Comparative Efficacy of Novel DMARDs as Monotherapy and in Combination with Methotrexate in Rheumatoid Arthritis Patients with Inadequate Response to Conventional DMARDs: A Network Meta-Analysis

Felicity Buckley, MA; Axel Finckh, MD, PhD; Tom W. J. Huizinga, MD, PhD; Fred Dejonckheere, MD, MSc; and Jeroen P. Jansen, PhD

ABSTRACT

BACKGROUND: Given the availability of a number of alternative biologic treatment options and other novel disease-modifying antirheumatic drugs (DMARDs) for the treatment of patients with rheumatoid arthritis (RA), clinicians are faced with an increasingly challenging choice regarding optimal treatment. Biologics are usually combined with traditional DMARDs, primarily methotrexate (MTX), but some biologics and tofacitinib (together referred to in this article as novel DMARDs) have been shown to be efficacious as monotherapy as well. In real-world practice, approximately one-third of RA patients receiving biologics are on monotherapy, primarily because of intolerance of, or noncompliance with, MTX. Limited data, however, are available analyzing the effectiveness of monotherapy compared with combination therapy across novel DMARDs.

OBJECTIVE: To compare American College of Rheumatology (ACR) responses to approved novel DMARDs used as monotherapy or as combination therapy with methotrexate (MTX) at 24 weeks in RA patients who have shown inadequate response to conventional DMARDs (DMARD-IR).

METHODS: Through a systematic review of the literature, we identified randomized controlled trials that assessed approved novel DMARDs used as monotherapy or as combination therapy with MTX in DMARD-IR RA patients. Twenty-eight RCTs were identified that evaluated abatacept, anakinra, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab, or tofacitinib. ACR responses at 24 weeks were extracted and combined by means of Bayesian network meta-analyses.

RESULTS: With the exception of anakinra plus MTX, which was less efficacious, most novel DMARDs, when used in combination with MTX, demonstrated comparable ACR responses. When novel DMARDs were used as monotherapies, greater ACR20/50/70 responses were observed with tocilizumab than with anti-tumor necrosis factor agents (aTNF) or tofacitinib. Furthermore, ACR20/50/70 responses with tocilizumab plus MTX were similar to those with tocilizumab monotherapy (odds ratio [OR] for the indirect comparison = 1.08, 95% credible interval [CrI] = 0.40-2.84; OR = 1.24, CrI = 0.44-3.61; OR = 0.95, CrI = 0.33-2.72, respectively), whereas greater responses were observed with aTNF plus MTX than with aTNF monotherapy (OR = 2.41, CrI = 0.51-11.61; OR = 2.85, CrI = 0.51-17.67; OR = 1.28, CrI = 0.21-8.42, respectively). Relative efficacy estimates for the indirect comparison of tofacitinib plus MTX with tofacitinib monotherapy were very uncertain.

CONCLUSIONS: Results suggest that in combination with MTX most of the available novel DMARDs have similar levels of efficacy in DMARD-IR patients. As monotherapy, however, tocilizumab displayed higher ACR responses than aTNF or tofacitinib. ACR responses with tocilizumab plus MTX were similar to those with tocilizumab as monotherapy, whereas aTNF in combination with MTX demonstrated greater ACR responses than aTNF as monotherapy.

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What is already known about this subject

- Biologics and tofacitinib—referred to as novel disease-modifying antirheumatic drugs (DMARDs)— are usually combined with traditional DMARDs, primarily methotrexate (MTX). In real-world practice, however, approximately one-third of rheumatoid arthritis (RA) patients receiving biologics are on monotherapy mainly because of intolerance of, or noncompliance with, MTX.
- In the past few years, several network meta-analyses of novel DMARDs for RA have been published. Most network meta-analyses have shown that in combination therapy, the efficacy of most novel DMARDs is comparable; this is confirmed by the current analysis. Comparisons of the efficacy of novel DMARDs as monotherapy and comparisons of monotherapy with combination therapy, however, are rare and none include all currently approved treatments.

What this study adds

- Contrary to several earlier published network meta-analyses, this study did not group patients with inadequate response to conventional DMARDs (DMARD-IR) with DMARD-naive or biologic-experienced patients. Additionally, monotherapy and combination therapies were considered different regimens, and all currently approved novel DMARDs were included in the analysis.
- Agents in combination with MTX and agents as monotherapy were evaluated simultaneously as part of a single network and could, therefore, also be indirectly compared (monotherapy vs. combination therapy).

Patients with rheumatoid arthritis (RA), a chronic inflammatory joint disorder, experience alternating episodes of joint stiffness, swelling, and pain. Without treatment, most patients become severely disabled over time. The primary goal of treating patients with RA is to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, normalization of function, and social participation. Amelioration of inflammation is the most important way to achieve these goals.[1-3]

According to American College of Rheumatology (ACR) and European League Against Rheumatism recommendations for the management of RA, treatment should begin with the use (alone or in combination) of traditional (nonbiologic) disease-modifying antirheumatic drugs (DMARDs), most commonly methotrexate (MTX).[4,5] Patients who are intolerant of, or show an inadequate response (IR) to, traditional DMARDs (DMARD-IR) are often treated with a biologic agent. Five classes of biologic agents are approved to treat patients with RA: (1) tumor necrosis factor blockers, otherwise known as anti-tumor necrosis factor agents (aTNF; etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab); (2) interleukin-1 receptor antagonists (anakinra); (3) a selective T-cell costimulatory modulator (abatacept); (4) a monoclonal antibody that inhibits B cells (rituximab); and (5) a monoclonal antibody that inhibits the interleukin-6 receptor (tocilizumab). Recently, data for tofacitinib, an oral Janus kinase inhibitor, have also become available. For DMARD-IR patients, biologics are usually combined with traditional DMARDs, primarily MTX, but some biologics and tofacitinib (together referred to in this article as novel DMARDs) have been shown to be efficacious as monotherapy as well.[6-8] In real-world practice, approximately one-third of RA patients receiving biologics are on monotherapy mainly because of intolerance of, or noncompliance with, MTX.[9-11] Side effects (primarily gastrointestinal symptoms, respiratory symptoms, and hepatotoxicity) are the main reason (>75%) for MTX withdrawal.[12]

Given the availability of a number of alternative biologic treatment options and other novel DMARDs, clinicians are faced with an increasingly challenging choice regarding optimal treatment. No all-encompassing, head-to-head randomized controlled trial (RCT) has been conducted to evaluate all the different novel DMARDs to help inform medical decision making. Rather, the available evidence base consists of many placebo-controlled trials and only a limited number of head-to-head RCTs comparing not more than 2 interventions each. In general, when the available RCTs of interest do not compare the same interventions but each instead compares only a subset of the interventions of interest, it is possible to develop a network of RCTs in which all trials have at least 1 intervention in common. The results of these trials in such an evidence network can be synthesized by means of a network meta-analysis.

Network meta-analysis is a generalization of standard pairwise meta-analysis and includes multiple pairwise comparisons across a range of interventions.[13,14] In addition to obtaining pooled results of multiple studies comparing the same interventions, network meta-analysis provides estimates of relative treatment effects of interventions not studied in a head-to-head fashion. In the past few years, several network meta-analyses of biologic treatments for RA have been published.[15] In terms of methodology, some published network meta-analyses focus only on combination therapy (i.e., a biologic with MTX), whereas others include monotherapy and combination therapy and either ignore the effect of MTX or explicitly acknowledge the effect of MTX in a meta-regression model. None of the latter analyses, however, include all currently approved biologic agents.

The recent review by Thorlund et al. (2013) provides an overview of recently published network meta-analyses of biologic treatments in RA and discusses why findings vary.[15] The authors recommended that DMARD-naïve and DMARD-experienced patients not be grouped together in an analysis.[15] Similarly, patients who have previously experienced treatment failure with a biologic should not be pooled with those who are biologic-naïve. Furthermore, the authors questioned whether the concomitant use of DMARDs and MTX does, in fact, yield a modification of the relative treatment effect. Accordingly, a robust approach would consider monotherapy and combination therapy as different regimens but would still investigate their comparative effectiveness in 1 network meta-analysis to allow comparisons of monotherapy and combination therapy.[15]

The objective of the present study was to compare the efficacy of available novel DMARDs as monotherapy and as combination therapy in the treatment of biologic DMARD-naïve and DMARD-IR RA patients based on evidence from RCTs identified by means of a systematic literature review, providing prescribers and payers an additional piece of evidence when comparing the efficacy of RA treatment options. Indeed, given the devastating nature of RA, these patients should be administered the best treatment option first.

