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Comparative efficacy of biological agents in methotrexate-refractory rheumatoid arthritis patients: a Bayesian mixed treatment comparison

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Background/Aims: Biological agents (biologics) targeting proinflammatory signaling have emerged as an important treatment option in rheumatoid arthritis (RA). Despite the clinical effectiveness of biologics for patients with RA who do not respond to 'traditional' disease-modifying anti-rheumatic drugs (DMARDs), there are concerns regarding their cost and long-term safety. In this study, we aimed to compare the efficacy of various biologics and traditional DMARDs in RA patients refractory to methotrexate (MTX).

Methods: Four DMARDs (hydroxychloroquine, sulfasalazine, MTX, leflunomide) and five anti-tumor necrosis factor drugs (adalimumab, etanercept, golimumab, infliximab, and certolizumab) were selected. A systematic search of published studies was performed from inception through July 2013. Randomized trials of adults with MTX-refractory RA comparing two or more of the selected medications were included. Among 7,938 titles identified, in total, 16 head-to-head trials were selected. Two reviewers independently abstracted the study data and assessed methodological quality using the Cochrane Risk of Bias. Comparative efficacy was analyzed using a Bayesian mixed treatment comparison (MTC).

Results: In total, 9, 4, and 11 studies were included for the outcome measures of the Health Assessment Questionnaire (HAQ), Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) < 2.6 (remission), and American College of Rheumatology (ACR) 70 response, respectively. The treatments with the highest efficacy for each outcome measure were certolizumab combined with MTX, golimumab combined with MTX, and certolizumab combined with MTX, respectively.

Conclusions: Based on MTC analysis, using data from published randomized controlled trials, certolizumab and golimumab combined with MTX showed the highest efficacy in the three outcome measures (HAQ, DAS28-ESR < 2.6, and ACR 70 response) in MTX-refractory RA patients.

Keywords: Arthritis, rheumatoid; Antirheumatic agents; Biological products; Mixed treatment comparison

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INTRODUCTION

Traditional disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX), sulfasalazine, and leflunomide, have been the cornerstone of the treatment of rheumatoid arthritis (RA). Recently biological agents (biologics), especially tumor necrosis factor antagonists (anti-TNFs, TNF-i), have demonstrated considerable efficacy in treating patients with RA who do not respond or show intolerance to traditional DMARDs [1-3]. Many randomized controlled trials (RCTs) comparing their efficacy with placebo treatment in DMARD-refractory patients have been published, as well as systematic reviews (SRs) and overviews of SRs of these RCTs [4]. Because of their high costs and long-term adverse effects, however, biologics have been under strict regulatory control in many countries, including Korea. One study showed that the majority of RA patients satisfying the American College of Rheumatology (ACR), British Society for Rheumatology, and Japan College of Rheumatology guidelines for use of the TNF-α blockers did not meet the Korean National Health Insurance reimbursement criteria [5]. Because the cost of biologics is much higher than traditional DMARDs, discretion in their use is warranted even in patients refractory to MTX.

Although some DMARD combinations, such as leflunomide or sulfasalazine with MTX, have been shown to be effective in RA patients not responding to MTX monotherapy [5], few studies have compared biologics and combination DMARDs head-to-head in patients refractory to MTX. In the absence of head-to-head trials with relevant comparators, it is possible to compare multiple treatment groups simultaneously by using all the outcomes from direct and indirect comparisons [6]. Mixed treatment comparison (MTC) is one methodology for indirect comparisons, requiring at least one 'closed loop' between non-head-to-head trials and trials should be connected by a common control group (usually, placebo). The similarity and comparability of study designs and other elements should be considered for appropriate use of MTC. However, studies that have applied the MTC methodology to compare DMARDs or biologics in RA patients are few because of the diversity of medications and target outcomes. Thus, the purpose of this study was to find the most effective treatment, including biologics and DMARDs, for MTX-refractory RA patients using the MTC methodology.

