ORIGINAL ARTICLE - CLINICAL TRIALS

Comparative efficacy and safety of tofacitinib, with or without methotrexate, in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials

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Abstract This study aimed to assess the relative efficacy and safety of tofacitinib 5 and 10 mg twice daily, or in combination with methotrexate (MTX), in patients with active RA. Randomized controlled trials (RCTs) examining the efficacy and safety of tofacitinib in patients with active RA were included in this network meta-analysis. We performed a Bayesian network meta-analysis to combine the direct and indirect evidence from the RCTs. Ten RCTs including 4867 patients met the inclusion criteria. There were 21 pairwise comparisons including 11 direct comparisons of seven interventions. The ACR20 response rate was significantly higher in the tofacitinib 10 mg + MTX group than in the placebo and MTX groups (OR 7.56, 95 % credible interval (CrI) 3.07–21.16; OR 3.67, 95 % CrI 2.60–5.71, respectively). Ranking probabilities based on the surface under the cumulative ranking curve (SUCRA) indicated that tofacitinib 10 mg + MTX had the highest probability of being the best treatment for achieving the ACR20 response rate (SUCRA = 0.9254), followed by tofacitinib 5 mg + MTX (SUCRA = 0.7156), adalimumab 40 mg + MTX (SUCRA = 0.6097),

tofacitinib 10 mg (SUCRA = 0.5984), tofacitinib 5 mg (SUCRA = 0.4749), MTX (SUCRA = 0.1674), and placebo (SUCRA = 0.0086). In contrast, the safety based on the number of withdrawals due to adverse events did not differ significantly among the seven interventions. Tofacitinib, at dosages 5 and 10 mg twice daily, in combination with MTX, was the most efficacious intervention for active RA and was not associated with a significant risk for withdrawals due to adverse events.

Keywords Tofacitinib · Efficacy · Safety · Rheumatoid arthritis · Network meta-analysis

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovial joint inflammation, which leads to disability and loss of quality of life [1, 2]. Intracellular pathways that include Janus kinases (JAKs) are critical to immune cell activation, proinflammatory cytokine production, and cytokine signaling [3]. Tofacitinib (CP-690,550) is a novel orally administered JAK inhibitor [4]. It selectively inhibits JAK-1, JAK-2, and JAK-3, with functional cellular specificity for JAK-1 and JAK-3 over JAK-2 [5, 6]. Tofacitinib subsequently modulates adaptive and innate immunity [6].

Disease-modifying antirheumatic drugs (DMARDs) have been used to decrease inflammation, delay bone erosion, and improve functional ability in patients with RA. Several clinical trials have attempted to evaluate the efficacy and safety of tofacitinib in patients with active RA who had an incomplete response to DMARD or methotrexate (MTX) [7–16]. A previous meta-analysis has shown that tofacitinib is effective in active patients with RA who

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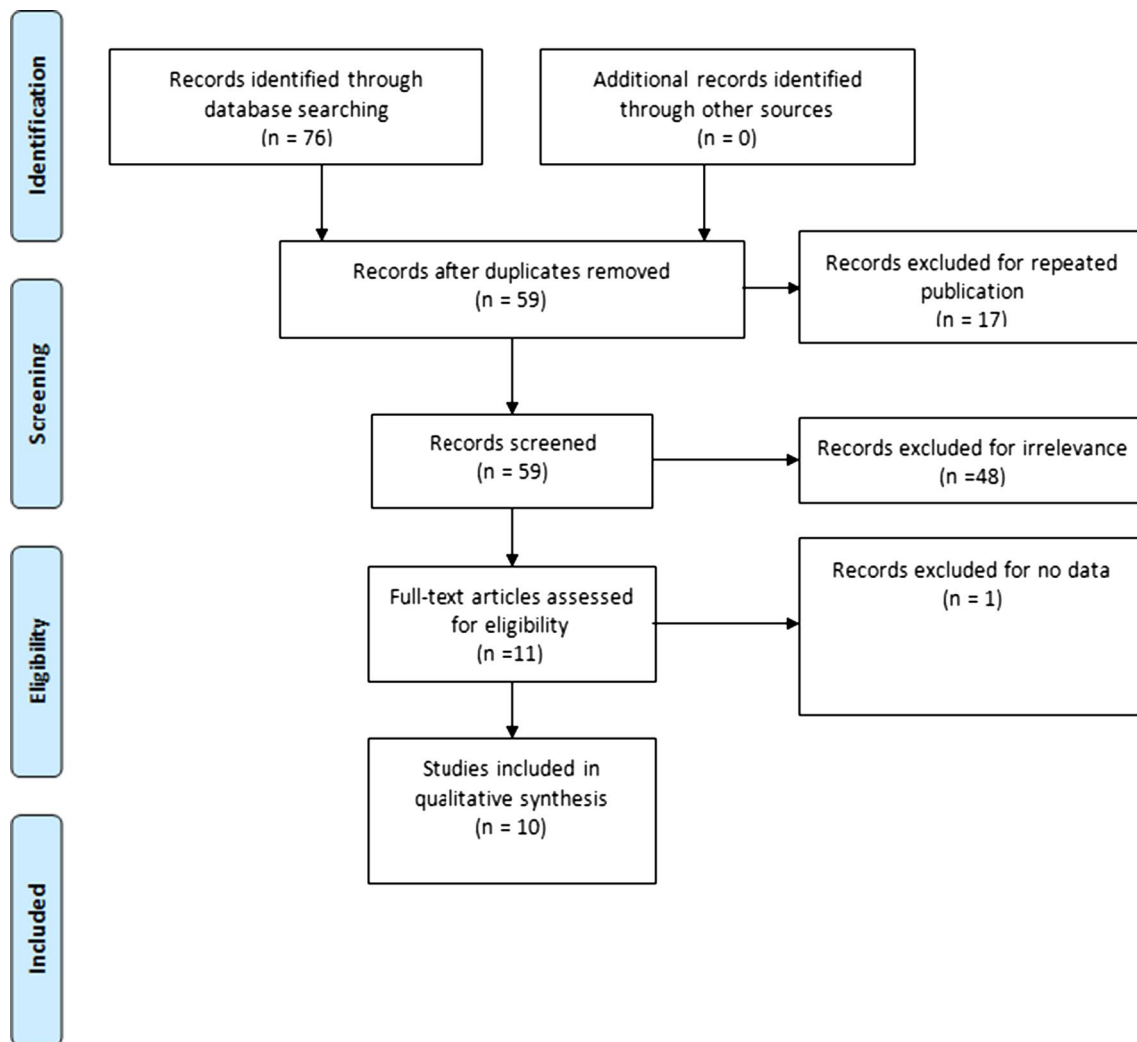
Fig. 1 Study flow chart

