Tofacitinib Versus Biologic Treatments in Patients With Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Tumor Necrosis Factor Inhibitors: Results From a Network Meta-analysis

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ABSTRACT

Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). This analysis compared the efficacy and safety of tofacitinib with biologic disease-modifying antirheumatic drugs in patients with RA and a prior inadequate response (IR) to tumor necrosis factor inhibitors (TNFi).

Methods: A systematic literature review identified 5 randomized placebo-controlled trials that evaluated tofacitinib or biologic disease-modifying antirheumatic drugs (bDMARDs) against placebo in patient populations with RA with a prior IR to TNFi. The definition of TNFi-IR varied across studies, and included patients with an IR or who had failed treatment with TNFi for any reason. A network meta-analysis was conducted comparing study data with regard to American College of Rheumatology response rates and Health Assessment Questionnaire-Disability Index improvement at weeks 12 and 24, rates of treatment withdrawal due to all causes; adverse events (AEs) and lack of efficacy; and rates of AEs, serious AEs, and serious infections.

Findings: The 5 trials included a total of 2136 patients. Tofacitinib 5 mg twice daily combined with methotrexate was found to have relative risk estimates of American College of Rheumatology responses and change from baseline in Health Assessment Questionnaire-Disability Index score comparable with abatacept, golimumab, rituximab, and tocilizumab combined with conventional synthetic disease-modifying antirheumatic drugs. Withdrawal rates from trials due to all causes and AEs were comparable between treatments, and tofacitinib had a lower rate of withdrawals due to lack of efficacy. Rates of AEs and HAQ-DI were comparable between tofacitinib, other active treatments, and placebo. No serious infections were reported with tofacitinib during the placebo-controlled period (up to week 12) in this study population; rates of serious infection with other active treatments were generally low and similar to placebo.

Implications: During a 24-week period, tofacitinib had efficacy and rates of AEs comparable with currently available bDMARDs in the treatment of patients with RA who had a prior IR to TNFi. ClinicalTrials.gov identifiers: ORAL Step, NCT00960440; ATTAIN, NCT00124982; GO-AFTER, NCT00299546; RADIATE, NCT00106522; REFLEX, NCT00462345. (*Clin Ther*. 2016;38:2628–2641) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: disease-modifying antirheumatic drugs, rheumatoid arthritis, tofacitinib, tumor necrosis factor inhibitors.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and disabling autoimmune disease that leads to inflammation and destruction of the joints and surrounding tissues. The ultimate goal of treatment is to achieve remission or to slow disease progression if remission is not possible, with low disease activity recognized as an acceptable therapeutic goal.[1–3] Current RA management guidelines[1–4] recommend initial treatment with

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conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate. Patients with an inadequate response (IR) or intolerance to csDMARDs are generally prescribed biologic disease-modifying antirheumatic drugs (bDMARDs),[5] usually in combination with methotrexate. Patients who do not respond adequately to treatment with tumor necrosis factor inhibitors (TNFi)—the largest class of bDMARDs (etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab)—are generally prescribed another drug of the same class or a bDMARD with an alternative mechanism of action.[6] Other bDMARDs recommended by the American College of Rheumatology (ACR), European League Against Rheumatism, and National Institute for Health and Care Excellence, include monoclonal antibodies against B cells (rituximab), blockers of T-cell activation (abatacept), and the interleukin-6 receptor antagonist tocilizumab.

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. Tofacitinib preferentially inhibits signaling by receptors associated with JAK1 and JAK3, with functional selectivity over JAK2.[7,8] By interfering with signaling pathways, tofacitinib disrupts the inflammatory process and leads to improvement in disease activity.[9] Six Phase III randomized controlled trials (RCTs) and 2 long-term extension studies have reported the efficacy and safety of tofacitinib 5 and 10 mg BID, as monotherapy or in combination with csDMARDs, in patients with an IR to csDMARDs or bDMARDs, and in methotrexate-naïve patients with active RA.[10–16]

The ORAL Step trial (ClinicalTrials.gov identifier: NCT00960440) investigated the effectiveness of tofacitinib in patients with an IR to TNFi (TNFi-IR population).[10] This 6-month randomized, double-blind, Phase III trial assessed the efficacy safety of tofacitinib 5 and 10 mg BID combined with methotrexate in TNFi-IR patients with moderate to severe RA. Patients treated with tofacitinib 5 and 10 mg BID demonstrated rapid improvements in RA symptoms and physical function compared with placebo, with a safety profile consistent with previous studies of tofacitinib for RA.[10]

The available evidence for the efficacy of bDMARDs in TNFi-IR patients is limited to a small number of RCTs, none of which directly compared bDMARD treatments. In the absence of an RCT providing direct comparison of all treatments of interest, a network meta-analysis can be utilized to combine data from multiple RCTs to allow inferences on treatment comparisons not directly available.[17–20] The objective of the present analysis was to compare the efficacy and safety of tofacitinib 5 mg BID relative with bDMARDs for the treatment of RA in TNFi-IR patients by means of a network meta-analysis based on the available evidence from RCTs. The tofacitinib 5 mg BID dose was chosen for comparison, rather than 10 mg BID, as this is the recommended dose in the majority of countries in which tofacitinib has been approved for the treatment of RA. Published literature is available comparing efficacy and safety of bDMARDs in TNFi-IR patients using network meta-analyses. Therefore, the aim of this analysis was to specifically compare bDMARDs with the more recently approved drug, tofacitinib, and not with one another.[21,22]

METHODS

Retrieval of Published Studies

A systematic literature search was performed to identify studies evaluating the efficacy and safety of bDMARDs as monotherapy or in combination with csDMARDs in TNFi-IR patients, published from January 1990 to June 2013. The Ovid (comprising MEDLINE and Embase) and Cochrane databases, and abstracts from the ACR 2012 conference and the European League Against Rheumatism 2012 and 2013 conferences, were searched using a predefined search strategy with terms related to RA, tofacitinib, bDMARDs, and RCTs (Supplemental Material).

Inclusion and Exclusion Criteria

The analysis included RCTs of Phase II or beyond that fulfilled the criteria described here. Each identified study was assessed for inclusion by 2 independent reviewers.

Each trial must have studied an adult patient population with moderate to severe RA with IR or failed treatment with TNFi, as defined in each trial. The definition of TNFi-IR could include IR to, or intolerance of, TNFi therapy, patients discontinued primarily due to lack of efficacy and patients who had been treated with more than 1 dose of TNFi therapy and could have discontinued for any reason. Each study must have assessed tofacitinib or 1 or more of

the following bDMARDs: abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, and tocilizumab, either as monotherapy or in combination with other csDMARDs. The drugs selected were all currently approved for patients with moderate to severe RA. Certolizumab pegol and anakinra were not included, as there were no data available in the TNFi-IR population. Within each trial, the bDMARD must have been presented in comparison with either placebo or 1 of the other active interventions. Comparisons were excluded if they were limited to different doses or routes of administration of the active agent. In addition, only studies published in English were included, and studies on exclusively Asian populations were excluded.