METHODS

Selection of medications

An expert group consisting of rheumatologists, pharmacists, and evidence-based healthcare methodologists reviewed a list of medications including DMARDs and biologics. They considered feasibility, prescription frequency, and value for patients. Finally, four DMARDs (hydroxychloroquine, sulfasalazine, MTX, leflunomide) and five anti-TNF drugs (adalimumab, etanercept, golimumab, infliximab, and certolizumab) were selected according to the expert group consensus.

Search strategy

The literature databases searched included four domestic databases, KoreaMed, Korean Medicine Database (KMBASE), Korean Studies Information Service System (KISS), and Korean Institute of Science and Technology Information (KISTI), and the core databases MEDLINE, EMBASE, and the Cochrane Library.

Studies that met the following criteria were included: (1) subjects were RA patients not responsive to MTX, (2) treatment consisted of one of the nine medications selected for evaluation, (3) RCT study design, and (4) reported patient outcomes included ACR responders 20/50/70, the Health Assessment Questionnaire (HAQ), or the Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR).

Studies of animal trials or preclinical studies and non-original articles, such as review articles, editorials, letter, and comments, were excluded. Articles not published in Korean or English and studies with duplicate subjects (studies using the same outcome indicators published in duplicate) were also excluded.

Two reviewers screened all titles and abstracts identified by the searches independently. Full manuscripts of studies screened as potentially relevant by either reviewer were obtained and assessed by the two reviewers independently. Discrepancies were resolved by consensus.

Data extraction and quality assessment

The two reviewers extracted data from each study in-

dependently. The data were reviewed for consistency between the two extractors, and disagreements were resolved by consensus. For each study, data extraction details included design, selection criteria, population characteristics, treatments, outcome measures, length of follow-up, and results.

Major outcomes

(1) The HAQ survey has eight sections on how the treatment improves daily activities, such as dressing, arising, eating, walking, hygiene, reaching, gripping, and activities.
(2) The ACR responder rate is the rate of patients with a 20%/50%/70% improvement in tender and swollen joint counts and improvement in three of the five remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute phase reactant.
(3) DAS28 is a combined index using tender/swollen joint count, ESR, and a general health assessment on a visual analog scale.

Two reviewers independently assessed the methodological quality of the included studies using the Cochrane Risk of Bias (RoB). The results of the RoB evaluation were converted to graphical displays using the RevMan 5.2 program (The Nordic Cochrane Center, Copenhagen, Denmark).

Statistical analysis

Bayesian MTC was carried out by designating the control group as placebo combined with MTX due to lack of clinical trials with direct comparisons. A random effects model was applied because of the heterogeneity between trials. Continuous variables, such as mean change from baseline, median range, and standard deviation, were converted according to the formula in the Cochrane Handbook [7].

Comparative efficacy was analyzed using a MTC. In a Bayesian meta-analysis, inference on a parameter of interest is made based on the posterior distribution obtained from a prior distribution combined with the likelihood function. The 'posterior probability distribution' allows calculating the probability of the case in which the competing intervention is best. In addition, a pooled estimate with a credible interval (CrI), referring to the probability of including a parameter, is obtained using a posterior probability distribution and the hypothesis of interest is tested [6]. If the CrI does not include '1' and if the probability is close to 1, then the treatment could be interpreted as effective. The 'best' is the relative estimate effect for all treatments in a comparison ranking. The highest effective treatment was decided based on considering the 'best' and the 'posterior probability distribution.' Consistency between evidence sources was assessed by comparing models with and without inconsistency factors. The software used for statistical analyses was WinBUGS 14 (MRC Biostatistics Unit, Cambridge, UK).

RESULTS

Selected studies

Of the 7,938 citations identified through our literature search, 7,789 were excluded through exclusion of duplicates and screening of titles and abstracts. In addition, an overview of SRs was performed up to May 2013 according to a previously published methodology [8]. Among 52 SRs, we selected two high-quality SRs, one each for biologics [9] and DMARDs [10]. Three more SRs including trials with DMARDs were added [5,11,12]. All randomized trials obtained from SRs were pooled and updated from January 2009 to July 2013 (Table 1, Fig. 1) [13-28].

