieve an ACR50 response. The correlation between outcomes was similar for patients with moderate and high disease activity (0.58 and 0.51, respectively), which was higher than for patients with low disease activity (0.26). The pooled correlation for moderate or high disease activity was 0.51 (moderately strong), which we used for the bivariate NMA.

Bivariate NMA

Network structure. The bivariate NMAs included 34 trials (11 793 patients) and 46 trials (12 599 patients) for the MTX-naïve and MTX-IR analyses, respectively, in the networks of connected trials (Figure 1 and Appendix F). For the MTX-naïve analysis, 18 trials reported both outcomes, 12 reported only ACR50 response, and 4 reported only DAS28 remission. For the MTX-IR analysis, 22 trials reported both outcomes, 23 reported only ACR50 response, and 1 reported only DAS28 remission. In the MTX-IR analysis, there was a cluster of treatments (MTX + etanercept, triple therapy, MTX + sulfasalazine, MTX + hydroxychloroquine) that were only connected to the rest of the network through the outcome ACR50 response (Figure 1). These treatments could only be linked into the network with the bivariate model.

Treatment effects relative to oral methotrexate. The treatment effects relative to MTX in the bivariate model are presented alongside the results from the univariate analyses in Figures 2 (MTX-naïve) and 3 (MTX–IR), with detailed results in Appendix G. For MTX-naïve patients, most biologic DMARDs in

Figure 2. Methotrexate (MTX)-naïve population. Comparison of univariate and bivariate network meta-analysis results. See Appendix F for all pairwise comparisons. Abbreviations: ABAT, abatacept; ADA, adalimumab; CTZ, certolizumab; CQ, chloroquine; ETN, etanercept; CyA, ciclosporin; GOL, golimumab; HCQ, hydroxychloroquine; IFX, infliximab; IM, intramuscular; IV, intravenous; RTX, rituximab; sc, subcutaneous; SSZ, sulfasalazine; TOFA, tofacitinib; TCZ, tocilizumab.

combination with MTX were statistically superior to MTX alone for both ACR50 response and remission, with some exceptions. MTX + golimumab (subcutaneous) was not statistically superior to MTX for either ACR50 response or remission, and MTX + abatacept (subcutaneous) and MTX + certolizumab were statistically superior to MTX for remission only. Triple therapy was the only nonbiologic DMARD statistically superior to MTX for either outcome, and it was for both ACR50 response (OR [95% CrI]: 2.13 [1.00, 4.28]) and remission (OR [95% CrI]: 2.49 [1.03, 5.84]). The estimated absolute response with triple therapy was 60% (95% CrI: 41%, 75%) for ACR50 response and 44% (95% CrI: 24%, 65%) for DAS28 remission, similar to the values for MTX + biologic therapy (Appendix H). In the MTX-IR analysis, all treatments except MTX + sulfasalazine were statistically superior to MTX alone in both univariate and bivariate models (Figure 3). The estimated absolute response for triple therapy was 61% (95% CrI: 38%, 80%) for ACR50 response and 50% (95% CrI: 26%, 74%) for DAS28 remission, again, similar to the values for MTX + biologic therapy (Appendix H).

When comparing the results to the univariate model, treatment effects in the bivariate approach were similar to, but often more precise than, the univariate estimate (Figures 2 and 3). We did not detect any statistical inconsistency between the analyses (Appendix I). For the MTX-naïve analysis, some treatment effects that were not statistically significant for the univariate analysis reached statistical significance in the bivariate model: MTX + tocilizumab (4 mg/kg) for ACR50 response, and both MTX + infliximab and MTX + tofacitinib for remission (Figure 2). Additionally, there were six treatments in each the MTX-naïve and MTX-IR analyses where data for remission were unavailable. In the bivariate approach, remission could be estimated for all treatments.