Quality Assessment

Each of the trials identified by the systematic literature review were evaluated for validity by applying 2 quality-assessment instruments, the Jadad Criteria[23] and the Quality Assessment of Studies according to Centre for Reviews and Dissemination.[24] Study quality was not a criterion for exclusion, and so no minimum score was adopted a priori. The Quality Assessment of Studies tool comprises 7 detailed questions about studies. Quality assessments were conducted by 1 rater and 1 checker, and were not explicitly used for analysis but provided additional information to determine quality of evidence to support interpretation of the results. All studies were randomized and double-blind, and included a description of withdrawals.

Data Extraction

For each study meeting the inclusion criteria, data were extracted on study design, baseline population characteristics, interventions, and the following efficacy and safety outcomes: improvement in ACR criteria of 20%, 50%, and 70% from baseline (ACR20, ACR50, and ACR70 response) at weeks 12 and 24; change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at weeks 12 and 24; withdrawals due to all causes, AEs, and lack of efficacy; and AEs, serious adverse events (SAEs), and infections.

Statistical Analysis

Data from the included studies were combined and indirectly compared by means of a network meta-analysis.[17-20] The network meta-analysis was performed within a Bayesian framework and involved data, a likelihood distribution, a model with parameters, and prior distributions for these parameters.[25]

The ACR response rate data were analyzed separately for ACR20, ACR50, and ACR70 responses with a binomial likelihood function and logit link. An alternative model with a multinomial likelihood function and probit link was employed to analyze the ACR20, ACR50, and ACR70 response criteria simultaneously.[26] This model assumes an underlying continuous ACR distribution, which had been categorized by specifying different cutoffs ($\geq$20%, $\geq$50% and $\geq$70% improvement), at which point an individual moves from one category to the next and assumes that the treatment effect is the same regardless of the cutoff. The treatment effects for ACR20, ACR50, and ACR70 estimated with the 2 models might not be consistent if not all studies provide data for all categories.

Continuous data for change from baseline in HAQ-DI score were analyzed using a normal likelihood function and identity link. The data on withdrawals and AEs were transformed into rates and analyzed with a log-linear model with a Poisson likelihood. Using the models, the relative treatment effect of each intervention compared with placebo was estimated, and these basic parameters were used to subsequently obtain estimates of the relative efficacy between tofacitinib and each of the comparator interventions.

To avoid the influence of the prior distributions required for the Bayesian analyses, non-informative prior distributions were used for all model parameters; prior distributions were normal with a mean of 0 and a variance of 10^4. The parameters of the different models were estimated using a Markov chain Monte Carlo method as implemented in the OpenBUGS software.[27] Relative risk estimates were calculated along with 95% credible intervals (CrIs; when using Bayesian probability distributions, CrI are analogous to confidence intervals) obtained from the posterior distributions.

RESULTS

Study Selection

The literature search of the Ovid and Cochrane databases returned 2737 potentially relevant publications (Figure 1). Review of these abstracts led to exclusion of 2680 records, primarily due to duplication (n = 1130) and failure to meet the

selection criteria for study population (n = 357) or design (n = 589). Review of the remaining 57 full-text publications led to exclusion of a further 49 records that did not meet the selection criteria for study population (n = 23), study design (n = 19), intervention (n = 1), comparator (n = 1), study outcomes (n = 4), or were duplicates (n = 1). The remaining 8 publications, relating to 5 separate RCTs, were selected for the analysis.[10,28-34]

A search of conference abstracts returned 1053 abstracts (Figure 1). After review of abstract titles, 818 abstracts were excluded. After a full review, all other abstracts were excluded because they did not meet the selection criteria for the study population (n = 98), study design (n = 55), intervention (n = 6), comparator (n = 9), study outcomes (n = 24), or they were duplicates (n = 43).

Study Characteristics

The characteristics of the 5 RCTs identified for inclusion in this analysis are summarized in the Table. The included studies investigated the efficacy and safety of tofacitinib (ORAL Step, ClinicalTrials.gov identifier: NCT00960440),[10] abatacept (ATTAIN trial, NCT00124982),[30,34] golimumab (GO-AFTER trial, NCT00299546),[32] tocilizumab (RADIATE trial, NCT00106522),[29,33] and rituximab (REFLEX trial, NCT00462345)[28,31] (Figure 2).

All were multicenter, randomized, double-blind, and international Phase III trials. In all trials except 1, the treatment drug was administered in combination with csDMARDs: tofacitinib, tocilizumab, and rituximab were administered in combination with methotrexate; and golimumab was administered with methotrexate, sulfasalazine, or