had an inadequate response to DMARD or MTX and has a manageable safety profile [17]. However, the comparative efficacy and safety of tofacitinib in various treatment regimens with different dosages or in combination with MTX remains unclear due to the lack of multiple comparisons.

Standard meta-analysis compares only two treatments at a time [18, 19]. On the other hand, network meta-analysis, also called multiple-treatments meta-analysis, simultaneously combines direct and indirect evidence of the relative treatment effects [20]. Network meta-analysis can assess the comparative effectiveness of multiple interventions and combines evidence across a network of randomized controlled trials (RCTs), even if there are no head-to-head comparisons [21]. The present study aimed to compare the efficacy and safety of tofacitinib 5 and 10 mg twice daily, or in combination with methotrexate (MTX), in patients with active RA, by using a network meta-analysis.

Methods

Identification of eligible studies and data extraction

We performed an exhaustive search for studies that examined the efficacy and safety of tofacitinib in patients with active RA who showed inadequate response to DMARD or MTX. A literature search was performed using MED-LINE, EMBASE, and the Cochrane Controlled Trials Register to identify available articles (up to January 2015). The following key words and subject terms were used in the search: "tofacitinib," "rheumatoid arthritis," and "RA." All references in the studies were reviewed to identify additional works not included in the electronic databases. RCTs were included if they met the following criteria: (1) the study compared tofacitinib with placebo or MTX in the treatment for RA, (2) the study provided
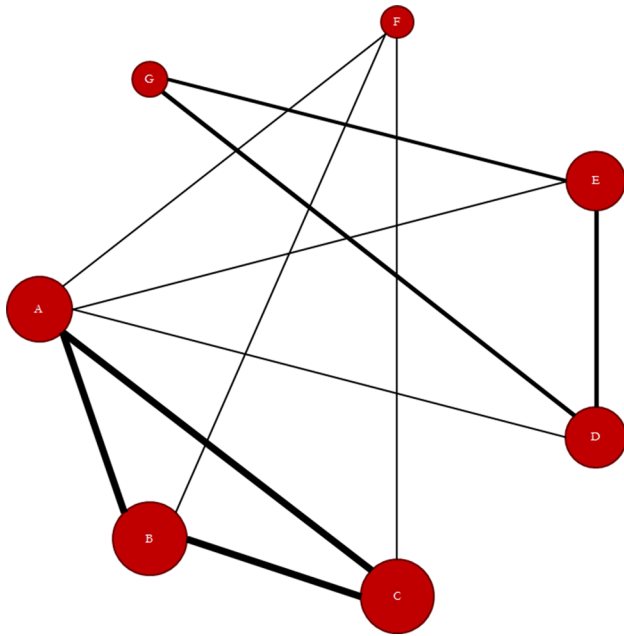
Fig. 2 Evidence network of comparisons for network meta-analysis. The width of each edge in the evidence network is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size). *A* MTX, *B* tofacitinib 5 mg + MTX, *C* tofacitinib 10 mg + MTX, *D* tofacitinib 5 mg, *E* tofacitinib 10 mg, *F* adalimumab + MTX, *G* Placebo