Methods

Identification and Selection of Studies and Data Extraction

A predefined search strategy of the MEDLINE, Embase, and Cochrane databases used terms related to RA, novel DMARDs, and RCTs to allow for a search of studies published between January 1990 and April 2013 (see Appendix A for search strategy terms). Titles and abstracts were screened to ascertain whether studies met predefined selection criteria. Studies that either met the criteria or had unclear criteria were further screened using the full text report.

The following criteria were used when considering published studies for inclusion:

- *Study design:* RCTs.
- *Population of interest:* biologic DMARD-naïve and DMARD-IR RA patients. Although some studies had patients from

non-Western countries, populations that were exclusively non-Western were not considered to be comparable; therefore, studies conducted in these populations were excluded.

- *Interventions:* tocilizumab (subcutaneous [SC] or intravenous [IV]), TNF blockers, abatacept (SC or IV), anakinra and tofacitinib in their usual dose, alone and in combination with conventional DMARDs. Rituximab was not considered because its label is restricted to TNF-IR patients.
- *Comparators:* placebo or 1 of the regimens described under interventions. Comparison of different dosages of the same intervention only and comparison of the same interventions with different background treatments were excluded.
- *Outcomes/end points:* American College of Rheumatology (ACR) response criteria.[16,17]

For each identified study that met the selection criteria, details were extracted on study design, study population characteristics, interventions, and number of patients with a 20% improvement in ACR criteria (ACR20 response), ACR50 response, and ACR70 response, all assessed at 24 weeks follow-up. The ACR criteria require a percentage improvement (for example, ACR20 requires 20%) in both tender and swollen joint counts and that same percentage improvement in 3 of the following 5 parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein (or erythrocyte sedimentation rate), and degree of disability according to the Health Assessment Questionnaire–Disability Index.[16,17]

Network Meta-Analysis

To synthesize the results of the included studies, Bayesian network meta-analysis models were used.[13,14,18,19] For the analysis, we grouped the different aTNFs. Additionally, because head-to-head comparisons of SC and IV administration of individual therapies did not show any meaningful difference, these modes of delivery were grouped for each of these therapies.[20,21] Within a Bayesian framework, analysis involves data, a likelihood distribution, a model with parameters, and prior distributions for these parameters.[22] A logistic regression model with a binomial likelihood relates the data from the individual studies to basic parameters reflecting the (pooled) treatment effect of each intervention compared with placebo. Based on these basic parameters, the relative efficacy was calculated between each of the interventions as monotherapy and as combination therapy.

Both fixed and random effects models were considered and were compared regarding the goodness-of-fit to the data, calculated as the posterior mean residual deviance. The deviance information criterion (DIC) provides a measure of model fit that penalizes model complexity.[23] In general, a more complex model will result in a better fit to the data, demonstrating a smaller residual deviance. The model with the lowest DIC is the model providing the "best" fit to the data adjusted for the number of parameters. The random effects model resulted in the lowest DIC for ACR20 and ACR50 and was considered appropriate for the synthesis of the available evidence. Regarding ACR70, the DICs of the fixed and random effects models were similar. Despite the lack of strong evidence against the fixed effects model on statistical grounds, we preferred using the random effects model for ACR70 to be consistent with the ACR20 and ACR50 analyses. In addition, the random effects model can be considered more plausible because it assumes that the studies included in the analysis are clinically and methodologically diverse, and it addresses associated between-study heterogeneity in treatment effects. This is especially relevant for the current analysis because we compare different drug classes and pool different aTNFs.

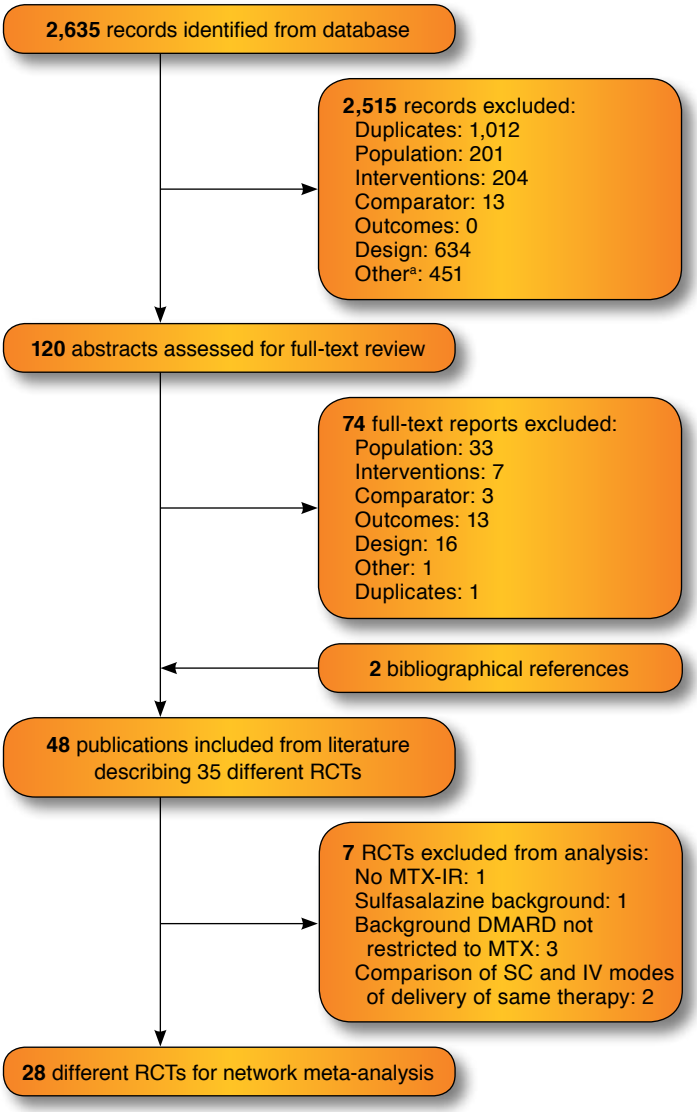
To avoid the influence of prior distributions required for Bayesian analyses on the results, noninformative prior distributions were used. Prior distributions of the treatment effects (i.e., the log-odds ratio of ACR response) were normal distributions with a mean of 0 and a variance of 10,000. A uniform distribution with range of 0 to 2 was used for the prior distribution of heterogeneity needed for the random effects analyses. WinBUGS statistical software was used for the analyses.[24] Results of the network meta-analysis provided us with posterior distributions of relative treatment effects of each treatment compared with another in terms of odds ratio (OR). To transform the OR into an expected ACR response, the OR of each regimen compared with placebo was combined with the average estimate of the odds of response with placebo across studies. Posterior distribution of OR and the expected response were summarized with the median to represent the most likely estimate and the 2.5th and 97.5th percentiles reflecting each 95% credible interval (95% CrI). Unlike 95% confidence intervals obtained with frequentist analysis that show that with repeated analyses the calculated confidence interval would contain the true estimate 95% of the time, the 95% CrI can be interpreted in terms of probability. The 95% CrI reflects with 95% probability that the true OR or the expected response would fall between the boundaries of the 95% CrI. Given the posterior distributions of relative treatment effects corresponding to the different comparisons obtained, we were also able to calculate the probability that a certain intervention was more efficacious than a competitor intervention.

Results

Study Identification

The literature search resulted in 2,635 potentially relevant citations; abstract review excluded 2,515 (95%; Figure 1). Of the remaining 120 retrieved full-text publications, 74 (3%) were excluded through the full-text review, leaving 46 publications plus 2 additional publications identified through bibliography searching, corresponding to 35 different RCTs that met the selection criteria.