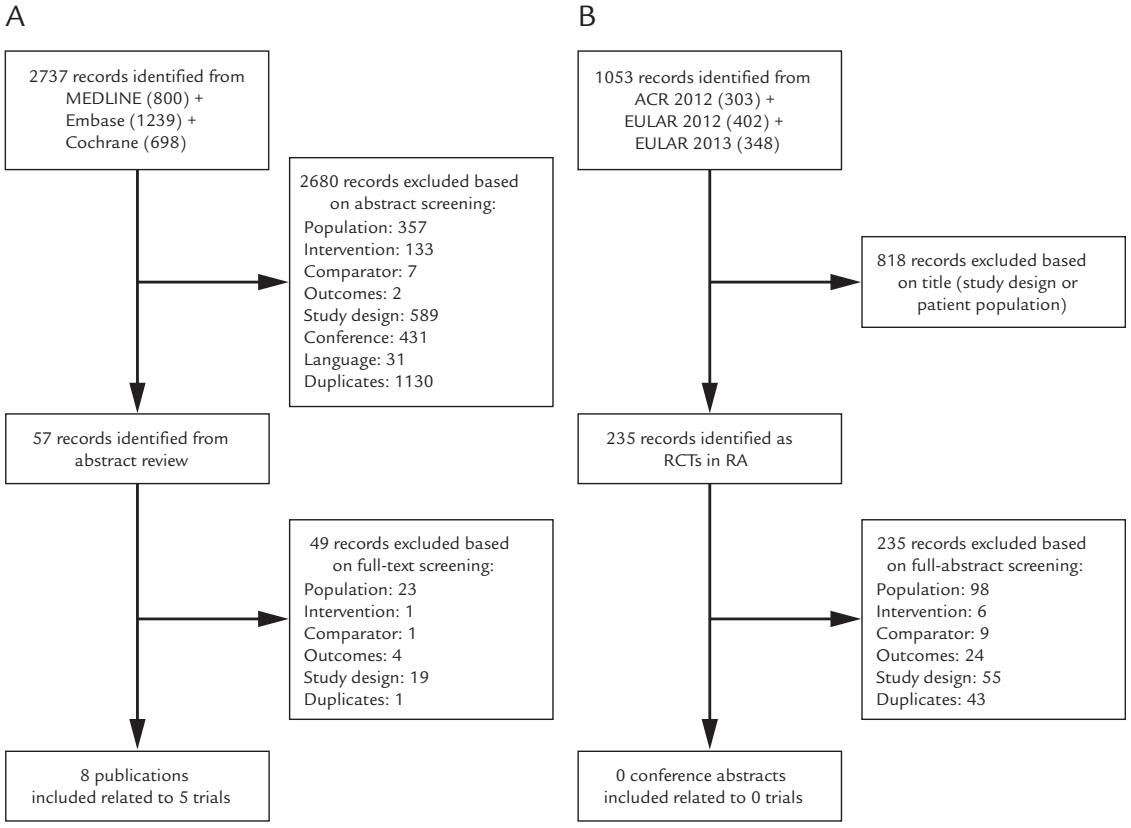

Figure 1. Flow diagram of study identification and selection process. (A) Ovid (MEDLINE and Embase) and Cochrane searches; and (B) conference abstract search. ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; RCT = randomized controlled trial; RA = rheumatoid arthritis.

Table. Summary of study characteristics, patient demographics and baseline characteristics (all studies were multicenter, randomized, double-blinded, Phase III trials).

Study Characteristics	Tofacitinib	Abatacept	Golimumab	Tocilizumab	Rituximab
First author, year	Burmester, 2013	Genovese, 2005 Westhovens, 2006	Smolen, 2009	Emery, 2008 Strand, 2012	Cohen, 2006 Keystone, 2008
Trial name	ORAL Step	ATTAIN	GO-AFTER	RADIATE	REFLEX
Dosage	5 mg BID	10 mg/kg, days 1, 15, and 29, then q4wk	50 mg, q4wk	8 mg/kg, q4wk	1000 mg, 2 wk apart
Concomitant DMARD treatment	Methotrexate	Oral DMARD,* anakinra	Methotrexate; sulfasalazine; hydroxychloroquine	Methotrexate	Methotrexate
Trial duration	6 mo	24 wk	24 wk	24 wk	2 y
Centers/countries	82 centers; North America, Europe and Latin America	89 centers	82 centers; Europe, Australasia, USA	North America and Western Europe	114 centers; USA, Canada, Europe, and Israel
Definition of TNFi-IR	Treated with ≥1 TNFi, withdrawn due to IR or intolerance	TNFi-IR after ≥3 mo treatment	Treated with ≥1 dose of a TNFi, ≥8–12 wk before the study drug, withdrawn due to IR or intolerance	Treated with ≥1 TNFi within the past year, withdrawn due to IR or intolerance	TNFi-IR after ≥3 mo or intolerant to ≥1 dose
Reported outcomes	Wk 12 ACR20, ACR50, and ACR70 response rates; Wk 24 ACR20, ACR50, and ACR70 response rates†; week 12 HAQ-DI; withdrawals AEs, SAEs, infections	Wk 12 ACR20, ACR50, and ACR70 response rates; wk 24 ACR20, ACR50, and ACR70 response rates; withdrawals AEs, SAEs, infections	Wk 12 ACR20, ACR50, and ACR70 response rates; wk 24 ACR20, ACR50, and ACR70 response rates; wk 12 HAQ-DI; withdrawals; AEs, SAEs, infections	Wk 12 ACR20, ACR50, and ACR70 response rates; wk 24 ACR20, ACR50, and ACR70 response rates; wk 12 HAQ-DI; withdrawals; AEs, SAEs, infections	Wk 12 ACR20, ACR50, and ACR70 response rates; wk 24 ACR20, ACR50, and ACR70 response rates; wk HAQ-DI; withdrawals; AEs, SAEs, infections

(continued)

Table. (continued).

Study Characteristics	Tofacitinib		Abatacept		Golimumab		Tocilizumab		Rituximab	
Jadad score Patient	5		4		5		3		3	
Demographics and Baseline Characteristics	Placebo	Tofacitinib	Placebo	Abatacept	Placebo	Golimumab	Placebo	Tocilizumab	Placebo	Rituximab
Patients, n	132[‡]	133[‡]	133[§]	258[§]	155[‡]	153[‡]	158[‖]	170[‖]	209[‡]	308[‡]
Age, y, mean (SD)	54.4 (11.3)	55.4 (11.5)	52.7 (11.3)	53.4 (12.4)	54.0[¶] (46.0–64.0)[#]	55.0[¶] (46.0–63.0)[#]	53.4 (13.3)	53.9 (12.7)	52.8 (12.6)	52.2 (12.2)
Female, %	80	85	80	77	85	74	79	84	81	81
Disease duration, y, mean (SD)	11.3 (0.4–47.0)[#]	13.0 (1.2–55.0)[#]	11.4 (8.9)	12.2 (8.5)	9.8[¶] (4.9–17.6)[#]	9.6[¶] (5.6–17.2)[#]	11.4 (9.2)	12.6 (9.3)	11.7 (7.7)	12.1 (8.3)
HAQ-DI score, mean (SD)	1.6 (0.7)	1.6 (0.7)	1.8 (0.6)	1.8 (0.6)	1.8[¶] (1.3–2.1)[#]	1.6[¶] (1.1–2.0)[#]	1.7 (0.6)	1.7 (0.6)	1.9 (0.5)	1.9 (0.6)
SJC, mean (SD)	17.2 (10.7)	16.2 (10.1)	22.0 (10.0)	22.3 (10.2)	14.0[¶] (9.0–23.0)[#]	14.0[¶] (9.0–25.0)[#]	18.9 (11.1)	18.9 (10.9)	22.9 (12.7)	23.4 (11.9)
TJC, mean (SD)	28.2 (16.7)	28.4 (18.3)	32.8 (13.4)	31.2 (13.0)	26[¶] (15.0–43.0)[#]	27[¶] (16.0–42.0)[#]	30.4 (16.8)	31.7 (15.4)	32.9 (15.6)	33.9 (15.2)

ACR20, ACR50, ACR70 = improvement in American College of Rheumatology criteria of 20%, 50%, and 70%, respectively; AE = adverse event; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire-Disability Index; IR = inadequate response; SAE = serious adverse event; SJC = swollen joint count; TNFi = tumor necrosis factor inhibitor; TJC = tender joint count.

[*]Oral DMARDs included methotrexate, azathioprine, penicillamine, gold, hydroxychloroquine, chloroquine, leflunomide, sulfasalazine, NSAIDs, and corticosteroids.

[†]No placebo data available.

[‡]Randomly assigned.

[§]Randomly assigned and treated.