The mean age of patients included in the trials was 52.9 years and the mean rheumatoid factor-positive rate was 76.6%. RA treatment duration was from 4 to 13.1 years. The follow-up period was from 1.6 months to 1 year. Characteristics of each study are shown in Table 1.

Risk of bias

The quality of the 16 selected randomized trials was assessed using the Cochrane RoB tool (Fig. 2). Generally, studies without the phrase 'random assignment' and without a specific method for random number generation and assignment number-concealing measures were considered to be 'uncertain.' There were many studies in which the risk of selection bias was perceived as 'uncertain.' However, most studies had a low risk in terms of attrition or reporting bias.

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Table 1. Description of included studiess

Study	RCT name	Treatments comparison	Biologic, mg	No.	Mean age, yr	Female sex, %	RF (+), %	Anti-CCP (+), %	Follow-up, mon	Outcome measure
Genovese et al. (2012) [13]	GO-FORWARD	Placebo + MTX	-	133	52	82	81.2	80.5	3.5	HAQ, QOL
		Golimumab + placebo	100	133	51	78.9	83.5	79.7	3.5	
		Golimumab + MTX	50	89	52	80.9	86.5	80.9	3.5	
		Golimumab + MTX	100	89	50	80.9	84.3	76.4	3.5	
Huang et al. (2013) [14]		Infliximab	-	24	49	92	-	-	2.5	DAS28-ESR
		Placebo	-	6	56	100	-	-	2.5	
Keystone et al. (2009) [20]	GO-FORWARD	Placebo + MTX	-	133	52	82	81.2	80.5	3.5	HAQ, DAS28-ESR < 2.6 EULAR good responder ACR 20/50/70
		Golimumab + placebo	100	133	51	78.9	83.5	79.7	3.5	
		Golimumab + MTX	50	89	52	80.9	86.5	80.9	3.5	
		Golimumab + MTX	100	89	50	80.9	84.3	76.4	3.5	
Jobanputra et al. (2012) [15]		Adalimumab	-	63	55	75	-	-	3	EQ-5D, DAS28
		Etanercept	-	62	53.2	70	-	-	3	
Kay et al. (2008) [18]		Placebo + MTX	-	35	52	74.3	-	-	4	ACR 20/50/70 DAS28-ESR < 2.6
		Golimumab + MTX	50	35	57	85.7	-	-	4	
		Golimumab + MTX	50	34	48	67.6	-	-	4	
		Golimumab + MTX	100	34	57.2	76.5	-	-	4	
		Golimumab + MTX	100	34	53.5	79.4	-	-	4	
Schiff et al. (2008) [22]	ATTEST	Infliximab + MTX	-	165	49.1	82.4	84.8	-	6	DAS28- ESR HAQ
		MTX	-	110	49.4	87.3	77.3	-	6	
Strand et al. (2009) [23]	RAPID1	MTX	-	199	-	-	-	-	3	DAS28-ESR < 2.6 EULAR good responder (%) ACR 20/50/70
		Certolizumab + MTX	200	393	-	-	-	-	3	
		Certolizumab + MTX	400	390	-	-	-	-	3	
Strand et al. (2011) [24]	RAPID2	MTX	-	127	-	-	-	-	6	QOL, HAQ
		Certolizumab + MTX	-	246	-	-	-	-	6	
		Certolizumab + MTX	-	246	-	-	-	-	6	
Weinblatt et al. (2013) [26]	GO-FURTHER	MTX	-	197	51.4	79.7	-	-	3.5	ACR 20/50/70 HAQ DAS28-ESR < 2.6
		Golimumab + MTX	-	395	51.9	82.5	-	-	3.5	
van Vollenhoven et al. (2009) [25]	Swefot	MTX + hydroxychloroquine + sulfasalazine	-	130	52.9	78	65	-	12	EULAR good responder (%) ACR 20/50/70
		Infliximab + MTX	-	128	51.1	76	69	-	12	