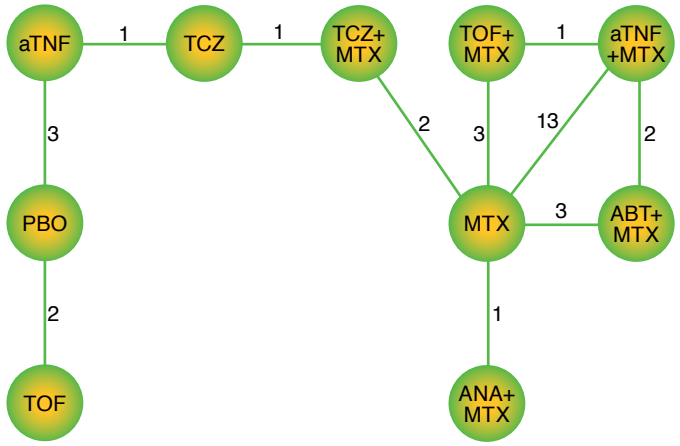
FIGURE 1 Flow Diagram of Study Identification and Selection



[a]*Studies excluded for other reasons were either non-English language or not full-text publications (i.e., conference abstracts).*

DMARD = disease-modifying antirheumatic drug; IR = inadequate response; IV = intravenous; MTX = methotrexate; RCTs = randomized controlled trials; SC = subcutaneous.

FIGURE 2 Network of RCTs Evaluating Agents for DMARD-IR RA Patients in Terms of ACR20/50/70 Response at 24 Weeks



ABT = abatacept; ACR20/50/70 = 20%/50%/70% improvement in American College of Rheumatology criteria; ANA = anakinra; aTNF = anti-tumor necrosis factor; DMARD = disease-modifying antirheumatic drug; IR = inadequate response; MTX = methotrexate; PBO = placebo; RA = rheumatoid arthritis; TCZ = tocilizumab; TOF = tofacitinib.

Evidence Base

All studies were double-blind, parallel RCTs. Most of the trials (28/35) were explicitly reported as having been conducted at multiple centers and included patients predominantly from Europe and North America. Some of these studies were also reported to include patients from South America (7 studies) and Asia (3 studies).

Most studies included adult patients with diagnoses of RA based on the 1987 revised ACR classification criteria, with active disease in spite of previous treatment with traditional DMARDs, including MTX. The TEMPO trial included patients who were DMARD-IR but disqualified patients for whom MTX treatment failed.[25] Definitions of active disease varied around the minimum levels of erythrocyte sedimentation rate (ESR; 10 millimeters per hour [mm/h], 28 mm/h) and C-reactive protein (CRP; 2 milligrams per deciliter [mg/dL], 1 mg/dL, 1.5 mg/dL, 7 milligrams per milliliter [mg/mL]) and around the minimum number of required tender (6-12) and swollen (6-10) joints. Not all studies reported whether RA disease duration and DMARD treatment duration were eligibility criteria.

In almost all RCTs evaluating the efficacy of biologics in combination with a traditional DMARD (29 studies), MTX was the background treatment of choice (25/29 studies). The exception was the study by Combe et al. (2006, 2009) in which sulfasalazine was used.[26,27] Three studies allowed multiple DMARDs as background therapy.

To achieve a group of studies sufficiently comparable to allow for indirect comparison of ACR responses at 24 weeks, 7 of the 35 identified studies were excluded (Klareskog et al., 2004 [TEMPO, MTX failures excluded],[25] Combe et al. [sulfasalazine background treatment],[26,27] 3 studies that allowed background DMARD therapy with multiple DMARDs,[28-30] and 2 studies that compared IV and SC modes of delivery of the same treatment[20,21]). Given that modes of delivery of each

TABLE 1 Study and Patient Baseline Characteristics Grouped by Intervention

Study	Interventions	Patients (n)	Mean Age (years)	Female (%)	Mean Disease Duration (years)	SJC	TJC	ESR (mm/h)	CRP (mg/L)	RF + (%)
Kremer 2003[37]	ABT 10 mg/kg Q4W + MTX	115	56	75	10	21.3	30.8	NR	29	90
	Placebo + MTX	119	55	66	9	21.8	29.2	NR	32	90
Kremer 2006[38]	ABT 10 mg/kg Q4W + MTX	433	52	78	9	21.4	31	NR	33	82
	Placebo + MTX	219	50	82	9	22.1	32.3	NR	28	79
Kay 2008[33]	GLB 50 mg Q4W + MTX	35	57[M]	86	8	NR	NR	NR	21[M]	NR
	Placebo + MTX	35	52[M]	74	6	NR	NR	NR	20[M]	NR
Keystone 2009[34] (GO-FORWARD)	GLB 50 mg Q4W + MTX	89	52[M]	81	4.5[M]	13[M]	26[M]	NR	10[M]	81
	Placebo + MTX	133	52[M]	82	6.5[M]	12[M]	21[M]	NR	8[M]	81
Maini 1999[39] (ATTRACT)	IFX 3 mg/kg Q8W + MTX	86	54	81	10	22	32	49	39	84
	Placebo + MTX	88	51	80	11	21	31	49	40	77
Westhovens 2006[46] (START)	IFX 3 mg/kg Q8W + MTX	360	53	80	8	15	22	NR	16	83
	Placebo + MTX	363	42	83	8	15	22	NR	12	81
Schiff 2008[40] (ATTEST)	ABT 10 mg/kg Q4W + MTX	156	49	83	8	21.3	31.6	49.4	31	87
	IFX 3 mg/kg Q8W + MTX	165	49	87	8	20.1	30.3	47	27	77
	Placebo + MTX	110	49	82	7	20.3	31.7	47.8	33	85
Cohen 2004[55]	ANA 100 mg QD + MTX	250	56	79	11	20.1	26.8	41.5	27	76
	Placebo + MTX	251	57	75	10	20	24.5	42.9	26	78
Keystone 2004[35]	ADA 40 mg Q2W + MTX	207	56	76	11	19.3	27.3	NR	18	82
	Placebo + MTX	200	56	73	11	19	28.1	NR	18	90
Weinblatt 2003[45] (ARMADA)	ADA 40 mg Q2W + MTX	67	57	75	12	17.3	28	NR	21	NR
	Placebo + MTX	62	56	82	11	16.9	28.7	NR	31	NR
van Vollenhoven 2011[48] (AUGUST-2)	ADA 40 mg Q2W + MTX	79	53	81	8.8	16.2	27.8	41.7	16.6	81
	Placebo + MTX	76	54	84	8.4	16.4	24.3	39.3	16.5	83
van de Putte 2004[8]	ADA 40 mg Q2W	113	53	80	11	20.5	33.7	55.8	52.6	80
	Placebo	110	54	77	12	19.8	35.5	56.1	57	82
Weinblatt 2013[49] (AMPLE)	ABT 125 mg QW SC + MTX	318	51.4	81.4	1.9	15.8	25.4	NR	16	75.5
	ADA 40 mg Q2W + MTX	328	51	82.3	1.7	15.9	26.3	NR	15	77.4
Keystone 2008[36] (RAPID 1)	CTZ 200 mg Q2W + MTX	393	51	82	6	9.9[M]	12.4[M]	43.5[M]	16[M]	80
	Placebo + MTX	199	52	84	6	9.7[M]	13[M]	45[M]	16[M]	83
Smolen 2009[41] (RAPID 2)	CTZ 200 mg Q2W + MTX	246	52	84	6	20.5	30.1	43.7	14.2	78
	Placebo + MTX	127	52	84	6	21.9	30.4	40.8	13.5	78
Choy 2012[50]	CTZ 400 mg Q4W + MTX	126	53	72.2	9.4	22.8	29	24.4	11.9	73.8
	Placebo + MTX	121	55.6	66.1	9.9	22.2	31	25.9	13.1	78.5
Fleischmann 2009[31] (FAST4WARD)	CTZ 400 mg Q4W	111	53	78	9	21.2	29.6	30.9	11.6	100
	Placebo	109	55	89	10	19.9	28.3	35.6	11.3	100

TABLE 1 Study and Patient Baseline Characteristics Grouped by Intervention *(continued)*