[‖]With baseline characteristics.

[¶]Median.

[#]Range.

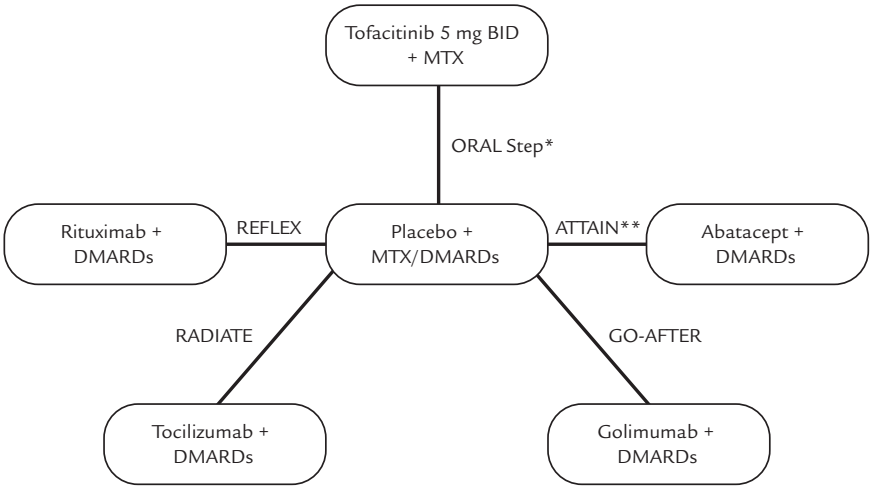

Figure 2. Network diagrams of randomized controlled trials selected for inclusion in the meta-analysis. Diagrams evaluating each outcome measure for rheumatoid arthritis patients with an inadequate response to tumor necrosis factor inhibitors. All trials reported ACR response at weeks 12 and 24, change from baseline in HAQ-DI score at week 12 compared with placebo, and withdrawals and adverse events, unless otherwise stated. *ORAL Step had no placebo arm at week 24. Comparisons for ACR responses and HAQ-DI score at week 24 used the data last observed at week 12 for the placebo arm and the data actually observed at week 24 for the active treatment arm; **ATTAIN did not report change from baseline in HAQ-DI score at week 12. ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire Disability-Index; MTX = methotrexate.

hydroxychloroquine. Abatacept was administered with either an oral csDMARD or the bDMARD anakinra.

The definition of TNFi-IR varied across studies; IR to, or intolerance of, TNFi therapy was the most common definition (tofacitinib, tocilizumab, and rituximab).[10,28,29,31,33] In the abatacept study, patients classed as TNFi-IR were discontinued primarily due to lack of efficacy.[30,34] Patients enrolled in the golimumab trial were only required to have been treated with more than 1 dose of TNFi therapy and could have discontinued for any reason before being termed TNFi-IR.[32]

Patient characteristics are summarized in the Table. The studies randomly assigned between 132 and 308 patients per treatment arm. The percentage of females ranged from 74% to 85% and mean age and disease duration were consistent across studies, ranging from 52.2 to 55.4 years and 9.6 to 13.0 years, respectively. Mean baseline HAQ-DI scores of included patients were comparable across trials, ranging from 1.6 to 1.9.

Efficacy Outcomes

ACR Response Rates at Week 12

All included RCTs reported ACR response rates around week 12. The abatacept trial[30,34] reported data for ACR20 response rates only, with data collected during week 12. The golimumab trial[32] reported ACR response rates at week 14.

All studies reported a greater proportion of patients achieving ACR20, ACR50, or ACR70 response for the active treatment group compared with each study's respective placebo at week 12 (Supplemental Table I).

Higher ACR response rates were reported with tofacitinib 5 mg BID than placebo (Figure 3) (relative risk = 2.10; 95% CrI, 1.50–2.83; relative risk = 2.86; 95% CrI, 1.77–4.44; and relative risk = 3.80; 95% CrI, 2.05–6.80, for ACR20, ACR50, and ACR70, respectively). Risk estimates of ACR response rates for tofacitinib 5 mg BID were comparable with abatacept, golimumab, rituximab, and tocilizumab at week 12 (Figure 3), demonstrating comparable efficacy between these active treatments.

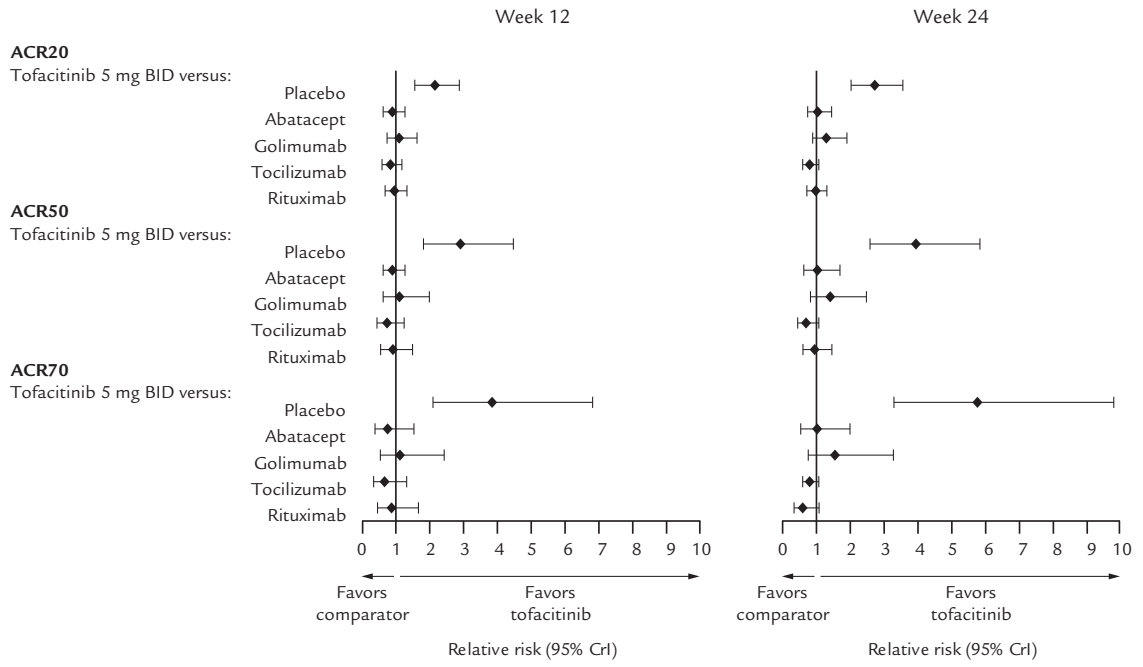

Figure 3. Forest plot for ACR20, ACR50, and ACR70 response criteria at weeks 12 and 24. Data were obtained using fixed-effects multinomial likelihood models. Diamonds show the relative risk estimate of each biologic DMARD combined with conventional synthetic DMARDs compared with tofacitinib 5 mg BID combined with methotrexate. Arms show the 95% CrI associated with each relative risk estimate. ACR20, ACR50, and ACR70 = improvement in American College of Rheumatology criteria of 20%, 50%, and 70%, respectively; CrI = credible interval; DMARD = disease-modifying antirheumatic drug.