Table 1. Continued

Study	RCT name	Treatments comparison	Biologic, mg	No.	Mean age, yr	Female sex, %	RF (+), %	Anti-CCP (+), %	Follow-up, mon	Outcome measure
Weinblatt et al. (2003) [27]	ARMADA	Placebo + MTX	-	62	56	82.3	-	-	6	ACR 20/50/70
		Adalimumab + MTX	20	69	53.5	75.4	-	-	6	HAQ
		Adalimumab + MTX	40	67	57.2	74.6	-	-	6	
		Adalimumab + MTX	80	73	55.5	75.3	-	-	6	
Kameda et al. (2010) [17]		Etanercept + MTX	-	75	56.5	80	86.7	-	6	ACR 20/50/70
		Etanercept	-	71	58.1	62	65	-	6	HAQ EULAR good responder
Wong et al. (2009) [28]		Infliximab	30	17	48	82.4	44	-	4	DAS28
		Placebo	-	9	50	89	87.5	-	4	
Keystone et al. (2008) [19]	RAPID1	Placebo + MTX	-	199	52.2	83.9	82.8	-	6	ACR 20/50/70
		Certolizumab + MTX	200	393	51.4	82.4	79.3	-	6	% reduction join
		Certolizumab + MTX	400	390	52.4	83.6	83.6	-	6	HAQ
Joo et al. (2013) [16]		Leflunomide + MTX	-	9	54.6	100	-	-	-	ACR 20
		Etanercept + MTX	-	20	50	90	-	-	-	
Keystone et al. (2004) [21]		Adalimumab + MTX	40	207	56.1	76.3	81.6	-	13	Radiologic outcome
		Adalimumab + MTX	20	212	57.3	75.5	81.2	-	13	ACR 20/50/70
		Placebo + MTX	-	200	56.1	73	89.5	-	13	

RCT, randomized controlled trial; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; GO, golimumab; MTX, methotrexate; HAQ, Health Assessment Questionnaire; QOL, quality of life; DAS28-ESR, Disease Activity Score 28-erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; ACR, American College of Rheumatology response rates; ATTEST, Abatacept or infliximab vs placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis; RAPID, Rheumatoid Arthritis the Public InformeD; ARMADA, Anti-Tumor Necrosis Factor Research Study Program of the Monoclonal Antibody Adalimumab (D2E7) in Rheumatoid Arthritis .

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Comparative efficacy of treatments based on the Health Assessment Questionnaire

In total, nine studies were included in the HAQ analysis (Fig. 3). The treatment that showed the highest efficacy in improving HAQ scores (with the highest mean difference and probability of distribution) was the combination of certolizumab with MTX, followed by the combinations of golimumab with MTX and adalimumab with MTX (Table 2). The effect size for each treatment was similar in direction to the mean difference, with the highest value for certolizumab with MTX (Table 3). No study included in this analysis had a traditional DMARD arm for comparison.

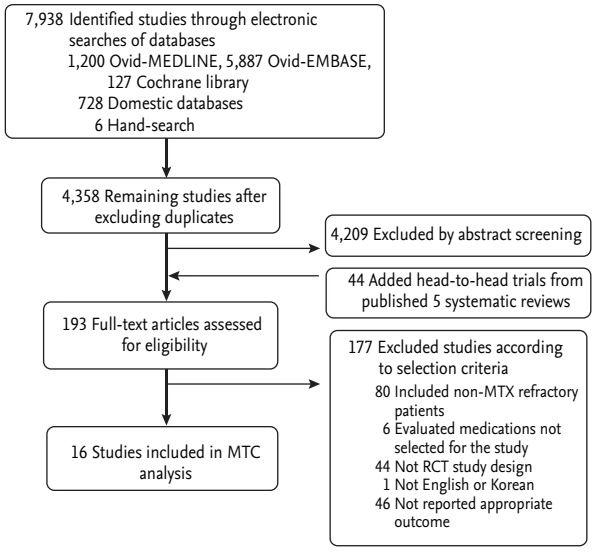

Figure 1. Flow diagram of study selection. MTX, methotrexate; MTC, mixed treatment comparison.