end points for the clinical efficacy and safety of tofacitinib, and (3) the study included patients diagnosed with RA based on the American College of Rheumatology (ACR) criteria for RA. The exclusion criteria were as follows: (1) the study included duplicate data, and (2) the study did not contain adequate data for inclusion. Efficacy outcome was the number of patients who achieved an ACR20 response, and the safety outcome was the number of patients withdrawn due to adverse events (AEs). Data were extracted from original studies by two independent reviewers. Any discrepancy between the reviewers was resolved by consensus or a third reviewer. The following information was extracted from each study: first author, year of publication, country in which the study was conducted, tofacitinib dose, length of follow-up, time when outcomes were evaluated, and outcomes for efficacy and safety. We assessed the methodological qualities using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [22]. The following parameters were considered: random sequence generation, blinding, concealed allocation, selective reporting, incomplete outcome data, and other biases. We conducted a network meta-analysis in accordance with the guidelines provided by the PRISMA statement [23].

Evaluations of statistical associations for network meta-analysis

For RCTs that compared multiple doses of tofacitinib in different arms, the results from different arms were analyzed simultaneously. The efficacy and safety of tofacitinib in different arms were ordered according to the probability of being ranked as the best performing regimen. We used a Bayesian random-effects model for network meta-analysis using NetMetaXL [24] and WinBUGS statistical analysis program version 1.4.3 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK). We used the Markov Chain Monte Carlo method to obtain the pooled effect sizes [21]. All chains were run with 10,000 burn-in iterations followed by 10,000 monitoring iterations. Information of relative effects was converted to a probability that a treatment is best, second best, and so on, or the ranking of each treatment, called the surface under the cumulative ranking curve (SUCRA) [25], which is expressed as a percentage—the SUCRA would be 100 % when a treatment is certain to be the best and 0 % when a treatment is certain to be the worst. The league table arranges the presentation of summary estimates by ranking the treatments in order of the most pronounced impact on the outcome under consideration based on SUCRA [25]. We reported the pairwise OR and 95 % credible interval (CrI) (or Bayesian CI) and adjusted for multiple-arm trials. Pooled results were considered statistically significant if the 95 % CrI did not contain the value 1.

Test for inconsistency

Inconsistency refers to the extent of disagreement between direct and indirect evidence [26]. Assessment of inconsistency is important for conducting a network meta-analysis [27]. We plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to assess the network inconsistency between direct and indirect estimates in each loop [28]. We assessed the robustness of the results by performing network meta-analysis after eliminating outlier studies.

Results

Studies included in the meta-analysis

A total of 76 studies were identified by electronic or manual search, 17 were excluded for repeated publications, and 48 were excluded for irrelevance. Eleven studies were selected for a full-text review based on the title and abstract details. However, one of the eleven was excluded because it contained no outcome data (Fig. 1). Thus,

Table 1 Characteristics of individual studies included in the meta-analysis and systematic review

References	Patient number	Subjects	Doses, twice daily (numbers)	Follow-up period	Follow-up point for evaluation
A					
Lee et al. [7]	956	MTX-naïve, IR	MTX (186), Tb 5 mg (373), Tb 10 mg (397)	24 months	24 months
Kremer et al. [8]	795	DMARD-IR	MTX (159), Tb 5 mg + MTX (318), Tb 10 mg + MTX (318)	12 months	6 months
Van der Heijde et al. [9]	797	MTX-IR	MTX (160), Tb 5 mg + MTX (321), Tb 10 mg + MTX (316)	24 months	6 months
Burmester et al. [10]	399	TNF-IR	MTX (132), Tb 5 mg + MTX (133), Tb 10 mg + MTX (134)	6 months	3 months
Van Vollenhoven et al. [11]	717	MTX-IR	MTX (108), Tb 5 mg + MTX (204), Tb 10 mg + MTX (201), adalimumab 40 mg once a week + MTX (204)	12 months	3 months
Fleischmann et al. [12]	610	DMARD-IR	Placebo (122), Tb 5 mg (243), Tb 10 mg (245)	6 months	3 months
Kremer et al. [13]	214	MTX-IR	MTX (69), Tb 5 mg + MTX (71), Tb 10 mg + MTX (74)	6 months	3 months
Fleischmann et al. [14]	169	DMARD-IR	Placebo (59), Tb 5 mg (49), Tb 10 mg (61)	6 months	6 months
Tanaka et al. [15]	84	MTX-IR	MTX (28), Tb 5 mg + MTX (28), Tb 10 mg + MTX (28)	36 months	3 months
Kremer et al. [16]	126	MTX, biologic-IR	Placebo (65), Tb 5 mg (61)	6 weeks	6 weeks

References	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
B						
Lee et al. [7]	Low	Unclear	Low	Low	Low	Unclear
Kremer et al. [8]	Unclear	Unclear	Low	Low	Low	Unclear
Van der Heijde et al. [9]	Low	Low	Low	Low	Low	Unclear
Burmester et al. [10]	Low	Low	High	Low	Low	Unclear
Van Vollenhoven et al. [11]	Low	Low	High	Low	Low	Unclear
Fleischmann et al. [12]	Unclear	Unclear	Low	Low	Low	Unclear
Kremer et al. [13]	Unclear	Unclear	Low	Low	Low	Unclear
Fleischmann et al. [14]	Low	Low	Low	Low	Low	Unclear
Tanaka et al. [15]	Unclear	Unclear	Low	Low	Low	Unclear
Kremer et al. [16]	Unclear	Unclear	Low	Low	Low	Unclear