ACR Response Rates at Week 24

All included studies reported ACR20, ACR50, and ACR70 response rates at week 24. However, due to the reassignment design of the tofacitinib trial, the analyses at week 24 used the data last observed at week 12 for the placebo arm and the data actually observed at week 24 for the active arm. In addition, the golimumab, rituximab, and tocilizumab trials offered rescue therapy to nonresponders at or after week 16. For the tocilizumab and rituximab trials, patients who received rescue therapy were classified as nonresponders for week 24 analyses; for the golimumab trial, week 16 efficacy data were carried forward for week 24 analyses.

All studies reported a greater proportion of patients achieving ACR20, ACR50, and ACR70 response for the active treatment group compared with each study's respective placebo at week 24 (Supplemental Table II). The relative risk for tofacitinib 5 mg BID versus placebo at week 24 was 2.69 (95% CrI, 1.98–3.53) for ACR20, 3.92 (95% CrI, 2.54–5.84) for ACR50, and 5.77 (95% CrI, 3.26–9.84) for ACR70 (Figure 3). Relative risks for bDMARDs versus tofacitinib at week 24 ranged from 0.74 (95% CrI, 0.53–1.01) to 1.24 (95% CrI, 0.83–1.86) for ACR20, 0.63 (95% CrI, 0.38–1.01) to 1.36 (95% CrI, 0.76–2.44) for ACR50, and from 0.53 (95% CrI, 0.27–1.02) to 1.50 (95% CrI, 0.70–3.25) for ACR70.

HAQ-DI Outcomes at Week 12

HAQ-DI data for week 12 were reported in only 4 studies; the abatacept trial did not report HAQ-DI data at this time point. The change from baseline in mean HAQ-DI score at week 12 ranged from −0.20 to 0.02 in the placebo groups and from −0.44 to −0.21 in the active treatment groups, across studies (Supplemental Table III).

Comparison of changes from baseline in HAQ-DI score suggested that tofacitinib 5 mg BID was more efficacious than placebo, and had efficacy comparable

with other interventions in terms of HAQ-DI (Figure 4). The difference in change from baseline for tofacitinib 5 mg BID versus placebo was −0.25 (95% CrI, −0.36 to −0.14). Difference in change from baseline versus bDMARDs ranged from −0.04 (95% CrI, −0.19 to 0.11) to 0.10 (95% CrI, −0.05 to 0.25).

HAQ-DI Outcomes at Week 24

All included studies reported HAQ-DI data at week 24. In the tofacitinib trial, the analyses at week 24 used the data last observed at week 12 for the placebo arm and the data actually observed at week 24 for the active arm.

Consistent with the data at week 12, tofacitinib 5 mg BID was more efficacious than placebo, and its efficacy was comparable with other interventions (Figure 4). For tofacitinib 5 mg BID versus placebo, the difference in change from baseline was −0.33 (95% CrI, −0.46 to −0.20). Difference in change from baseline versus bDMARDs ranged from −0.12 (95% CrI, −0.28 to 0.04) to 0.04 (95% CrI, −0.11 to 0.19).

Safety Outcomes

Withdrawals

Safety analyses were conducted by comparing data reported on withdrawals due to all causes, AEs, and lack of efficacy (the rituximab trial did not report withdrawals due to lack of efficacy). Because all trials but the abatacept trial imposed reassignment and rescue schemes between weeks 12 and 24, withdrawals due to all causes were defined as any patient who withdrew before reassignment or rescue therapy, and analyses were adjusted based on treatment exposure.

The percentage of patients withdrawing due to all causes, AEs, and lack of efficacy in placebo and treatment groups is summarized in Supplemental Table IV. The percentage of patients withdrawing due to all causes varied widely across studies, from

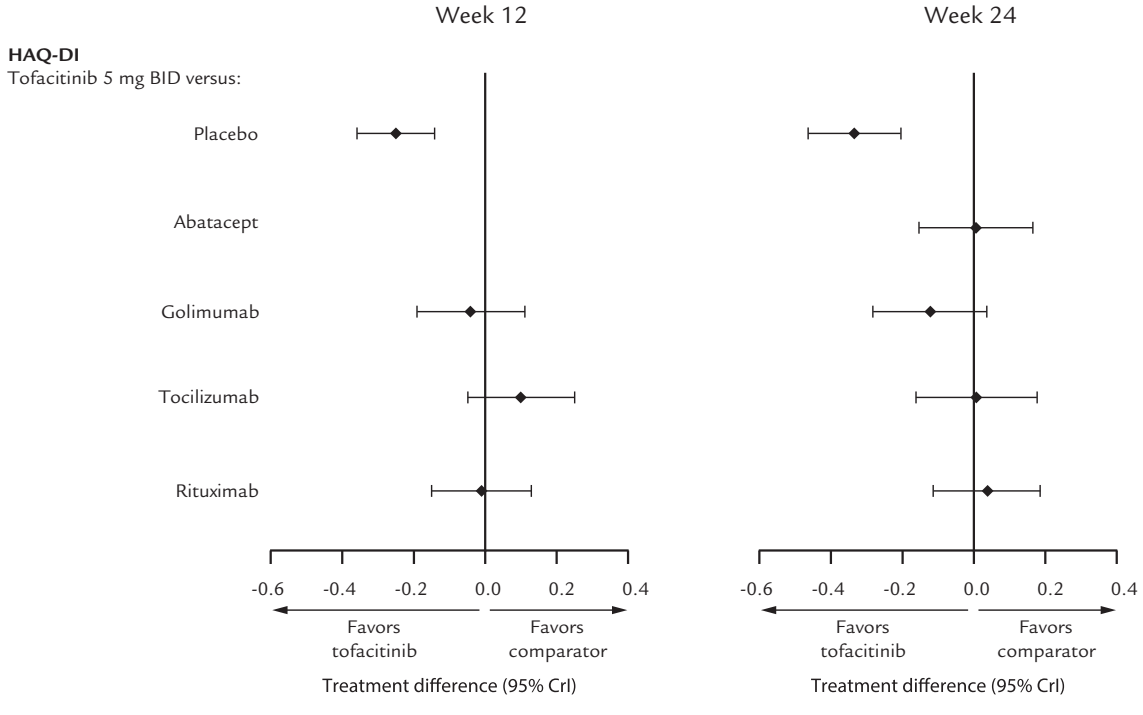

Figure 4. Forest plot for change from baseline in HAQ-DI score at weeks 12 and 24. Data were obtained using fixed-effects normal likelihood models. Diamonds show the difference in change from baseline of each biologic DMARD combined with conventional synthetic DMARDs compared with tofacitinib 5 mg BID combined with methotrexate. Arms show the 95% CrI associated with each treatment difference. CrI = credible interval; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire-Disability Index.