Study	Interventions	Patients (n)	Mean Age (years)	Female (%)	Mean Disease Duration (years)	SJC	TJC	ESR (mm/h)	CRP (mg/L)	RF + (%)
Weinblatt 1999[44]	ETN 25 mg BW + MTX	59	48	90	13	20	28	25	22	84
	Placebo + MTX	30	53	73	13	17	28	36	26	90
Moreland 1999[7]	ETN 25 mg BW	78	53	74	11	25	33	35	47	79
	Placebo	80	51	76	12	25	35	39	41	79
Kremer 2012[51]	TOF 5 mg BID + MTX	71	52	80	9.0	14.1	21.5	NR	18	82.8
	Placebo	69	53	81	9.2	15.7	21.6	NR	19	83
van der Heijde 2013[43]	TOF 5 mg BID + MTX	321	53.7	83.8	8.9	14.1	24.1	50.1	15.5	75.2
	Placebo + MTX	NR	NR	NR	NR	NR	NR	NR	NR	NR
van Vollenhoven 2012[52]	TOF 5 mg BID + MTX	204	53	85	7.6	16.7	28.5	48.6	15	66.8
	ADA + MTX	204	52.5	79	8.1	16.4	26.7	48.5	18	68.2
	Placebo + MTX	108	NR	NR	NR	NR	NR	NR	NR	NR
Fleischmann 2012[28]	TOF 5 mg BID	49	54	87.8	8.1	17.4	27.1	47.4	24.5	77.5
	Placebo	59	53	88.1	10.8	16.9	25.9	46.2	23.5	74.5
Fleischmann 2012[53] (ORAL SOLO)	TOF 5 mg BID	243	52.2	85.2	8.0	16.3	29.4	53.1	22.9	
	Placebo	122	49.7	86.1	7.7	17.3	28.9	50.9	17.8	68
Smolen 2008[42] (OPTION)	TCZ 8 mg/kg Q4W + MTX	205	51	NR	8	19.5	31.9	51.2	26	83
	Placebo + MTX	204	51	NR	8	20.7	32.8	49.7	24	71
Kremer 2011[47] (LITHE)	TCZ 8 mg/kg Q4W + MTX	398	53.4	82	9.3	17.3	29.3	46.4	23	NR
	TCZ 4 mg/kg Q4W + MTX									
	Placebo + MTX	393	51.3	83	9	16.6	27.9	46.5	22	NR
Dougados 2013[54] (ACT-RAY)	TCZ 8 mg/kg Q4W + MTX	277	53	81.9	8.2	14.4	25.8	39.9	NR	NR
	TCZ 8 mg/kg Q4W	276	53.6	78.6	8.3	15.3	26.6	39.6	NR	NR
Gabay 2013[32] (ADACTA)	TCZ 8 mg/kg	163	54.4	79	7.3	11.3	15.9	50.5	26	NR
	ADA 40 mg	162	53.3	82	6.3	12.4	16.5	45.5	25	NR

ABT = abatacept; ADA = adalimumab; ANA = anakinra; BID = twice a day; BW = body weight; CRP = C-reactive protein; CTZ = certolizumab; ESR = erythrocyte sedimentation rate; ETN = etanercept; GLB = golimumab; IFX = infliximab; M = median; mg = milligram; mg/kg = milligram per kilogram; mg/L = milligram per liter; mm/h = millimeters per hour; MTX = methotrexate; NR = not reported; QD = every day; QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; RF = rheumatoid factor; SC = subcutaneous; SJC = swollen joint count; TCZ = tocilizumab; TJC = tender joint count; TOF = tofacitinib.

therapy were grouped for the purpose of analysis, these studies could not contribute to the network.

Table 1 provides information on the characteristics of the patients included in the 28 RCTs.[7,31-54] Mean age in the study arms ranged from 42 to 57 years. Female patients were predominant; the participation of women in the study arms ranged from 66% to 90%. Average disease duration ranged from 1.7 to 13 years. Rheumatoid factor positivity ranged from 67% to 100%; ESR ranged from 24.4 to 56.1 mm/h; average swollen and tender joint counts (66/68 count) ranged from 11.3 to 25 and from 15.9 to 35.5, respectively. In Figure 2, the network of the 28 RCTs is presented such that each line between nodes reflects the available direct comparisons The right side of the network, which concerns biologics in combination with MTX, shows multiple connections between the different interventions. The left side of the network, which concerns interventions as monotherapy, consists of 1 path with a limited number of studies for each edge. This means that any comparison between interventions on the left side of the network and interventions on the right side will be uncertain.

Network meta-analysis allows a treatment effect of an intervention compared with another intervention in the same network to be obtained. Despite some variation in patient characteristics across studies (e.g., duration of disease), no differences beyond what can be expected due to chance were observed across the different types of comparisons, indicating the feasibility of the network meta-analysis. ACR responses at 24 weeks by study are provided in Table 2.[7,8,31-55]

TABLE 2 Proportions of ACR20/50/70 Responders at 24 Weeks with Treatments Reported in Individual Studies Used for Network Meta-Analysis

	Placebo	Placebo + MTX	ADA	CTZ	ETN	TOF	TCZ	ABT + MTX	ANA + MTX	GLB + MTX	IFX + MTX	ADA + MTX	CTZ + MTX	ETN + MTX	TOF + MTX	TCZ + MTX
van de Putte 2004[48]	0.19 0.08 0.02		0.46 0.22 0.12													
Fleischmann 2009[31]	0.09 0.04 0.00			0.46 0.23 0.06												
Moreland 1999[7]	0.13 0.05 0.10				0.59 0.40 0.15											
Fleischmann 2012[28]	0.25 0.10 0.07					0.51 0.35 0.20										
Fleischmann 2012[53]	0.27					0.70										
Gabay 2013[32]			0.49 0.28 0.18				0.65 0.47 0.33									
Kremer 2003[37]		0.35 0.12 0.02						0.60 0.37 0.17								
Kremer 2006[38]		0.40 0.18 0.07						0.68 0.38 0.20								
Schiff 2008[40]		0.42 0.20 0.09						0.67 0.40 0.21			0.59 0.37 0.24					
Cohen 2004[55]		0.22 0.08 0.02							0.38 0.17 0.06							
Kay 2008[33]		0.37 0.06 0.00								0.60 0.37 0.09						
Keystone 2009[34]		0.28 0.14 0.05								0.60 0.37 0.20						
Maini 1999[39]		0.20 0.05 0.00									0.52 0.27 0.08					
Westhovens 2006[46]		0.24 0.09 0.04									0.55 0.31 0.13					
Keystone 2004[35]		0.30 0.10 0.03										0.63 0.39 0.21				
Weinblatt 2003[45]		0.15 0.08 0.05										0.67 0.55 0.27				
van Vollenhoven 2011[48]		0.46 0.15 0.05										0.71 0.38 0.18				
Weinblatt 2013[49]								0.66 0.46 0.24				0.65 0.43 0.22				
Keystone 2008[36]		0.14 0.08 0.03											0.59 0.37 0.21			
Smolen 2009[41]		0.09 0.03 0.01											0.57 0.33 0.16			

TABLE 2 Proportions of ACR20/50/70 Responders at 24 Weeks with Treatments Reported in Individual Studies Used for Network Meta-Analysis *(continued)*

	Placebo	Placebo + MTX	ADA	CTZ	ETN	TOF	TCZ	ABT + MTX	ANA + MTX	GLB + MTX	IFX + MTX	ADA + MTX	CTZ + MTX	ETN + MTX	TOF + MTX	TCZ + MTX
Choy 2012[50]		0.23 0.06 0.02											0.46 0.18 0.00			
Weinblatt 1999[44]		0.27 0.03 0.00												0.71 0.39 0.15		
Kremer 2012[51]		0.34 0.23 0.07													0.48 0.34 0.20	
van der Heijde 2013[43]		0.25 0.09 0.02													0.52 0.32 0.16	
van Vollenhoven 2012[52]		0.28										0.47 0.28 0.09			0.52 0.37 0.20	
Smolen 2008[42]		0.26 0.11 0.02														0.59 0.44 0.22
Kremer 2011[47]		0.27 0.10 0.02														0.57 0.32 0.12
Dougados 2013[54]							0.70 0.40 0.25									0.72 0.46 0.25

ABT = abatacept; ACR20/50/70 = 20%/50%/70% improvement in American College of Rheumatology criteria; ADA = adalimumab; ANA = anakinra; CTZ = certolizumab; ETN = etanercept; GLB = golimumab; IFX = infliximab; MTX = methotrexate; TCZ = tocilizumab; TOF = tofacitinib.