DMARD disease-modifying antirheumatic drug; *MTX* methotrexate; *IR* incomplete response; *Tb* tofacitinib

10 RCTs including 4867 patients (2470 events for efficacy and 301 events for safety) met the inclusion criteria [7–16]. There were 21 pairwise comparisons including 11 direct comparisons and seven interventions, such as MTX, tofacitinib 5 mg + MTX, tofacitinib 10 mg + MTX, tofacitinib 5 mg, tofacitinib 10 mg, adalimumab 40 mg once a week + MTX, MTX, and placebo for the network meta-analysis (Fig. 2). The recommended dosage of tofacitinib is 5 mg twice daily [29], but patients may benefit from an increase to 10 mg twice a day. Thus, we chose the dosages of 5 and 10 mg of tofacitinib twice daily. Relevant features of the studies included in the meta-analysis are provided in Table 1. Although sequence generation, concealed allocation, and selective reporting were not mentioned in all the studies, blinding and incomplete outcome data were mentioned in all (Table 1, Supplementary data).

Table 2 Network meta-analyses comprising effects for all contrasts along with ORs and 95 % credible intervals

Tofacitinib 10 mg + MTX	Tofacitinib 5 mg + MTX	Adalimumab + MTX	Tofacitinib 10 mg	Tofacitinib 5 mg	MTX	Placebo
A. Efficacy						
1.24 (0.81–1.72)						
1.40 (0.68–2.91)	1.13 (0.58–2.47)					
1.49 (0.65–3.56)	1.19 (0.55–3.02)	1.06 (0.37–3.13)				
1.65 (0.76–4.24)	1.34 (0.65–3.65)	1.18 (0.44–3.72)	1.12 (0.71–1.92)			
3.67 (2.60–5.71)	2.97 (2.17–4.89)	2.63 (1.32–5.77)	2.48 (1.19–5.46)	2.12 (1.01–4.63)		
7.56 (3.07–21.16)	6.11 (2.58–18.02)	5.35 (1.78–18.09)	5.06 (2.93–9.45)	4.54 (2.59–7.78)	2.05 (086–4.99)	

Tofacitinib 5 mg	Tofacitinib 10 mg	MTX	Adalimumab + MTX	Placebo	Tofacitinib 10 mg + MTX	Tofacitinib 5 mg + MTX
B. Safety						
0.88 (0.40–1.65)						
0.70 (0.29–1.53)	0.79 (0.36–1.92)					
0.49 (0.13–1.75)	0.56 (0.14–2.13)	0.69 (0.26–1.92)				
0.44 (0.15–1.18)	0.50 (0.17–1.45)	0.63 (0.18–2.18)	0.88 (0.18–4.36)			
0.42 (0.15–1.12)	0.49 (0.18–1.36)	0.62 (0.35–1.05)	0.89 (0.33–2.27)	0.95 (0.24–3.85)		
0.39 (0.14–1.05)	0.45 (0.17–1.30)	0.57 (0.31–1.01)	0.82 (0.31–2.21)	0.88 (0.23–3.68)	0.93 (0.60–1.50)	

Network meta-analysis of the efficacy of tofacitinib in RCTs

Tofacitinib 10 mg + MTX is listed in the top left of the diagonal of the league table (Table 2) because it was associated with the most favorable SUCRA for the ACR20 response rate, while placebo is listed in the bottom right of the diagonal of the league table because it was associated with the least favorable results. For interpretation purposes, the results are read from top to bottom and left to right. The ACR20 response rate was significantly higher in the tofacitinib 10 mg + MTX group than in the placebo or MTX groups (OR 7.56, 95 % CrI 3.07–21.16; OR 3.67, 95 % CrI 2.60–5.71, respectively) (Table 2; Fig. 3). Similarly, the ACR20 response rate was significantly higher in the tofacitinib 5 mg + MTX group than in the placebo or MTX groups (OR 6.11, 95 % CrI 2.58–18.02; OR 2.97, 95 % CrI 2.17–4.89, respectively) (Table 2; Fig. 3). Compared with the placebo or MTX groups, adalimumab 40 mg + MTX, tofacitinib 10 mg, and tofacitinib 5 mg groups showed a significantly higher ACR20 response rate (Table 2; Fig. 3). A trend of tofacitinib 10 mg + MTX being more efficacious than tofacitinib 5 mg + MTX, adalimumab + MTX, tofacitinib 10 mg, and tofacitinib 5 mg was noted (Table 2; Fig. 3). Ranking probability based on SUCRA indicated that tofacitinib 10 mg + MTX had the highest probability of being the best treatment for achieving the ACR20 response rate (SUCRA = 0.9254), followed by tofacitinib 5 mg + MTX (SUCRA = 0.7156), adalimumab 40 mg + MTX (SUCRA = 0.097), tofacitinib 10 mg (SUCRA = 0.5984), tofacitinib 5 mg (SUCRA = 0.4749), MTX (SUCRA = 0.1674), and placebo (SUCRA = 0.0086) (Table 3).