5% to 65% with placebo and from 2% to 33% with active treatments; the highest rate of withdrawals was reported with golimumab and the lowest with tofacitinib.

The rate of withdrawal due to all causes was similar for tofacitinib, bDMARDs, and placebo (Figure 5); the relative risk estimate for tofacitinib versus placebo was 0.46 (95% CrI, 0.09–1.84) and, compared with bDMARDs, ranged from 0.92 (95% CrI, 0.17–3.98) to 1.40 (95% CrI, 0.27–5.91). Similarly, withdrawal rates due to AEs were comparable for tofacitinib, bDMARDs, and placebo, with relative risk estimates versus tofacitinib ranging from 0.56 (95% CrI, 0.06–3.61) to 4.18 (95% CrI, 0.87–23.31). Tofacitinib 5 mg BID treatment was associated with reduced withdrawals due to lack of efficacy compared with placebo and comparator interventions, with the relative risk estimates comparing tofacitinib with placebo, abatacept, golimumab, and tocilizumab equal to zero in each case.

Adverse Events

Analyses were conducted for AEs, SAEs, and serious infections. All included studies reported data on these outcomes: at week 24 for abatacept, tocilizumab, and rituximab; at week 16 for golimumab; and at week 12 for tofacitinib. As with withdrawal analyses, each analysis took into account the different rescue therapy and reassignment schemes for each study and was adjusted for treatment exposure.

The percentages of patients experiencing AEs, SAEs, and serious infections are summarized in Supplemental Table V.

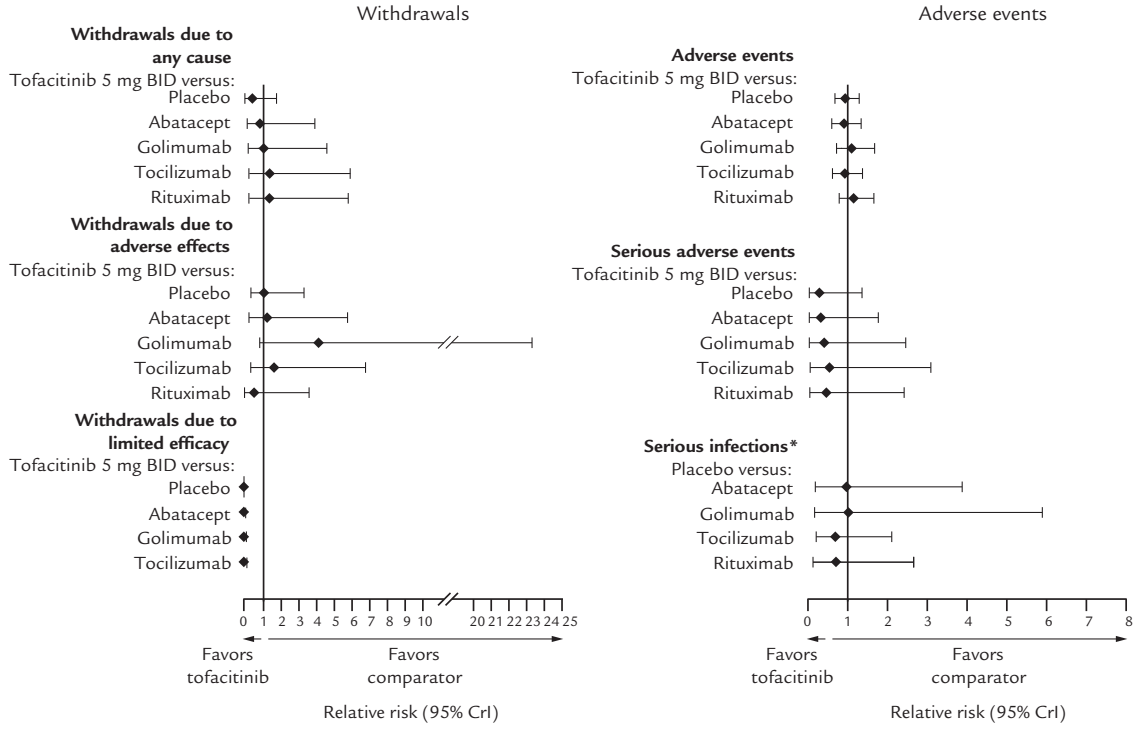

Figure 5. Forest plot for withdrawal rates (all causes, adverse events and lack of efficacy) and adverse events (all adverse events, serious adverse events and serious infections). *Risk estimates for serious infections are presented compared with placebo. Data were obtained using fixed-effects Poisson likelihood models. Diamonds show the relative risk estimate of each biologic DMARD combined with conventional synthetic DMARDs compared with tofacitinib 5 mg BID combined with methotrexate. Arms show the 95% CrI associated with each relative risk estimate. CrI = credible interval; DMARD = disease-modifying antirheumatic drug.

Tofacitinib 5 mg BID was comparable with placebo and all other interventions in terms of AEs and SAEs (Figure 5). Network meta-analysis estimates found that the risk ratios (95% CrI) of AEs for active treatment compared with placebo ranged from 0.81 (95% CrI, 0.67–0.99) (rituximab) to 1.04 (95% CrI, 0.82–1.33) (abatacept). The risk ratio for tofacitinib 5 mg BID versus placebo was 0.94 (95% CrI, 0.68–1.29). For SAEs, risk ratios versus placebo ranged from 0.29 (95% CrI, 0.04–1.36) (tofacitinib) to 0.87 (95% CrI, 0.48–1.70) (abatacept). There were no reported occurrences of serious infection up to week 12 in the trial assessing tofacitinib and, therefore, the risk ratio versus placebo could not be calculated; after week 12, 2 cases of serious infection were reported for tofacitinib 5 mg BID. For the other 4 interventions, risk ratios versus placebo of serious infections ranged from 0.98 (95% CrI, 0.17–5.76) (golimumab) to 1.45 (95% CrI, 0.47–4.85) tocilizumab) (Figure 5).

DISCUSSION

The objective of this network meta-analysis was to compare the efficacy and safety of tofacitinib 5 mg BID relative to bDMARDs for the treatment of patients with RA and a prior IR to TNFi. Indirect comparisons were made between RCTs reporting ACR response rates, HAQ-DI improvement and rates of withdrawals, AEs, SAEs, and serious infections. Five RCTs were identified that assessed tofacitinib 5 mg BID and the comparators abatacept, golimumab, tocilizumab, and rituximab in combination with DMARD therapy.