Comparative efficacy of treatments based on DAS28 < 2.6 (remission)

In total, four studies were included in the DAS28-ESR < 2.6 (remission) analysis (Fig. 3). The most effective treatment for DAS28-ESR < 2.6 (remission), with the highest odds ratio (OR) and probability OR, compared with MTX, was golimumab with MTX (OR, 24.500; 95% CrI, 3.508 to 99.520) (Table 4). The effect size was highest for golimumab with MTX (Table 5). No study included in this analysis had a traditional DMARD arm for comparison.

Comparative efficacy of treatments based on ACR response

In total, 11 studies were included for the ACR 70 response analysis (Fig. 3). The most effective treatment based on ACR 70 response was certolizumab with MTX (OR, 10.460; 95% CrI, 3.660 to 24.410) (Table 6); this combination also had the highest effect size (Table 7). ACR 20 and ACR 50 response rates could not be analyzed because of an insufficient number of studies. Combi-

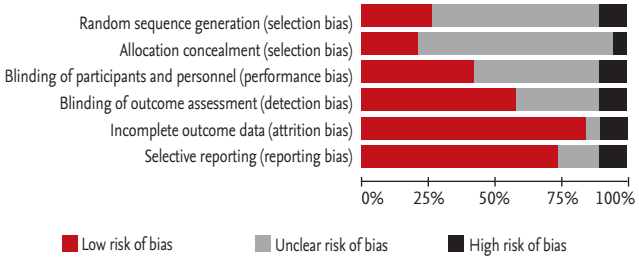

Figure 2. Risk of bias assessment summary.

Table 2. Comparative effectiveness on Health Assessment Questionnaire scores

Treatment	No. of studies	No. of participants	Mean difference (95% CrI)	Best[a]	Prob.d[b] (mean)
MTX (placebo + MTX)	8	1,004	-	0.001	-
CERT + MTX	1	246	−0.400 (−0.945 to 0.131)	0.2347	0.9572
GOL + MTX	2	200	−0.125 (−0.571 to 0.379)	0.0382	0.7256
ADAL + MTX	2	274	−0.354 (−1.557 to 0.839)	0.3072	0.7191
ADAL	1	67	−0.341 (−2.053 to 1.363)	0.3778	0.6530
GOL	2	200	−0.082 (−0.689 to 0.526)	0.0413	0.6220

CrI, credible interval (the probability to include a parameter); Prob.d, probability distribution; MTX, methotrexate; CERT, certolizumab; GOL, golimumab; ADAL, adalimumab.

[a]The relative estimate effect for all treatment comparison ranking.

[b]Statistical significance: probability distribution > 0.9.

Table 3. Effect sizes for Health Assessment Questionnaire

Comparator	Effect size by treatment, mean difference (95% CI)				
	ADAL	ADAL + MTX	CERT + MTX	GOL	GOL + MTX
Placebo + MTX	−0.35 (−0.56 to −0.14)	−0.34 (−0.44 to −0.25)	−0.40 (−0.41 to −0.39)	−0.12 (−0.16 to −0.08)	−0.09 (−0.12 to −0.06)
ADAL	-	0.01 (−0.22 to 0.24)	−0.05 (−0.26 to 0.16)	0.23 (0.16 to 0.44)	0.26 (0.48 to 0.47)
ADAL + MTX	-	-	−0.06 (−0.16 to 0.04)	0.22 (0.12 to 0.32)	0.25 (0.15 to 0.35)
CERT + MTX	-	-	-	0.28 (0.08 to 0.48)	0.31 (0.28 to 0.34)
GOL	-	-	-	-	0.2 (−0.02 to 0.08)

CI, confidence interval; ADAL, adalimumab; MTX, methotrexate; CERT, certolizumab; GOL, golimumab.