Pairwise comparisons. In pairwise comparisons for the MTX-naïve analysis, MTX + etanercept was statistically superior to MTX + sulfasalazine, MTX + hydroxychloroquine, and subcutaneous MTX for ACR50 response but not remission (Appendix G). No other pairwise comparisons were statistically significant. In the MTX-IR analysis, MTX + etanercept and triple therapy
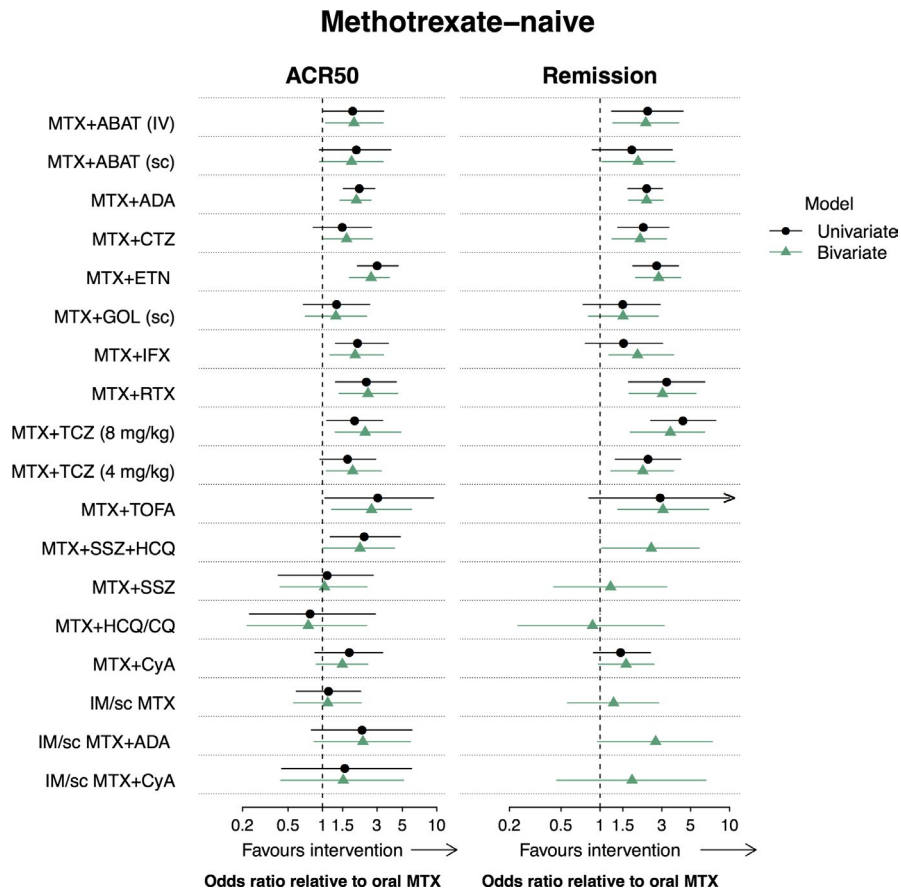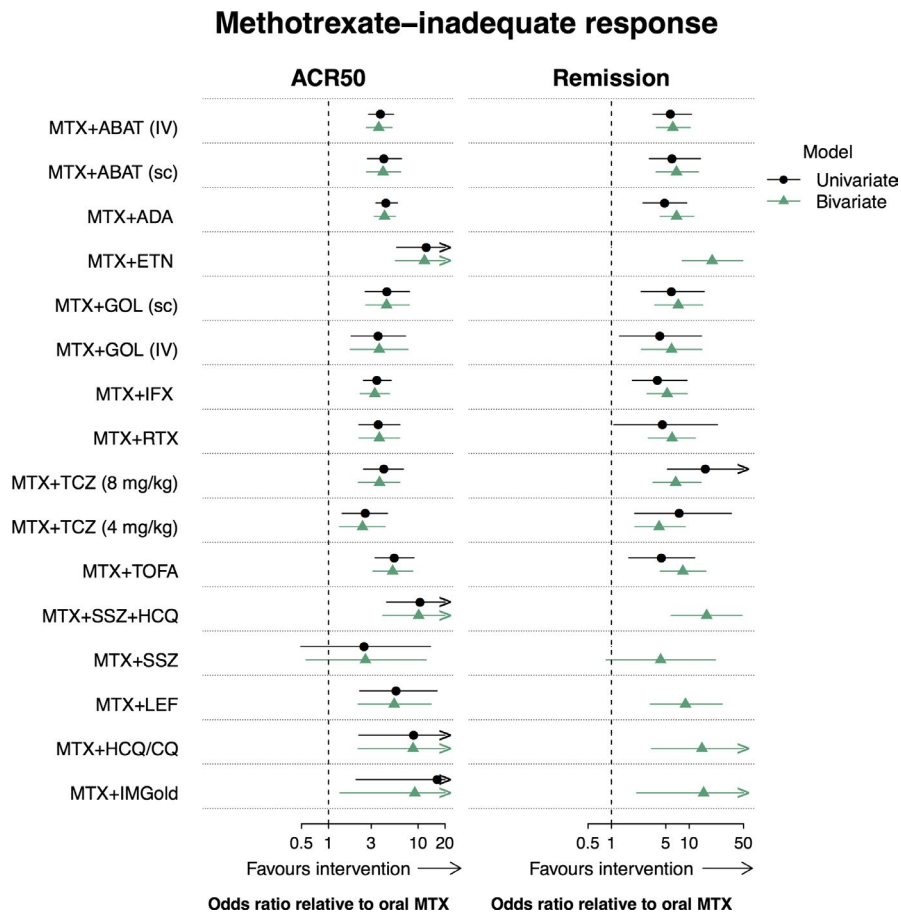