Network meta-analysis of the safety of tofacitinib in RCTs

We considered the number of patient withdrawals due to AE as the safety outcome. The number of patients withdrawn due to AEs was lower in the placebo group than in the tofacitinib 10 mg + MTX and tofacitinib 5 mg + MTX groups, but the difference did not reach statistical significance (OR 0.95, 95 % CrI 0.24–3.85; OR 0.88, 95 % CrI 0.23–3.68, respectively) (Table 2; Fig. 4). However, the number of patients withdrawn due to AEs did not differ significantly among the seven interventions (Tables 2, 3; Fig. 4).

Inconsistency and sensitivity analysis

An inconsistency plot provides information that can help identify the loops in which inconsistency is present [27]. Although the contributions to the deviance were likely to be similar and close to 1 for both models, two points in both plots of the efficacy (tofacitinib 5 mg of Fleischmann et al. study, tofacitinib 10 mg + MTX of van der Heijde et al. study) and safety (tofacitinib 5 mg of Fleischmann et al. study, MTX of Kremer et al. study) appeared to have a higher than expected posterior mean deviance (Fig. 5).

Fig. 3 Results of Bayesian network meta-analysis of randomized controlled studies on the relative efficacy of tofacitinib

Treatment 1 vs. Treatment

O.R. (95% Cr.I.)

Treatment 1 vs. Treatment	O.R. (95% Cr.I.)
Tofacitinib 10mg versus Tofacitinib 5mg	1.08 (0.87 – 1.34) / 1.06 (0.37 – 3.13)
Adalimumab+MTX versus Tofacitinib 10mg	1.08 (0.66 – 1.77) / 1.12 (0.71 – 1.92)
Tofacitinib 5mg+MTX versus Adalimumab+MTX	1.08 (0.77 – 1.53) / 1.13 (0.58 – 2.47)
Adalimumab+MTX versus Tofacitinib 5mg	1.16 (0.71 – 1.92) / 1.18 (0.44 – 3.72)
Tofacitinib 5mg+MTX versus Tofacitinib 10mg	1.17 (0.78 – 1.75) / 1.19 (0.55 – 3.02)
Tofacitinib 5mg+MTX versus Tofacitinib 5mg	1.26 (0.84 – 1.89) / 1.24 (0.81 – 1.72)
Tofacitinib 10mg+MTX versus Tofacitinib 5mg+MTX	1.28 (1.08 – 1.52) / 1.34 (0.65 – 3.65)
Tofacitinib 10mg+MTX versus Adalimumab+MTX	1.38 (0.98 – 1.95) / 1.40 (0.68 – 2.91)
Tofacitinib 10mg+MTX versus Tofacitinib 10mg	1.49 (1.00 – 2.23) / 1.49 (0.65 – 3.56)
Tofacitinib 10mg+MTX versus Tofacitinib 5mg	1.60 (1.08 – 2.41) / 1.65 (0.76 – 4.24)
MTX versus Placebo	2.07 (1.29 – 3.30) / 2.05 (0.86 – 4.99)
Tofacitinib 5mg versus MTX	2.22 (1.58 – 3.14) / 2.21 (1.01 – 4.63)
Tofacitinib 10mg versus MTX	2.39 (1.71 – 3.37) / 2.48 (1.19 – 5.46)
Adalimumab+MTX versus MTX	2.58 (1.79 – 3.72) / 2.63 (1.32 – 5.77)
Tofacitinib 5mg+MTX versus MTX	2.79 (2.26 – 3.46) / 2.97 (2.17 – 4.89)
Tofacitinib 10mg+MTX versus MTX	3.56 (2.89 – 4.42) / 3.67 (2.60 – 5.71)
Tofacitinib 5mg versus Placebo	4.58 (3.24 – 6.54) / 4.54 (2.59 – 7.78)
Tofacitinib 10mg versus Placebo	4.94 (3.48 – 7.14) / 5.06 (2.93 – 9.45)
Adalimumab+MTX versus Placebo	5.33 (2.95 – 9.64) / 5.35 (1.78 – 18.09)
Tofacitinib 5mg+MTX versus Placebo	5.77 (3.45 – 9.64) / 6.11 (2.58 – 18.02)
Tofacitinib 10mg+MTX versus Placebo	7.37 (4.42 – 12.33) / 7.56 (3.07 – 21.16)

Heterogeneity (Vague) = 0.2484
Favours Treatment 2   Favours Treatment 1
Fixed Effects — Random Effects (Vague Prior)

However, a sensitivity analysis removing outlier studies did not meaningfully change the network meta-analysis results. Three studies were considered as low (or unclear) quality [8, 13, 16]. Excluding these studies did not significantly affect the results of the network meta-analysis, indicating statistically robust results from this network meta-analysis.