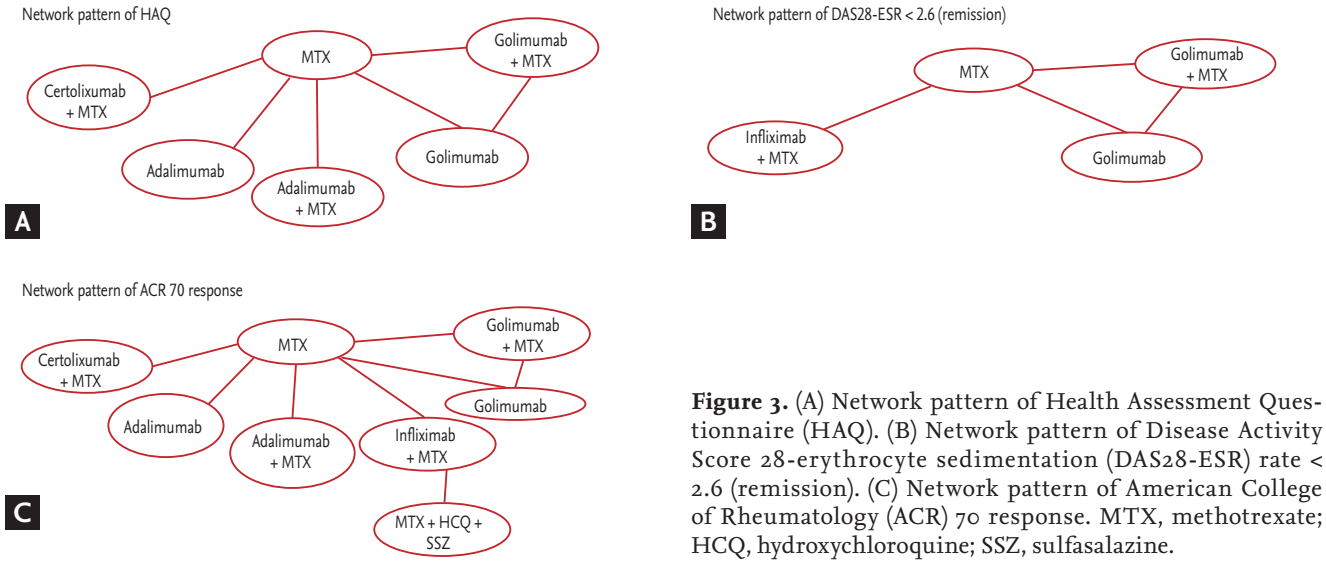

Figure 3. (A) Network pattern of Health Assessment Questionnaire (HAQ). (B) Network pattern of Disease Activity Score 28-erythrocyte sedimentation (DAS28-ESR) rate < 2.6 (remission). (C) Network pattern of American College of Rheumatology (ACR) 70 response. MTX, methotrexate; HCQ, hydroxychloroquine; SSZ, sulfasalazine.

Table 4. Comparative effectiveness on Disease Activity Score 28-erythrocyte sedimentation rate < 2.6 (remission)

Treatment	No. of studies	No. of participants	OR (95% CrI)	Best[a]	Probability OR (mean)
MTX (placebo + MTX)	4	368	-	0.00003	-
GOL + MTX	3	213	24.500 (3.508–99.520)	0.6545	0.9989
GOL	1	133	18.830 (0.625–93.290)	0.1606	0.9537
IFX + MTX	1	165	15.160 (0.552–73.820)	0.1849	0.9459

OR, odds ratio; CrI, credible interval (the probability to include a parameter); MTX, methotrexate; GOL, golimumab; IFX, infliximab.
[a]The relative estimate effect for all treatment comparison ranking.

nation DMARDs with MTX, hydroxychloroquine, and sulfasalazine had the lowest probability OR among the treatments compared.