Monotherapy

Table 3 presents the results of the network meta-analysis. Each cell presents the OR of response at 24 weeks with the intervention (in the rows) relative to a comparator (in the column). Both aTNF and tocilizumab as monotherapy showed greater ACR20 response than placebo, with ORs of 6.67 and 12.89, respectively (see Table 3, under ACR20, where the tocilizumab row and the aTNF row intersect with the placebo column). Consistent with these estimates, the OR of tocilizumab relative to aTNF monotherapy obtained with the network meta-analysis equals 1.94 (95% CrI = 0.71-5.36; Table 3). Although this difference was not thought to be statistically significant because the 95% CrI includes the 1, this estimate still corresponds to a 91% probability that tocilizumab as monotherapy would result in a greater ACR20 response than aTNF as monotherapy. For ACR50 and ACR70 responses, similar findings were observed with ORs of 6.65 and 14.00 for aTNF relative to placebo and ORs of 15.51 and 31.19 for tocilizumab relative to placebo (Appendices B and C). The ORs of tocilizumab relative to aTNF were 2.34 and 2.22 for ACR50 and ACR70, respectively. Although this is not statistically relevant at a 95% level, it still indicates a greater than 93% chance that tocilizumab results in greater responses than aTNF. Tofacitinib showed greater ACR response than placebo (OR = 4.72/4.98/3.76 for ACR20/50/70, respectively). Figure 3 shows the expected ACR20/50/70 responses for each treatment, calculated by combining the ORs of each intervention compared with placebo obtained with the network meta-analysis and the average placebo response across all trials. This is a more tangible way of illustrating the findings, representing the most likely ACR responses at 24 weeks for all treatment options in the network as if they had been compared in a huge head-to-head study. However, we would like to stress that this figure cannot be used to identify "significant" differences between interventions because the whiskers concern both the uncertainty about the relative efficacy measures as presented in Table 3 and Appendices B and C and the uncertainty about the overall placebo response. The whiskers indicate the uncertainty in the expected ACR20/50/70 responses. To compare the efficacy of the different interventions, the ORs, along with the uncertainty measures presented in Table 3 and Appendices B and C, must be used.

Combination Therapy with Methotrexate

In combination therapy with MTX, all classes of novel DMARDs demonstrated greater ACR20/50/70 responses than MTX alone in this DMARD-IR population (Table 3 and Appendices B and C).

TABLE 3 Treatment Effects for All Contrasts in Terms of OR of ACR20 Response Along with 95% CrI and Probability That Treatment Is Better Than Comparator

Intervention		Comparator									
		Placebo	Placebo + MTX	aTNF	TOF 5 mg	TCZ	ABT + MTX	ANA + MTX	aTNF + MTX	TOF 5 mg + MTX	TCZ + MTX
Placebo	OR (95% CrI)	1 (1, 1)	0.26 (0.05, 1.34)	0.15 (0.08, 0.29)	0.21 (0.10, 0.47)	0.08 (0.02, 0.25)	0.07 (0.01, 0.40)	0.12 (0.02, 0.82)	0.06 (0.01, 0.33)	0.09 (0.01, 0.48)	0.07 (0.01, 0.32)
	P(better)	NA	0.05	<0.01	<0.01	<0.01	<0.01	0.02	<0.01	<0.01	<0.01
Placebo + MTX	OR (95% CrI)	3.80 (0.75, 20.53)	1.00 (1, 1)	0.57 (0.13, 2.68)	0.80 (0.14, 5.40)	0.30 (0.09, 0.97)	0.28 (0.17, 0.46)	0.46 (0.17, 1.24)	0.24 (0.18, 0.32)	0.33 (0.18, 0.59)	0.27 (0.14, 0.55)
	P(better)	0.95	NA	0.23	0.40	0.02	<0.01	0.06	<0.01	<0.01	<0.01
aTNF	OR (95% CrI)	6.67 (3.48, 13.08)	1.75 (0.37, 7.97)	1.00 (1, 1)	1.41 (0.51, 4.08)	0.52 (0.19, 1.41)	0.48 (0.10, 2.41)	0.79 (0.12, 5.02)	0.41 (0.09, 1.94)	0.57 (0.11, 2.94)	0.48 (0.12, 1.88)
	P(better)	>0.99	0.77	NA	0.75	0.09	0.18	0.4	0.13	0.24	0.14
TOF 5 mg	OR (95% CrI)	4.72 (2.11, 10.33)	1.24 (0.19, 7.34)	0.71 (0.24, 1.96)	1.00 (1, 1)	0.37 (0.08, 1.48)	0.34 (0.05, 2.22)	0.56 (0.07, 4.45)	0.29 (0.04, 1.77)	0.41 (0.06, 2.68)	0.34 (0.06, 1.78)
	P(better)	>0.99	0.60	0.25	NA	0.08	0.13	0.29	0.09	0.17	0.10
TCZ	OR (95% CrI)	12.89 (3.96, 44.39)	3.38 (1.03, 11.17)	1.94 (0.71, 5.36)	2.74 (0.68, 12.11)	1.00 (1, 1)	0.94 (0.26, 3.43)	1.55 (0.33, 7.54)	0.80 (0.23, 2.74)	1.10 (0.30, 4.22)	0.92 (0.35, 2.48)
	P(better)	>0.99	0.98	0.91	0.92	NA	0.46	0.72	0.35	0.56	0.43
ABT + MTX	OR (95% CrI)	13.72 (2.49, 79.12)	3.60 (2.18, 5.96)	2.06 (0.41, 10.45)	2.91 (0.45, 20.52)	1.06 (0.29, 3.86)	1.00 (1, 1)	1.64 (0.54, 5.04)	0.85 (0.51, 1.43)	1.17 (0.56, 2.55)	0.99 (0.42, 2.32)
	P(better)	>0.99	>0.99	0.82	0.87	0.54	NA	0.82	0.26	0.67	0.49
ANA + MTX	OR (95% CrI)	8.37 (1.22, 59.84)	2.19 (0.80, 5.98)	1.26 (0.20, 8.02)	1.77 (0.22, 15.29)	0.64 (0.13, 3.06)	0.61 (0.20, 1.87)	1.00 (1, 1)	0.52 (0.18, 1.49)	0.71 (0.22, 2.29)	0.60 (0.18, 2.10)
	P(better)	0.98	0.94	0.6	0.71	0.28	0.18	NA	0.10	0.27	0.19
aTNF + MTX	OR (95% CrI)	16.06 (3.07, 88.89)	4.22 (3.17, 5.69)	2.41 (0.51, 11.61)	3.40 (0.56, 23.22)	1.25 (0.37, 4.27)	1.17 (0.70, 1.98)	1.93 (0.67, 5.51)	1.00 (1, 1)	1.37 (0.74, 2.59)	1.16 (0.55, 2.51)
	P(better)	>0.99	>0.99	0.87	0.91	0.65	0.74	0.90	NA	0.86	0.66
TOF 5 mg + MTX	OR (95% CrI)	11.66 (2.07, 68.81)	3.08 (1.70, 5.46)	1.75 (0.34, 9.07)	2.46 (0.37, 17.67)	0.91 (0.24, 3.38)	0.86 (0.39, 1.80)	1.40 (0.44, 4.45)	0.73 (0.39, 1.34)	1.00 (1, 1)	0.84 (0.34, 2.09)
	P(better)	>0.99	>0.99	0.76	0.83	0.44	0.33	0.73	0.14	NA	0.34
TCZ + MTX	estimate (95% CrI)	13.86 (3.11, 66.90)	3.65 (1.81, 7.36)	2.09 (0.53, 8.35)	2.93 (0.56, 17.34)	1.08 (0.40, 2.84)	1.01 (0.43, 2.41)	1.66 (0.48, 5.66)	0.86 (0.40, 1.83)	1.18 (0.48, 2.97)	1.00 (1, 1)
	P(better)	>0.99	>0.99	0.86	0.90	0.57	0.51	0.81	0.34	0.66	NA

ABT = abatacept; ACR20 = 20% improvement in American College of Rheumatology criteria; ANA = anakinra; aTNF = anti-tumor necrosis factor; CrI = credible interval; mg = milligram; MTX = methotrexate; NA = not applicable; OR = odds ratio; P(better) = probability that treatment (in row) is showing greater response than comparator (in column); TCZ = tocilizumab; TOF = tofacitinib.