Discussion

Network meta-analysis, an extension of traditional meta-analysis, synthesizes all available evidence to allow for simultaneous comparisons of different treatment options that lack direct head-to-head comparisons [20, 21]. We conducted a network meta-analysis to compare the efficacy

Table 3 Rank probability of tofacitinib in terms of efficacy based on the number of patients who achieved an ACR20 response and the safety based on the number of withdrawals due to adverse events

Treatment	SUCRA
A. Efficacy	
Tofacitinib 10 mg + MTX	0.9254
Tofacitinib 5 mg + MTX	0.7156
Adalimumab + MTX	0.6097
Tofacitinib 10 mg	0.5984
Tofacitinib 5 mg	0.4749
MTX	0.1674
Placebo	0.0086
B. Safety	
Tofacitinib 5 mg	0.8768
Tofacitinib 10 mg	0.7843
MTX	0.6476
Adalimumab + MTX	0.3892
Placebo	0.316
Tofacitinib 10 mg + MTX	0.2757
Tofacitinib 5 mg + MTX	0.2104

and safety of different tofacitinib interventions in patients with active RA, because this analysis enables an indirect comparison of multiple treatments, which are either lacking in or have insufficient direct head-to-head comparisons.

This network meta-analysis assessed seven kinds of interventions on the number of patients who achieved an ACR20 response and the number of patients withdrawn due to AEs in patients with active RA. In regard to efficacy, our network meta-analysis suggests that tofacitinib 10 mg + MTX is most effective in the treatment for active RA, followed by tofacitinib 5 mg + MTX, adalimumab 40 mg + MTX, tofacitinib 10 mg, tofacitinib 5 mg, MTX, and placebo. Tofacitinib 10 mg + MTX and tofacitinib 5 mg + MTX are more efficacious than tofacitinib monotherapy. Tofacitinib with MTX had a higher probability of being the best treatment for achieving an ACR20 response than tofacitinib monotherapy. This may be explained by the inhibitory action of MTX on the activation and proliferation of lymphocytes; thus, the combination of tofacitinib with MTX fills the gap associated with each drug with respect to the mode of action [30].

With respect to safety based on the number of withdrawals due to AEs, tofacitinib 10 mg + MTX and tofacitinib 5 mg + MTX showed more withdrawals due to AEs and had a lower probability of being the best in terms of the number of withdrawals due to AEs than placebo. However, no significant difference was observed in withdrawals due to AEs among seven interventions, suggesting comparable safety among the different tofacitinib dosages, with or without MTX, and placebo.

Although this network meta-analysis showed that the number of tofacitinib-treated patients who discontinued medication due to AEs was not different from placebo groups, tofacitinib has been reported to have the risk of infections, cancer, and cytopenias [31, 32]. The common serious infections reported with tofacitinib included pneumonia, cellulitis, herpes zoster, and urinary tract infection [31]. Tuberculosis (TB) infection has been reported in the trials of tofacitinib [33, 34]. A study using a mouse model indicated a reactivation of LTBI in the presence of tofacitinib and suggested that tofacitinib should be prescribed with caution in patients with chronic inflammation, and screening for LTBI is necessary prior to use [35]. With respect to malignancy, lung cancer and renal cell carcinoma have been reported in the tofacitinib group [36, 37]. Tofacitinib reported other side effects, such as hypercholesterolemia, and rise in liver enzymes and serum creatinine [38]. Thus, monitoring should be conducted during the use of tofacitinib, and larger trials with longer duration of study with pharmacovigilance are needed to confirm the long-term safety.