DISCUSSION

In this study, we sought to compare the efficacy of various biologics and traditional DMARDs for MTX-refractory RA patients using a MTC methodology. Unfortunately, the number of traditional DMARD studies was not sufficient to allow an appropriate MTC analysis. The results showed that the combinations of golimumab with MTX and certolizumab with MTX were the most effective treatments in terms of DAS28 remission and ACR 70 responses for RA patients who did not respond

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Table 5. Effect sizes for Disease Activity Score 28-erythrocyte sedimentation rate < 2.6 (remission)

Comparator	Effect size by treatment, OR (95% CI)		
	GOL	GOL + MTX	IFX + MTX
Placebo + MTX	5.91 (1.28–27.18)	14.40 (5.34–38.79)	5.20 (1.51–17.89)
GOL	-	2.44 (0.39–15.06)	0.88 (0.12–6.28)
GOL + MTX	-	-	0.36 (0.07–1.77)

OR, odds ratio; CI, confidence interval; GOL, golimumab; MTX, methotrexate; IFX, infliximab.

Table 6. Comparative effectiveness on American College of Rheumatology 70 response

Treatment	No. of studies	No. of participants	OR (95% CrI)	Best	Probability OR (mean)
MTX (placebo + MTX)	10	1,289	-	0	-
CERT + MTX	2	786	10.460 (3.660–24.410)	0.3671	0.9990
ADAL	1	67	13.300 (1.708–52.970)	0.3602	0.9922
ADAL + MTX	2	274	8.086 (2.762–19.650)	0.1599	0.9985
GOL	1	133	3.422 (0.624–10.370)	0.0131	0.9276
GOL + MTX	4	608	6.917 (3.137–15.250)	0.0703	0.9997
IFX + MTX	2	293	4.084 (0.939–11.670)	0.0153	0.9713
MTX + HCQ + SSZ	1	130	3.457 (0.283–10.940)	0.0141	0.7695

OR, odds ratio; CrI, credible interval (the probability to include a parameter); MTX, methotrexate; CERT, certolizumab; ADAL, adalimumab; GOL, golimumab; IFX, infliximab; HCQ, hydroxychloroquine; SSZ, sulfasalazine.

Table 7. Effect sizes for American College of Rheumatology 70

Comparator	Effect size by treatment, OR (95% CI)					
	ADAL	ADAL + MTX	CERT + MTX	GOL	GOL + MTX	IFX + MTX
Placebo + MTX	7.22 (2.01–25.97)	6.61 (3.48–12.56)	8.74 (3.75–20.41)	2.08 (0.69–6.26)	5.69 (3.47–9.33)	3.10 (1.47–6.50)
ADAL	-	0.92 (0.22–3.83)	1.21 (0.26–5.62)	0.29 (0.53–1.56)	0.79 (0.2–3.11)	0.43 (0.10–1.89)
ADAL + MTX	-	-	1.32 (0.46–0.83)	0.32 (0.14–0.71)	0.86 (0.38–1.94)	0.47 (0.18–1.25)
CERT + MTX	-	-	-	0.24 (0.06–0.97)	0.65 (0.24–1.74)	0.36 (0.12–1.10)
GOL	-	-	-	-	2.74 (0.82–9.16)	1.49 (0.39–5.63)
GOL + MTX	-	-	-	-	-	0.55 (0.22–1.33)

OR, odds ratio; CI, confidence interval; ADAL, adalimumab; MTX, methotrexate; CERT, certolizumab; GOL, golimumab; IFX, infliximab.

to MTX treatment alone. For traditional DMARDs, only one trial was available for analysis of ACR 70 response, and the result showed that MTX combined with sulfasalazine and hydroxychloroquine was substantially inferior to biologics combinations (Table 6).

MTC analysis enables a comparison of the efficacy of biologic and DMARD treatment for MTX-refractory patients, even in the absence of direct comparisons. Indirect comparisons were unavoidable, because head-to-head trials for the medications of interest are rare, and often, biologics were compared with placebo, not to DMARDs or even other biologics [29]. While a 'traditional' meta-analysis summarizes the results of trials that have evaluated the same treatment/placebo combination, an MTC analysis consists of a network of treatment effects for all possible pairwise comparisons from RCTs, including both direct and indirect comparisons. A common comparator should exist, on which the treat-

ment effects compared are anchored [30].