ACR20/50/70 responses with aTNF, abatacept, tocilizumab, and tofacitinib were comparable. Response with anakinra was lower than with other novel DMARDs.

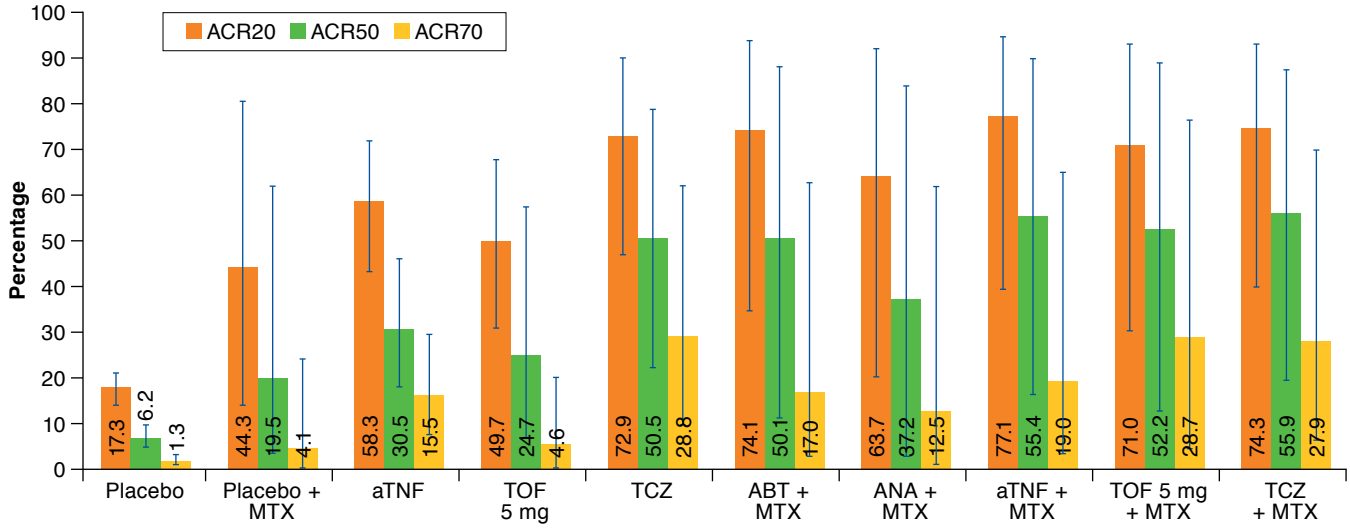
Comparison Between Monotherapy and Combination Treatment with Methotrexate

There is an 87% probability that aTNF in combination with MTX results in greater ACR20 response than aTNF monotherapy (OR = 2.41, 95% CrI = 0.51-11.61). For ACR50, the probability of a higher response in combination therapy than in monotherapy was 90% (OR = 2.85, 95% CrI = 0.51-17.67). For ACR70, the probability was 63% that aTNF in combination with MTX would result in greater response than aTNF monotherapy (OR = 1.28, 95% CrI = 0.21-8.42). For tocilizumab, however, ACR20/50/70 responses with MTX were similar to ACR20/50/70 responses without MTX at 24 weeks (ORs = 1.08/1.24/0.95). Greater ACR20/50/70 responses were observed for tofacitinib in combination with MTX than for tofacitinib monotherapy, but the estimates of relative efficacy were uncertain because of the long path in the network (Figure 2) required for this indirect comparison.

Discussion

The objective of this study was to compare the efficacy of different classes of novel DMARD treatments with or without MTX in biologic DMARD-naïve and DMARD-IR RA patients based on available RCT evidence. Agents in combination with MTX and agents as monotherapy were evaluated simultaneously as part of 1 network of RCTs by means of a network meta-analysis and could therefore be indirectly compared. The results of the present analysis are in line with previously conducted network meta-analyses, although many of these are limited to combination therapy or do not include all treatments. The results also align well with those of a recent independent analysis

FIGURE 3 Probability of ACR20/50/70 Response with 95% CrI for Different Classes of Biologic Treatment with and Without MTX



ABT = abatacept; ACR20/50/70 = 20%/50%/70% improvement in American College of Rheumatology criteria; ANA = anakinra; aTNF = anti-tumor necrosis factor; CrI = credible interval; mg = milligram; MTX = methotrexate; TCZ = tocilizumab; TOF = tofacitinib.

initiated by the National Institute for Health and Care Excellence that compared RA biologics (including agents as monotherapy and agents in combination with MTX in 1 network, as in our study)[56] and with another recently published network meta-analysis[57] that compared patient-reported outcomes between agents as monotherapy and agents in combination with MTX using a similar approach.

The results of this analysis do suggest that an aTNF as monotherapy is likely to be less effective than an aTNF in combination with MTX. This finding is corroborated by observational studies that demonstrate greater aTNF retention rates in combination with MTX than in monotherapy.[10,58-60] Tocilizumab monotherapy resulted in an ACR20/50/70 response similar to that of tocilizumab in combination with MTX. The findings of this network meta-analysis may have important clinical implications for patients who cannot tolerate or are not compliant with MTX. Indeed, in patients who require monotherapy, the analysis may suggest that tocilizumab results in a greater likelihood of good clinical response than aTNF or tofacitinib and may represent a better treatment option. However, additional randomized comparisons of aTNF or tofacitinib in combination with MTX compared with each respective monotherapy are required to validate this finding.

Limitations

The evidence of efficacy for all interventions was obtained from RCTs identified by means of a systematic literature review. We do not believe there were any unpublished primary trials that should have been consulted for this study. We came to this conclusion by comparing the identified trials with information from ClinicalTrials.gov. In general, funnel plots can help provide information regarding the presence of publication bias. However, the number of studies for each direct comparison is too small to generate meaningful funnel plots.

It is important to realize that the value of randomization holds within trials but not across trials. As such, it is possible that there are differences in study and patient characteristics across studies that are modifiers of the treatment effects. If the distribution of treatment effect modifiers is imbalanced across the different types of direct comparisons (i.e., the different edges), the indirect comparison obtained with the network meta-analysis will be biased. The longer the path concerning an indirect comparison of interest, the more we rely on the transitivity assumption and the more we trust that there are no systematic differences in treatment effect modifiers along all the edges of the path.

The studies do not show clear differences in demographics and patient characteristics regarding swollen and tender joint counts, ESR, and CRP levels, making these factors unlikely to have been sources of bias. Disease duration showed variation across studies, but we did not observe systematic differences in the distribution of disease duration across different types of direct comparisons. As such, disease duration could not have been a cause of heterogeneity (variation in true treatment effect across studies compared) but was unlikely to bias the indirect comparisons. Of course, there is always the risk of unmeasured

differences in patient characteristics or other differences in contextual factors between studies that result in unmeasured confounding bias in indirect comparisons.

In this context, it is relevant to mention that placebo responses were lower in the certolizumab trials than in the other aTNF trials.[36,41] Adjustment with a meta-regression model for differences in placebo response across the aTNF trials of certolizumab and other aTNFs resulted in similar ORs (analysis not shown), suggesting that the greater ORs observed in the certolizumab trials might have been attributed to the low placebo response in the trials and not to different efficacy. This finding supports our approach to consider the different aTNFs as 1 class. With the results of different aTNF trials pooled as 1 class, the heterogeneity in ORs across the different aTNF trials was acknowledged by a random effects approach. We did not adjust for differences in placebo response in the network meta-analysis because it did not result in biased indirect comparisons between the classes. That said, the responses for aTNF as a class in Figure 3 may be marginally overestimated compared with the presented placebo and MTX responses.

The indirect comparison of aTNF with and without MTX spans multiple connection nodes in the network (depicted in Figure 2). Not only does this require a greater assumption of transitivity, it also results in relative treatment effect estimates that are not very precise (i.e., relatively wide 95% CrIs). Tofacitinib monotherapy and tofacitinib in combination therapy with MTX are also linked through a long path that includes pooled aTNFs. This may artificially skew the comparison between these treatments, and caution must be taken when interpreting the results.