Network meta-analysis synthesizes all available evidence to allow for simultaneous comparisons of different treatment options that lack direct head-to-head comparisons, optimizing the use of all available data [21]. In comparison with the individual studies, network meta-analysis provides more accurate data by increasing the statistical power and resolution through pooling the results of independent analyses. Use of network meta-analysis has increased, but this is the first network meta-analysis that evaluated comprehensive and simultaneous assessment of tofacitinib for RA.
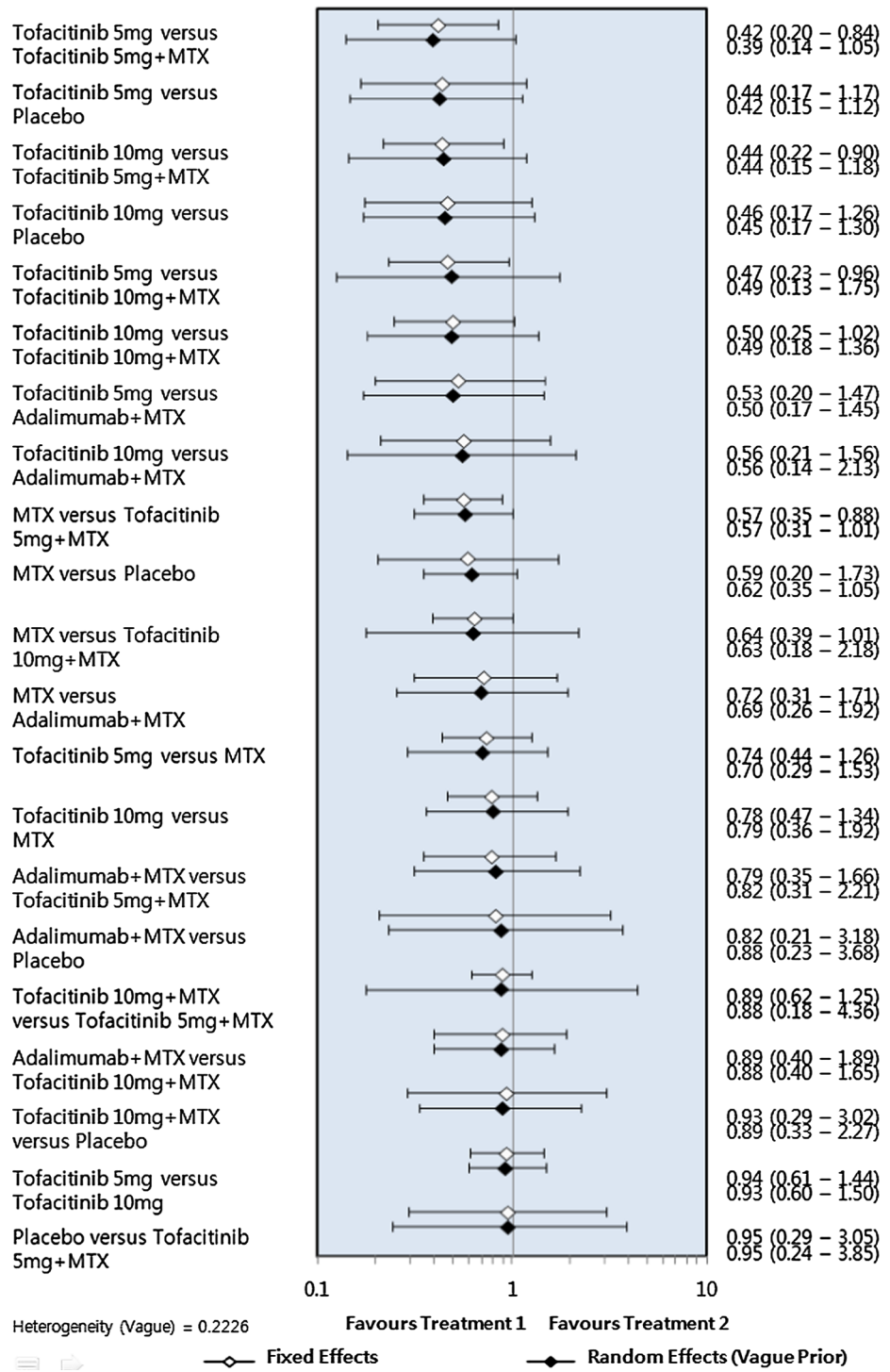
This network meta-analysis results, which combined evidence from both direct and indirect comparisons for evaluating the relative efficacy and safety of tofacitinib, were in agreement with a meta-analysis of direct comparisons showing that tofacitinib provided a statistically significant improvement according to the response criteria (ACR20) compared to placebo, and there were no statistically significant differences between tofacitinib and placebo in terms of treatment discontinuation due to adverse reactions [39]. However, our network meta-analysis differs from the previous meta-analysis, because we could generate a rank order for the efficacy and safety of tofacitinib or in combination with MTX in patients with active RA.

Our results should be interpreted with caution because of the several shortcomings of our study. First, the follow-up time points ranged widely from 3 to 24 months, with most being of a short duration (<6 months). The follow-up duration was therefore too short for an evaluation of the long-term effects. Longer comparative studies in the future are warranted. Second, there was heterogeneity in the design and patient characteristics of the included trials; thus, there is the possibility that these differences across

Fig. 4 Results of Bayesian network meta-analysis of randomized controlled studies on the relative safety of tofacitinib

Treatment 1 vs. Treatment   O.R. (95% Cr.I.)