Previously, many studies have reported direct comparisons of a biological agent combined with MTX and MTX monotherapy in MTX-refractory patients, which came to the conclusion that biologics are significantly more effective in these patients [31]. However, studies reporting the results of indirect comparisons of the efficacy of different biologics in RA found no statistically significant difference between them [2,32]. Certolizumab pegol was found superior to infliximab in some studies [33], which is partly in line with our results, showing that certolizumab combined with MTX improved both HAQ scores and ACR 70 most effectively. Certolizumab pegol consists of a humanized Fab fragment fused to a polyethylene glycol (PEG) moiety. The addition of the PEG structure increases the half-life up to 14 days and facilitates distribution into inflamed tissues in animal models. This different structure may be the basis of the additional effectiveness [34,35]. However, the RAPID trials, which were included in our analysis, withdrew non-responsive patients at weeks 12 and 14, and accordingly showed a high early withdrawal rate in the placebo group, which could have resulted in the high OR rate of certolizumab pegol compared with the placebo [31]. Recent meta-analysis updates of the comparative safety of TNF inhibitors suggest a higher risk of serious infection associated with certolizumab pegol, as well as adalimumab and infliximab, guiding clinical decision-making in balancing efficacy and safety in the management of RA.

At the time of preparation of this manuscript, randomized trials directly comparing the combination of a biologic agent plus MTX with a combination of traditional DMARDs [36] had been published, showing no difference between the two treatments. The combination of traditional DMARDs versus biologics has rarely been reported in systemic reviews, despite the huge implications concerning the cost differences between treatments with and without biologics. A recent meta-analysis of 38 RCTs showed that combination treatment with a biologic agent (a TNF-i or abatacept) and a DMARD was not superior to two or three DMARDs in combination, including or excluding low-dose glucocorticoids, in preventing structural joint damage [30].

While the effectiveness of biologics in RA patients unresponsive to MTX has been settled in many clinical trials and meta-analyses thereof, therapeutic equivalence and noninferiority continue to be debated. In an equivalence analysis of seven RCTs, MTX plus adalimumab or certolizumab led to superior ACR 50 responses in comparison with MTX monotherapy, but not for MTX with etanercept or golimumab [37]. Head-to-head indirect comparisons between individual biologics showed no significant difference, but failed to demonstrate equivalence. The high degree of clinical heterogeneity in the included trials and short duration of follow-up, compromising external validity, were considered the main reasons for the failure to demonstrate equivalence.

Our study has several limitations. Although we included only RCTs, the MTC analysis still showed statistical heterogeneity and inconsistency. Indirect comparison requires similarity, homogeneity of trials, and consistency of evidence [38]. Study procedures, such as blinding and allocation concealment, may affect the heterogeneity [6,39]. Additionally, differences in disease duration and medication dose between trials might affect trial homogeneity. A second limitation of this study was publication bias, because only published studies were included. Although a comprehensive search was done, the final RCT studies included in the MTC analysis for comparison were more numerous for trials testing biologics than traditional DMARDs. Because of the timeframe, most recent studies comparing biologics and traditional DMARDs were not included.

In conclusion, based on an MTC analysis using data from published RCTs, the combinations of certolizumab or golimumab with MTX are most effective in improving HAQ, DAS28-ESR < 2.6, and ACR 70 response in MTX-refractory RA patients.

KEY MESSAGE

1. Mixed treatment comparison (MTC) analysis enables a comparison of efficacy of biologics and traditional disease-modifying anti-rheumatic drugs (DMARDs) treatment in the absence of direct comparison for methotrexate (MTX)-refactory rheumatoid arthritis (RA) patients.
2. The combination of cetolizumab or golimumab with MTX were the most effective treatment in MTX-refractory RA patients based on MTC analysis.

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3. The number of traditional DMARDs studies was not sufficient to allow an appropriate MTC analysis.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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