Another limitation of the current analysis is the sole focus on ACR responses. Although ACR response is a composite measure that captures improvement in tender and swollen joint counts, patient and physician global assessment of disease, pain, CRP, and disability, the analysis does not provide information about how the efficacy of biologics with and without MTX compares for these different components of ACR response. It also does not make a distinction in a response obtained from a patient with a reduction in all components and a response based on improvement in only 3 of the 5 components. Furthermore, because this study did not address differences in risk from adverse events, only the benefit, rather than the risk/benefit, can be compared. Unfortunately, such a risk/benefit analysis of relatively short-term RCT data would not provide a valid picture associated with long-term use.

Although the MTX doses used in the studies are not necessarily reflective of doses used in clinical practice, they decreased the variability between studies, which is a strength of the analysis and underscores the importance of comparing agents in combination with MTX and as monotherapy simultaneously as part of 1 network, showing the magnitude of the effect of concomitant MTX use for each treatment option.

It has often been suggested that the efficacy of tocilizumab, as measured by composite end points such as ACR and Disease Activity Score response, should be interpreted with caution because of its strong effect on CRP, a component of these end points. In the more recent tocilizumab trials, however (including ACT-RAY and ADACTA, which provide the monotherapy data for the network meta-analysis), these composite end points are exclusively calculated using ESR values, not CRP, thus avoiding this potential CRP bias. Post hoc analysis of ADACTA using the Clinical Disease Activity Index (CDAI)—a parameter that does not include CRP or ESR—to compare disease activity and remission rates confirms the significant efficacy difference between the 2 treatment arms, as shown by the primary end point.[61]

Conclusions

Based on a network meta-analysis involving indirect comparisons of RCT findings, we found that aTNF, abatacept, tocilizumab, and tofacitinib in combination with MTX had comparable ACR responses in DMARD-IR patient populations. Anakinra in combination with MTX was less efficacious than the other novel DMARDs in combination with MTX. In monotherapy, tocilizumab may be associated with a higher ACR response than observed with aTNF or tofacitinib. ACR responses with tocilizumab in combination with MTX were similar to those of tocilizumab monotherapy, whereas aTNF in combination with MTX demonstrated greater ACR responses than aTNF monotherapy. These findings suggest tocilizumab is a valuable treatment option for patients who cannot tolerate MTX or are not compliant with an MTX regimen. This conclusion is increasingly being reflected in clinical and payer guidelines in many countries, with some of these guidelines recommending, or even mandating, its use as a first-line biologic in patients who cannot take MTX.

Authors

FELICITY BUCKLEY, MA, was (at the time of this study) Senior Research Associate, Department of HEOR and Strategic Market Access, Mapi, Boston, Massachusetts; AXEL FINCKH, MD, PhD, is Professor, Rheumatology Division, Geneva University Hospital, Geneva, Switzerland; TOM W. J. HUIZINGA, MD, PhD, is Professor, Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands; FRED DEJONCKHEERE, MD, MSc, is International Payer Strategy Leader, Department of Global Pricing and Market Access, F. Hoffmann-La Roche, Basel, Switzerland; and JEROEN P. JANSEN, PhD, is Adjunct Assistant Professor of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Massachusetts.

AUTHOR CORRESPONDENCE: Felicity Buckley, MA, E-mail: felicitybuckley@gmail.com.

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Buckley and Jansen were responsible for study design, systematic review, analysis and interpretation of data, and writing the manuscript. Finckh and Huizinga were responsible for interpretation of data and writing the manuscript. Dejonckheere contributed to study design and writing the manuscript. All authors participated equally in revising and approving the final manuscript.

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APPENDIX A Search Strategy Terms

#1 rheumatoid arthritis
#2 antirheumatic agent
#3 (#1 AND #2)
#4 adalimumab OR Humira
#5 infliximab OR Remicade
#7 golimumab OR Simponi OR CNTO 148
#8 certolizumab OR Cimzia OR CDP870
#9 tocilizumab OR Actemra OR RoActemra
#10 rituximab OR Rituxan OR Mabthera
#11 abatacept OR Orencia
#12 anakinra OR Kineret
#13 (tofacitinib or tasocitinib or CP-690550).ti,ab.
#14 tumor necrosis factor OR tumor necrosis factor inhibitor OR tumor necrosis factor blocker OR tumor necrosis factor receptor OR anti- tumor necrosis factor OR TNF OR anti-TNF
#15 biologic OR biological
#16 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 randomized controlled trial OR randomized-controlled-trial OR controlled-clinical-trial OR randomized OR clinical trial OR random OR RCT OR random allocation OR double-blind method OR single-blind method OR placebo
#18 (#3 AND #16 AND #17)
#19 Limit #18 to Humans, Adults, and the years 1990-2011

APPENDIX B Treatment Effects for All Contrasts in Terms of OR of ACR50 Response Along with 95% CrI and Probability That Treatment Is Better Than Comparator

		Comparator									
Intervention		**Placebo**	**Placebo + MTX**	**aTNF**	**TOF 5mg**	**TCZ**	**ABT + MTX**	**ANA + MTX**	**aTNF + MTX**	**TOF 5mg + MTX**	**TCZ + MTX**
Placebo	OR (95% CrI)	1.00 (1,1)	0.27 (0.04, 1.80)	0.15 (0.06, 0.33)	0.20 (0.05, 0.83)	0.06 (0.02, 0.24)	0.07 (0.01, 0.47)	0.11 (0.01, 1.01)	0.05 (0.01, 0.35)	0.06 (0.01, 0.46)	0.05 (0.01, 0.29)
	P(better)	NA	0.08	<0.01	0.01	<0.01	0.01	0.03	<0.01	<0.01	<0.01
Placebo + MTX	OR (95% CrI)	3.66 (0.56, 26.40)	1.00 (1, 1)	0.56 (0.10, 3.17)	0.74 (0.07, 8.55)	0.24 (0.06, 0.88)	0.24 (0.14, 0.41)	0.41 (0.13, 1.25)	0.19 (0.13, 0.27)	0.22 (0.11, 0.44)	0.19 (0.09, 0.41)
	P(better)	0.92	NA	0.23	0.39	0.02	<0.01	0.05	<0.01	<0.01	<0.01
aTNF	OR (95% CrI)	6.65 (3.05, 15.43)	1.80 (0.32, 10.07)	1.00 (1, 1)	1.34 (0.25, 7.07)	0.43 (0.14, 1.26)	0.43 (0.07, 2.62)	0.74 (0.09, 5.64)	0.35 (0.06, 1.95)	0.40 (0.06, 2.59)	0.34 (0.07, 1.54)
	P(better)	>0.99	0.77	NA	0.64	0.05	0.16	0.37	0.10	0.15	0.07
TOF 5mg	OR (95% CrI)	4.98 (1.21, 21.62)	1.36 (0.12, 14.42)	0.75 (0.14, 3.95)	1.00 (1, 1)	0.32 (0.04, 2.31)	0.33 (0.03, 3.75)	0.55 (0.04, 7.56)	0.26 (0.02, 2.89)	0.30 (0.02, 3.63)	0.26 (0.03, 2.47)
	P(better)	0.99	0.61	0.36	NA	0.12	0.17	0.32	0.13	0.16	0.11
TCZ	OR (95% CrI)	15.51 (4.12, 62.04)	4.20 (1.14, 15.56)	2.34 (0.80, 7.05)	3.13 (0.43, 23.22)	1.00 (1, 1)	1.01 (0.24, 4.14)	1.72 (0.30, 9.58)	0.82 (0.20, 3.06)	0.93 (0.22, 4.12)	0.81 (0.28, 2.25)
	P(better)	>0.99	0.98	0.95	0.88	NA	0.51	0.75	0.37	0.46	0.32
ABT + MTX	OR (95% CrI)	15.25 (2.13, 122.40)	4.15 (2.43, 7.19)	2.30 (0.38, 14.49)	3.04 (0.27, 38.72)	0.99 (0.24, 4.12)	1.00 (1, 1)	1.71 (0.48, 5.92)	0.80 (0.45, 1.38)	0.92 (0.41, 2.16)	0.79 (0.31, 2.05)
	P(better)	0.99	>0.99	0.84	0.83	0.49	NA	0.81	0.20	0.42	0.30
ANA + MTX	OR (95% CrI)	8.95 (0.99, 87.80)	2.44 (0.80, 7.81)	1.35 (0.18, 10.59)	1.80 (0.13, 26.84)	0.58 (0.10, 3.35)	0.59 (0.17, 2.09)	1.00 (1, 1)	0.47 (0.14, 1.53)	0.54 (0.15, 2.12)	0.47 (0.12, 1.85)
	P(better)	0.97	0.95	0.63	0.68	0.25	0.19	NA	0.09	0.17	0.12
aTNF + MTX	OR (95% CrI)	18.83 (2.85, 148.01)	5.16 (3.74, 7.53)	2.85 (0.51, 17.67)	3.79 (0.35, 47.14)	1.22 (0.33, 4.94)	1.24 (0.73, 2.23)	2.11 (0.65, 7.05)	1.00 (1, 1)	1.15 (0.59, 2.42)	0.98 (0.44, 2.36)
	P(better)	>0.99	>0.99	0.90	0.87	0.63	0.80	0.91	NA	0.66	0.48
TOF 5mg + MTX	OR (95% CrI)	16.47 (2.19, 129.20)	4.49 (2.25, 8.70)	2.51 (0.39, 15.67)	3.30 (0.28, 42.02)	1.07 (0.24, 4.60)	1.08 (0.46, 2.46)	1.84 (0.47, 6.79)	0.87 (0.41, 1.68)	1.00 (1, 1)	0.86 (0.30, 2.33)
	P(better)	>0.99	>0.99	0.85	0.84	0.54	0.58	0.83	0.34	NA	0.38
TCZ + MTX	OR (95% CrI)	19.23 (3.45, 114.60)	5.22 (2.45, 11.39)	2.90 (0.65, 13.75)	3.86 (0.41, 38.66)	1.24 (0.44, 3.61)	1.26 (0.49, 3.24)	2.14 (0.54, 8.43)	1.02 (0.42, 2.29)	1.16 (0.43, 3.33)	1.00 (1, 1)
	P(better)	>0.99	>0.99	0.93	0.89	0.68	0.70	0.88	0.52	0.62	NA