Treatment 1 vs. Treatment 2	O.R. (95% Cr.I.)
Tofacitinib 5mg versus Tofacitinib 5mg+MTX	0.42 (0.20 – 0.84) / 0.39 (0.14 – 1.05)
Tofacitinib 5mg versus Placebo	0.44 (0.17 – 1.17) / 0.42 (0.15 – 1.12)
Tofacitinib 10mg versus Tofacitinib 5mg+MTX	0.44 (0.22 – 0.90) / 0.44 (0.15 – 1.18)
Tofacitinib 10mg versus Placebo	0.46 (0.17 – 1.26) / 0.45 (0.17 – 1.30)
Tofacitinib 5mg versus Tofacitinib 10mg+MTX	0.47 (0.23 – 0.96) / 0.49 (0.13 – 1.75)
Tofacitinib 10mg versus Tofacitinib 10mg+MTX	0.50 (0.25 – 1.02) / 0.49 (0.18 – 1.36)
Tofacitinib 5mg versus Adalimumab+MTX	0.53 (0.20 – 1.47) / 0.50 (0.17 – 1.45)
Tofacitinib 10mg versus Adalimumab+MTX	0.56 (0.21 – 1.56) / 0.56 (0.14 – 2.13)
MTX versus Tofacitinib 5mg+MTX	0.57 (0.35 – 0.88) / 0.57 (0.31 – 1.01)
MTX versus Placebo	0.59 (0.20 – 1.73) / 0.62 (0.35 – 1.05)
MTX versus Tofacitinib 10mg+MTX	0.64 (0.39 – 1.01) / 0.63 (0.18 – 2.18)
MTX versus Adalimumab+MTX	0.72 (0.31 – 1.71) / 0.69 (0.26 – 1.92)
Tofacitinib 5mg versus MTX	0.74 (0.44 – 1.26) / 0.70 (0.29 – 1.53)
Tofacitinib 10mg versus MTX	0.78 (0.47 – 1.34) / 0.79 (0.36 – 1.92)
Adalimumab+MTX versus Tofacitinib 5mg+MTX	0.79 (0.35 – 1.66) / 0.82 (0.31 – 2.21)
Adalimumab+MTX versus Placebo	0.82 (0.21 – 3.18) / 0.88 (0.23 – 3.68)
Tofacitinib 10mg+MTX versus Tofacitinib 5mg+MTX	0.89 (0.62 – 1.25) / 0.88 (0.18 – 4.36)
Adalimumab+MTX versus Tofacitinib 10mg+MTX	0.89 (0.40 – 1.89) / 0.88 (0.40 – 1.65)
Tofacitinib 10mg+MTX versus Placebo	0.93 (0.29 – 3.02) / 0.89 (0.33 – 2.27)
Tofacitinib 5mg versus Tofacitinib 10mg	0.94 (0.61 – 1.44) / 0.93 (0.60 – 1.50)
Placebo versus Tofacitinib 5mg+MTX	0.95 (0.29 – 3.05) / 0.95 (0.24 – 3.85)

0.1   1   10

Heterogeneity (Vague) = 0.2226   Favours Treatment 1   Favours Treatment 2

—◇— Fixed Effects   —◆— Random Effects (Vague Prior)

studies affected the results of this network meta-analysis. Third, this study did not comprehensively address the efficacy and safety outcomes of tofacitinib in RA. This study only focused on the effectiveness based on the number of patients who achieved an ACR20 response and on the safety according to the number of patients withdrawn due to AEs,

without assessing various outcomes. Specifically, the number of withdrawals due to AEs may not be sufficient for the safety outcome measure because of its frequency.

In conclusion, by using a Bayesian network meta-analysis involving 10 RCTs comparing seven different interventions, we found that tofacitinib 5 and 10 mg twice daily,
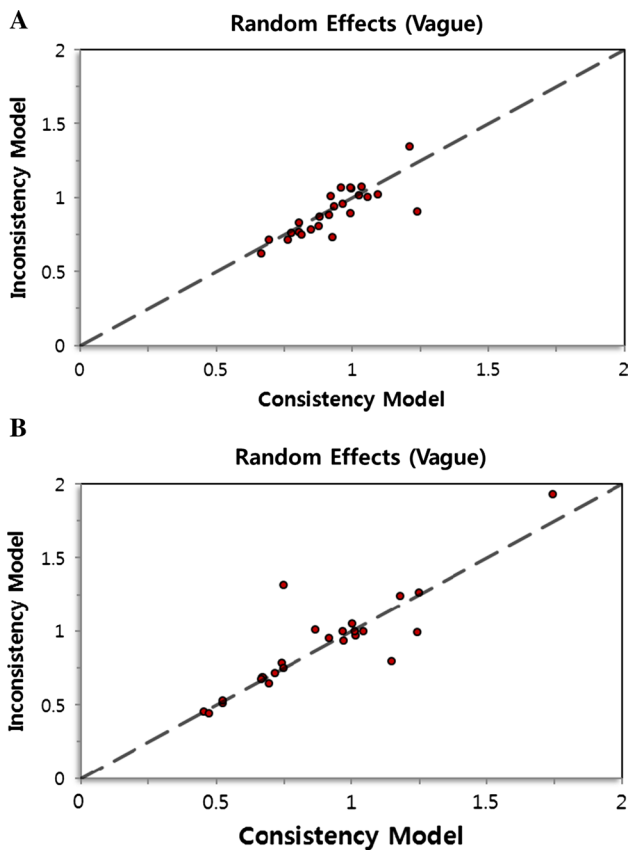
Fig. 5 Inconsistency plot for efficacy (**a**) and safety (**b**) of tofacitinib. Plot of the individual data points' posterior mean deviance contributions for the consistency model (*horizontal axis*) and the unrelated mean effects model (*vertical axis*) along with the line of equality

in combination with MTX, was most efficacious for active RA and was not associated with a significant risk for withdrawals due to AEs. Long-term studies are needed to determine the relative efficacy and safety of tofacitinib in a large number of patients with active RA.

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