The results of this network meta-analysis of tofacitinib and bDMARDs suggest that tofacitinib 5 mg BID was more efficacious than placebo and comparable with the bDMARDs in terms of efficacy, measured by ACR response rates at weeks 12 and 24, and HAQ-DI improvement at week 12. Safety of tofacitinib 5 mg BID, assessed by rate of withdrawals due to all causes, withdrawals due to AEs and risk of AEs and SAEs, was comparable with the bDMARDs assessed in this study. No serious infections were reported with tofacitinib over 12 weeks. These data were reported at an earlier time point in the tofacitinib study than in the comparator studies, however, the analyses were adjusted for treatment exposure. Tofacitinib 5 mg BID had a lower relative risk of withdrawals due to lack of efficacy than placebo and other comparator interventions.

Network meta-analyses are an accepted technique used to combine results of multiple RCTs, to allow treatment comparisons not directly made within trials. In recent years, several network meta-analyses of bDMARD treatments for RA have been published, including an analysis of TNFi-IR patients,[22] and give comparable findings despite differences in methodology.[22,35-40] However, when conducting network meta-analyses, randomization only holds within each trial, not across trials; therefore, only relative treatment effects can be assessed. This is because differences regarding study and patient characteristics may modify the treatment effects and introduce bias to the indirect comparisons made by the network meta-analyses.

One notable difference across the network of studies, but not a likely effect modifier, was that although in all studies bDMARDs were administered in combination with csDMARDs at stable doses, the type of csDMARD varied across studies. Most administered methotrexate therapy only; however, the golimumab[32] and abatacept[30,34] studies allowed concomitant treatment with a variety of different csDMARDs.

A potential source of bias is that the definition of TNFi-IR varied across studies. IR to, or intolerance of, TNFi therapy was the most common definition (tocilizumab,[29,33] rituximab,[28,31] and tofacitinib[10] studies). However, in the abatacept study, patients classed as TNFi-IR were discontinued primarily due to lack of efficacy,[30,34] and the golimumab study included patients who had discontinued TNFi treatment for any reason $\geq$8 weeks before the first dose of study drug,[32] which may indicate a less severely affected trial population. A further potential source of bias was the different rescue schemes for nonresponders after week 12 between studies, and reassignment of the placebo arm in the tofacitinib study. This reflects the lack of consensus at the time these studies were conducted around acceptable study designs to provide rescue of nonresponders and patients assigned to placebo. In the tofacitinib study, this resulted in comparison of tofacitinib data at week 24 with placebo data from week 12, which may have magnified the treatment effect.

Due to a scarcity of studies (only 1 study for each comparison intervention relative to placebo), it was

not possible to determine the extent of bias and the level of effect these differences may have had in modifying the observed treatment effects. All studies were given a validity rating of ≥ 3 based on the Jadad Criteria (scores can range from 0 to 5, with higher scores indicating greater study validity)[23] and reported the method of randomization, blinding, and a description of withdrawals. However, when interpreting the results of this network meta-analysis, the scarcity of studies must be taken into account. In addition, given the limited number of studies in this analysis, it was not possible to adjust for any differences across studies within a modeling framework. The impact of study and patient characteristics on the outcomes are reflected in the baseline risk. Extending network meta-analytic models with treatment by covariate interactions would allow heterogeneity to be explored and the impact of bias due to similarity or consistency violations to be reduced.[18-20,41] In addition, the high level of patient withdrawals observed in some studies, particularly in the placebo group, could potentially have affected the efficacy estimates of active treatments versus placebo. However, the variation in discontinuations in the placebo arm across studies does not automatically invalidate comparisons, as it is not clear if there would be any change in the treatment effects if rates of discontinuation were different in each trial.

The efficacy and safety of tofacitinib as a second-line therapy option in patients without IR to TNFi, but with an IR to csDMARDs (including methotrexate), have been described.[11,12,14] These studies reported generally higher efficacy at week 12 with tofacitinib 5 mg BID (ACR20 response rate: 52% to 60%; change from baseline in HAQ-DI: −0.44 to −0.55), compared with that reported in the TNFi-IR population analyzed here (ACR20 response rate: 42%; change from baseline in HAQ-DI: −0.43), with similar rates of AEs.

Tofacitinib is included in the 2015 ACR guidelines for the treatment of RA, which recommend tofacitinib as a second-line option (after DMARD monotherapy), administered as either monotherapy or combination therapy.[1] The ACR guidelines state that for patients with established RA and moderate or high disease activity despite DMARD monotherapy (including methotrexate), the use of combination DMARDs or the addition of a TNFi or non-TNFi biologic or tofacitinib (all choices with or without methotrexate) is strongly recommended, with no particular order of preference. Moreover, tofacitinib may also be used as monotherapy or in combination with csDMARDs.

For third-line use, ACR recommends that if disease activity remains moderate or high despite use of a single TNFi or non-TNFi biologic, another non-TNFi biologic should be used over tofacitinib (both with or without methotrexate). However, the ACR acknowledges that evidence for this guidance is "very low." This study provides additional evidence to support the use of tofacitinib as a well-tolerated and effective therapy for patients with moderate to high disease activity who have failed at least 1 bDMARD.

CONCLUSIONS

In the absence of head-to-head comparisons of bDMARDs with tofacitinib in patients with RA and an IR to TNFi, a network meta-analysis was performed based on currently available evidence from RCTs. This analysis concluded that oral tofacitinib 5 mg BID has efficacy and rates of AEs comparable with currently available bDMARDs during a 24-week period. However, longer-term follow-up data are required to fully understand the benefit−risk profile of tofacitinib compared with bDMARDs for the treatment of RA.

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CONFLICTS OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.11.004.

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SUPPLEMENTARY MATERIAL

See Additional Tables I–V.

Additional Table I. Percentage of patients achieving ACR20, ACR50 and ACR70 responses at week 12.

	N		ACR20		ACR50		ACR70	
Treatment	Placebo	Active Treatment	Placebo	Active Treatment	Placebo	Active Treatment	Placebo	Active Treatment
Abatacept	133	256	18%*	46%*				
Golimumab†	155	153	18%	35%	6%	16%	2%	10%
Tocilizumab	160	175	15%	43%	3%	23%	0%	8%
Rituximab	201	298	20%	48%	7%	22%	4%	7%
Tofacitinib	131	132	24%*	42%*	8%*	27%*	2%*	14%*

N, number of patients; ACR20, ACR50 and ACR70, improvement in American College of Rheumatology criteria of 20%, 50% and 70%.
*Calculated using data extracted from publications.
†Golimumab ACR responses were measured at week 14.

Additional Table II. Percentage of patients achieving ACR20, ACR50 and ACR70 responses at week 24.