ABT = abatacept; ACR50 = 50% improvement in American College of Rheumatology criteria; ANA = anakinra; aTNF = anti-tumor necrosis factor; CrI = credible interval; mg = milligram; MTX = methotrexate; NA = not applicable; OR = odds ratio; P(better) = probability that treatment (in row) is showing greater response than comparator (in column); TCZ = tocilizumab; TOF = tofacitinib.

APPENDIX C Treatment Effects for All Contrasts in Terms of OR of ACR70 Response Along with 95% CrI and Probability That Treatment Is Better Than Comparator

Intervention		Comparator									
		Placebo	Placebo + MTX	aTNF	TOF 5mg	TCZ	ABT + MTX	ANA + MTX	aTNF + MTX	TOF 5mg + MTX	TCZ + MTX
Placebo	OR (95% CrI)	1.00 (1, 1)	0.31 (0.03, 2.66)	0.07 (0.01, 0.24)	0.27 (0.05, 1.22)	0.03 (0.00, 0.16)	0.06 (0.00, 0.58)	0.09 (0.01, 1.17)	0.06 (0.00, 0.47)	0.03 (0.00, 0.34)	0.03 (0.00, 0.23)
	P(better)	NA	0.11	<0.01	0.04	<0.01	0.01	0.03	0.01	<0.01	<0.01
Placebo + MTX	OR (95% CrI)	3.26 (0.38, 39.62)	1.00 (1, 1)	0.23 (0.04, 1.38)	0.88 (0.06, 15.52)	0.11 (0.02, 0.42)	0.21 (0.11, 0.37)	0.30 (0.07, 1.22)	0.18 (0.11, 0.26)	0.11 (0.05, 0.24)	0.11 (0.04, 0.27)
	P(better)	0.89	NA	0.05	0.46	<0.01	<0.01	0.04	0.04	<0.01	<0.01
aTNF	OR (95% CrI)	14.00 (4.23, 75.38)	4.26 (0.73, 26.83)	1.00 (1, 1)	3.79 (0.50, 35.41)	0.45 (0.15, 1.39)	0.89 (0.13, 5.90)	1.29 (0.13, 13.11)	0.78 (0.12, 4.82)	0.45 (0.07, 3.57)	0.47 (0.10, 2.29)
	P(better)	>0.99	0.95	NA	0.90	0.06	0.44	0.60	0.37	0.18	0.13
TOF 5 mg	OR (95% CrI)	3.76 (0.82, 20.18)	1.14 (0.06, 17.29)	0.26 (0.03, 2.01)	1.00 (1, 1)	0.12 (0.01, 1.19)	0.24 (0.01, 3.70)	0.34 (0.01, 7.36)	0.21 (0.01, 3.08)	0.12 (0.01, 2.15)	0.12 (0.01, 1.61)
	P(better)	0.96	0.54	0.10	NA	0.03	0.13	0.23	0.11	0.06	0.05
TCZ	OR (95% CrI)	31.19 (6.23, 242.41)	9.42 (2.40, 40.26)	2.22 (0.72, 6.82)	8.36 (0.84, 103.30)	1.00 (1,1)	1.97 (0.43, 9.08)	2.85 (0.40, 21.09)	1.72 (0.40, 7.25)	1.00 (0.22, 5.62)	1.05 (0.37, 3.07)
	P(better)	>0.99	>0.99	0.94	0.97	NA	0.85	0.87	0.80	0.50	0.55
ABT + MTX	OR (95% CrI)	15.69 (1.71, 208.60)	4.80 (2.71, 9.34)	1.12 (0.17, 7.50)	4.19 (0.27, 83.54)	0.51 (0.11, 2.31)	1.00 (1, 1)	1.46 (0.30, 6.86)	0.88 (0.47, 1.59)	0.51 (0.21, 1.47)	0.54 (0.18, 1.60)
	P(better)	0.99	>0.99	0.56	0.87	0.15	NA	0.70	0.30	0.09	0.11
ANA + MTX	OR (95% CrI)	11.17 (0.85,192.01)	3.30 (0.82, 14.83)	0.78 (0.08, 7.42)	2.96 (0.14, 74.77)	0.35 (0.05, 2.52)	0.69 (0.15, 3.34)	1.00 (1, 1)	0.60 (0.13, 2.72)	0.36 (0.07, 1.99)	0.37 (0.07, 2.07)
	P(better)	0.97	0.96	0.40	0.77	0.13	0.30	NA	0.23	0.10	0.11
aTNF + MTX	OR (95% CrI)	17.84 (2.13, 237.71)	5.50 (3.80, 8.85)	1.28 (0.21, 8.42)	4.85 (0.32, 95.11)	0.58 (0.14, 2.51)	1.14 (0.63, 2.13)	1.66 (0.37, 7.44)	1.00 (1, 1)	0.59 (0.28, 1.47)	0.61 (0.23, 1.69)
	P(better)	0.99	>0.99	0.63	0.89	0.20	0.70	0.77	NA	0.11	0.15
TOF 5mg + MTX	OR (95% CrI)	30.84 (2.95, 403.71)	9.30 (4.10, 20.36)	2.21 (0.28, 14.55)	8.32 (0.47, 154.70)	1.00 (0.18, 4.62)	1.95 (0.68, 4.86)	2.81 (0.50, 13.39)	1.70 (0.68, 3.61)	1.00 (1, 1)	1.04 (0.29, 3.36)
	P(better)	>0.99	>0.99	0.82	0.94	0.50	0.91	0.90	0.89	NA	0.53
TCZ + MTX	OR (95% CrI)	29.53 (4.35, 295.43)	8.95 (3.72, 23.36)	2.12 (0.44, 9.84)	8.00 (0.62,122.50)	0.95 (0.33, 2.72)	1.86 (0.63, 5.61)	2.72 (0.48, 15.04)	1.63 (0.59, 4.40)	0.96 (0.30, 3.50)	1.00 (1, 1)
	P(better)	>0.99	>0.99	0.87	0.95	0.45	0.89	0.89	0.85	0.47	NA

ABT = abatacept; ACR70 = 70% improvement in American College of Rheumatology criteria; ANA = anakinra; aTNF = anti-tumor necrosis factor; CrI = credible interval; mg = milligram; MTX = methotrexate; NA = not applicable; OR = odds ratio; P(better) = probability that treatment (in row) is showing greater response than comparator (in column); TCZ = tocilizumab; TOF = tofacitinib.