Figure 3. Methotrexate (MTX)-inadequate response population. Comparison of univariate and bivariate network meta-analysis results. See Appendix F for all pairwise comparisons. Abbreviations: ABAT, abatacept; ADA, adalimumab; CQ, chloroquine; ETN, etanercept; GOL, golimumab; HCQ, hydroxychloroquine; IFX, infliximab; IM, intramuscular; IV, intravenous; LEF, leflunomide; RTX, rituximab; sc, subcutaneous; SSZ, sulfasalazine; TOFA, tofacitinib; TCZ, tocilizumab.

were superior to several treatments for ACR50 response and remission (Appendix G). These comparisons were based almost solely on indirect evidence; there were no head-to-head trials comparing either MTX + etanercept or triple therapy with most other treatments (Figure 3).

Sensitivity analyses. In sensitivity analyses, both the within-study correlation and between-study correlation were robust to changing the prior (Appendix D). Similarly, the results of the pairwise comparisons were similar when we varied the within-study correlation from 0.4 to 0.6 (not shown).

DISCUSSION

In this study, we conducted a bivariate NMA to jointly estimate ACR50 responses and remission across common MTX-based treatments for RA. The treatment effects were derived from RCTs, thereby preserving the randomized nature of the comparisons. However, by deriving the correlation between ACR50 response and remission from an observational cohort, we were able to jointly model the outcomes. This allowed us to estimate treatment effects for remission—the key RA clinical outcome—across all treatment comparisons. Notably, our results demonstrate a statistically significant benefit for remission for several MTX-based DMARD combinations (including triple therapy and biologic combinations) compared with MTX monotherapy. Additionally, many of the treatment effects for both outcomes were more precise, with narrower credible intervals. By providing more precise treatment effects on key RA outcomes across all treatments, these results can help inform decision making for RA drugs.

Choosing which outcomes to review is a critical decision when conducting a systematic review. However, authors of systematic reviews and guidelines are at the mercy of the available trials, which may not provide the outcomes that are most informative to clinicians. A multivariate approach may reduce bias associated with outcome selection, whereas in RA, multiple outcomes that measure the same underlying construct (disease activity) are available (15,16). In the context of an NMA, a multivariate approach can also prevent the exclusion of a group of trials that can only be linked to the main network through a single outcome. For example, in our MTX-IR, the multivariate approach allowed a cluster of trials of conventional synthetic DMARD combination therapy, including triple therapy, to be linked to the other treatments.

As with any meta-analysis or NMA, it is key to understand the assumptions that are made when pooling the results. If these are invalid, then the pooled estimates would be biased. In a NMA, the key additional assumption made over a traditional meta-analysis is that treatment effects are exchangeable across interventions (17). In the bivariate (or multivariate) approach, we further extend this by assuming that the between-study correla-

tion structure is also shared across interventions (12). Namely, in our analysis, the relationship between the remission and ACR50 response is the same, regardless of the interventions compared. In sensitivity analyses, our results were robust to different values of the within-study correlation, adding strength to our findings. However, authors need to carefully consider whether this assumption holds. For example, with RA treatments, biologic therapy has an effect on inhibition of radiographic joint damage somewhat independent from its effect on disease activity (18). Thus, a bivariate approach that assumes the correlation in these outcomes is exchangeable across nonbiologic and biologic therapy may not be appropriate.