	N		ACR20		ACR50		ACR70	
Treatment	Placebo	Active Treatment	Placebo	Active Treatment	Placebo	Active Treatment	Placebo	Active Treatment
Abatacept	133	256	20%	50%	4%	20%	2%	10%
Golimumab	155	153	17%	34%	5%	18%	3%	12%
Tocilizumab	160	175	10%	50%	4%	29%	1%	12%
Rituximab	201	298	18%	51%	5%	27%	1%	12%
Tofacitinib	131*	132	24%†	52%†	8%†	37%†	2%†	16%†

N, number of patients; ACR20, ACR50 and ACR70, improvement in American College of Rheumatology criteria of 20%, 50% and 70%.
*Results carried from week 12.
†Calculated using data extracted from publications.

Additional Table III. Mean change from baseline in HAQ-DI score at weeks 12 and 24.

	Week 12				Week 24			
	N		HAQ-DI score Mean CFB (SE)		N		HAQ-DI score Mean CFB (SE)	
Treatment	Placebo	Active Treatment	Placebo	Active Treatment	Placebo	Active Treatment	Placebo	Active Treatment
Abatacept‡	–	–	–	–	133	256	−0.11 (0.04*)	−0.45 (0.04*)
Golimumab	155	153	0.00 (0.03*)	−0.21* (0.04*)	155	153	0.00* (0.03*)	−0.21* (0.04*)
Tocilizumab	139	151	0.02 (0.03*)	−0.33 (0.04*)	62	130	−0.05 (0.04*)	−0.39 (0.04*)
Rituximab	201	298	−0.20 (0.03*)	−0.44 (0.04*)	201	298	−0.07 (0.03*)	−0.44 (0.00*)
Tofacitinib	118	117	−0.18 (0.04)	−0.43 (0.04)	118†	103	−0.18 (0.04)†	−0.51 (0.05)

N, number of patients; HAQ-DI, Health Assessment Questionnaire-Disability Index; CFB, change from baseline; SE, standard error of the mean.
*Calculated using data extracted from publications.
†Results carried from week 12.
‡The abatacept trial did not report HAQ-DI data at week 12.

Additional Table IV. Percentage of patients withdrawing due to all causes, adverse events and lack of efficacy.

	All causes				Adverse events				Lack of efficacy			
	Placebo		Active Treatment		Placebo		Active Treatment		Placebo		Active Treatment	
Treatment	Ns	%	Ns	%	Ns	%	Ns	%	Ns	%	Ns	%
Abatacept	133	26	258	14	133	4	258	3	133	20	258	5
Golimumab	155	65	152	33	83	11	111	4	83	11	111	3
Tocilizumab	160	60	175	25	94	9	155	6	94	20	155	3
Rituximab*	209	46	308	18	129	2	307	3	–	–	–	–
Tofacitinib	132	5	133	2	132	2	133	2	132	2	133	0

All withdrawals extracted at week 24, except for the tofacitinib trial which was extracted at Week 12.
Ns, starting population.
*The rituximab trial did not report lack of efficacy data.

Additional Table V. Percentage of patients experiencing adverse events, serious adverse events and serious infections.

	Adverse events				Serious adverse events				Serious infections			
	Placebo		Active Treatment		Placebo		Active Treatment		Placebo		Active Treatment	
Treatment	Ns	%	Ns	%	Ns	%	Ns	%	Ns	%	Ns	%
Abatacept	133	71	258	80	133	11	258	11	133	2	258	2
Golimumab	155	70	152	61	155	7	152	5	155	2	152	2
Tocilizumab	160	81	175	84	160	11	175	6	160	3	175	5
Rituximab	209	88	308	85	209	10	308	7	209	1	308	2
Tofacitinib	132	57	133	53	132	5	133	2	132	0	133	0

Adverse events, serious adverse events and serious infections were extracted at week 24 for the abatacept, tocilizumab and rituximab trials, at week 16 for the golimumab trial and at week 12 for the tofacitinib trial.
Ns, starting population.

ADDITIONAL APPENDIX:
Search strategy and results.

Table A1. Ovid search. Database: MEDLINE and Embase. Date of search: June 14, 2013.

ID	Search	Hits
1	"randomized controlled trial".pt.	366764
2	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	1598709
3	(retraction of publication or retracted publication).pt.	5751
4	1 or 2 or 3	1681204
5	(animals not humans).sh.	3813858
6	((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.	5972363
7	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.	94407
8	5 or 6 or 7	9690101
9	4 not 8	1341846
10	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	1598709
11	RETRACTED ARTICLE/	6157
12	10 or 11	1604733
13	(animal$ not human$).sh,hw.	6324971
14	(book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/	6513296
15	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/	91171
16	13 or 14 or 15	12577612
17	12 not 16	1200550
18	9 or 17	1375691
19	Arthritis, Rheumatoid/	172412
20	rheumatoid arthritis.ti,ab.	151700
21	19 or 20	206726
22	(adalimumab or Humira).ti,ab.	9077
23	(etanercept or Enbrel).ti,ab.	10932
24	(infliximab or Remicade).ti,ab.	18450
25	(golimumab or Simponi or CNTO 148).ti,ab.	825
26	(tocilizumab or Actemra or RoActemra).ti,ab.	1963
27	(abatacept or Orencia or CTLA-4Ig).ti,ab.	2178
28	(tofacitinib or tasocitinib or CP-690550).ti,ab.	279
29	(rituximab or Rituxan or Mabthera).ti,ab.	26169
30	(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).ti,ab.	305310
31	(biologic or biological).ti,ab.	976386
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	1301483
33	18 and 21 and 32	2575
34	limit 33 to human	2158
35	limit 34 to humans	2158
36	limit 35 to english language	2051
37	limit 36 to yr="1990 - Current"	2039
38	remove duplicates from 37	1342

Table A2. Cochrane search. Database: Cochrane Library. Date of search: June 14, 2013.

ID	Search	Hits
#1	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees	3982
#2	rheumatoid and arthritis:ti,ab,kw	5565
#3	#1 or #2	5691
#4	adalimumab or Humira:ti,ab,kw	373
#5	etanercept or Enbrel:ti,ab,kw	586
#6	infliximab or Remicade:ti,ab,kw	706
#7	golimumab or Simponi or CNTO148:ti,ab,kw	66
#8	tocilizumab or Actemra or RoActemra:ti,ab,kw	57
# 9	abatacept or Orencia or CTLA-4Ig:ti,ab,kw	110
#10	tofacitinib or tasocitinib or CP-690550:ti,ab,kw	13
#11	rituximab or Rituxan or Mabthera:ti,ab,kw	762
#12	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:ti,ab,kw	4713
#13	biologic or biological:ti,ab,kw	19154
#14	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	24343
#15	#3 and #14	986
#16	#15 from 1990	967
#17	#16 in trials	698