Another potential limitation is that we did not update the literature review. However, recent univariate NMAs in both MTX-naïve (19) and MTX-IR (20) populations have compared triple therapy to MTX + biologic DMARDs. Notably, neither review identified any new trials of triple therapy. The overall findings were similar to our univariate analyses. In both MTX-naïve and MTX-IR populations, triple therapy was not statistically different than MTX + biologic therapy for ACR50 response at 6 months, and data on remission were lacking for many treatments (19,20). Thus, although an updated search may impact the estimates for some of the treatments, it should not impact the core findings of our review.

With the bivariate (or multivariate) approach to NMAs we used, it should be possible to add in additional analyses that are possible with univariate NMAs. For example, meta-regression could theoretically be done to evaluate whether trial-level characteristics are associated with different outcome-specific or treatment-specific effects, although we are not aware of this having been previously implemented. As with any meta-analysis, this will add complexity to the model, and the analyses should be justified and planned beforehand to avoid data dredging that may result in spurious results. Building and evaluating these more complex models is an avenue for future research.

In our approach, we used data from both RCTs and an observational cohort. The correlation of the outcomes could have been derived from RCT data if published or from other published observational data sets, which was an approach used previously (12). The advantage of having access to individual data from a cohort was that it allowed us to calculate the correlation specifically for patients with moderate to high disease activity at baseline to match the clinical trials. Having access to the individual patient data, however, is not always feasible. As such, these analyses would be better facilitated by having published correlation values either from randomized or observational data sets. Although we used a single data set to estimate the correlation, we assumed this was just one sample from a distribution of possible values. Furthermore, the results were robust to sensitivity analyses where we varied the correlation across a plausible range, adding confidence to our findings.

The role of triple therapy in the treatment of RA is a subject of debate. Guidelines by both ACR and the European League Against Rheumatism (EULAR) do not recommend triple therapy over other options either as initial therapy or after failure of MTX, but both provide it as an option (2,21). Our data provide further evidence supporting the benefit of triple therapy in the short-term, but other factors need to be considered. In the NMA used in this article, triple therapy had a higher rate of gastrointestinal side effects but not withdrawals that were due to adverse events (3,4). Long-term data on the tolerability of triple therapy over time are conflicting. In a long-term extension of an RCT, triple therapy was associated with higher retention over time compared with MTX + etanercept (22), whereas in an administrative database of US veterans, triple therapy had lower retention over time as compared with MTX + anti–tumor necrosis factor therapy (23). In a cost-effectiveness analysis, triple therapy was found to be highly cost effective compared with MTX + etanercept (24). Ultimately, the decision of whether and when to use triple therapy versus alternate treatments should be a shared decision between the patient and physician (2).

In conclusion, we used a novel approach that allowed us to estimate remission and ACR50 response across MTX-based DMARD treatments, providing further evidence of remission for several MTX-based DMARD combinations, including triple therapy.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the manuscript or revising it critically for intellectual content, and all authors approved the final version to be published.
Study conception and design. Hazlewood, Pokharel, Deardon
Acquisition of data. Barnabe, Bykerk, Bartlett, Bessette, Boire, Hitchon, Keystone, Pope, Schieir, Tin, Thorne, Hazlewood
Analysis and interpretation of data. Hazlewood, Pokharel, Deardon

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APPENDIX A: THE CANADIAN EARLY ARTHRITIS COHORT (CATCH) INVESTIGATORS

Members of the Canadian Early Arthritis Cohort (CATCH) investigator are as follows: Murray Baron, Louis Bessette, Gilles Boire, Vivian Bykerk, Ines Colmegna, Sabrina Fallavollita, Derek Haaland, Paul Haraoui, Glen Hazlewood, Carol Hitchon, Shahin Jamal, Raman Joshi, Ed Keystone, Bindu Nair, Peter Panopoulos, Christopher Penney, Janet Pope, Laurence Rubin, Carter Thorne, Edith Villeneuve, Michel Zummer.