Comparative Efficacy (DAS28 remission) of Targeted Immune Modulators for Rheumatoid Arthritis: A Network Meta-Analysis

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Abstract

Background

The objective of the study was to evaluate the relative efficacy of targeted immune modulators (TIMs) in TIM-naïve/mixed (≤ 20% TIM-experienced) and TIM-experienced (> 20% TIM-experienced) adults with moderately-to-severe rheumatoid arthritis with an inadequate response or intolerance to conventional disease-modifying antirheumatic drugs (cDMARDs).

Methods

A fixed effects Bayesian network meta-analysis (NMA) was performed using published study-level data form 41 randomized controlled trials (RCTs), identified from 2 recent systematic literature reviews conducted by the Institute for Clinical and Economic Review, and 2 additional phase III trials for filgotinib (FINCH-1, FINCH-2). RCTs that compared TIMs to each other, cDMARD or placebo were included. Treatments included Janus kinase (JAK) inhibitors, tumor necrosis factor alpha inhibitors (TNFi), and other non-TNFis. Efficacy was defined as achieving remission with a DAS28 score < 2.6 at 12 and 24 weeks.

Results

In the 12-week analysis for the TIM-naïve/mixed population, all TIMs combined with cDMARD were more likely to achieve remission compared to cDMARD alone (statistically significant), with intravenous tocilizumab showing a substantially greater magnitude of effect (odds ratio = 19.36, 95% credible interval: 11.01, 38.16). Similarly, in the 24-week analysis, intravenous and subcutaneous tocilizumab showed the highest odds ratio of achieving DAS28 remission compared to cDMARD. Similar trends were observed for the analyses on monotherapy or TIM-experienced population.

Conclusion

This NMA demonstrated that tocilizumab is associated with a greater likelihood of remission (DAS28 < 2.6) at 12 and 24 weeks compared to most other TIMs including new JAK inhibitors, when used in combination with a cDMARD or as monotherapy, among TIM-naïve/mixed or TIM-experienced populations.

Background

Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis in adults, affecting between 1.3 and 1.8 million people in the United States (US) alone (1-3). RA is a chronic, systemic, progressive, and sometimes disabling autoimmune disease that causes swelling, stiffness, and tenderness in and

around the joints (4). It is characterized by persistent symmetric polyarthritis (synovitis) which may affect any joint lined by a synovial membrane such as hands (metacarpophalangeal and proximal interphalangeal joints), wrists, and feet and may also lead to extra-articular involvement of organs such as the skin, heart, lungs, and eyes (4). RA is considered a clinical syndrome that, if not controlled, can lead to permanent joint damage and deformity in some individuals (4).

As the guidelines from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) state, effective treatment of RA requires an integrated approach involving patient education, diet and exercise, psychosocial support, physical and occupational therapy, pharmacotherapy, and surgery (5, 6). Pharmacotherapies are broadly distinguished by whether they provide symptomatic relief only (such as nonsteroidal anti-inflammatory drugs [NSAIDs] and corticosteroids) or prevent disease progression and, thus, tissue damage (referred to as disease-modifying antirheumatic drugs [DMARDs]). Conventional synthetic DMARDs (cDMARDs) include older systemic agents such as methotrexate, hydroxychloroquine, sulfasalazine, leflunomide that decrease inflammation and slow radiographic progression. Methotrexate is the most frequently prescribed medication as an initial treatment, but it is estimated that only 30% of patients demonstrate low disease activity with methotrexate monotherapy, while the combinations of cDMARDs and biologics are significantly more effective than methotrexate alone in such patients (7). Therefore, in patients that fail initial therapy with cDMARDs, treatment guidelines recommend adding targeted therapies, such as interleukin (IL)-6 inhibitors, Janus kinase (JAK) inhibitors, tumor necrosis factor (TNF)-α inhibitors, T-cell inhibitor, and CD20-directed cytolytic B-cell antibodies, that selectively block mechanisms involved in the inflammatory response (5, 6). Collectively known as targeted immune modulators (TIMs), these biologic and non-biologic therapies have been extensively used and have shown benefits in reducing or preventing joint damage, as well as preserving joint integrity and function.

Treat-to-target (TTT) is a widely accepted guiding principle wherein patients are carefully managed to achieve and maintain clearly specified and sequentially measured goals that signal either remission or lowered disease activity (8). While treatment response assessment at 24 weeks is the standard in clinical trials, assessment as early as 4 to 12 weeks after the start of treatment is recommended by guidelines following a TTT approach (6). One key measure of disease activity in patients with RA is the 28-joint disease activity score DAS28 (9). The DAS28 combines single measures of 28 joints into an overall measure of disease that includes a composite of swelling, tenderness, blood markers of inflammation (*erythrocyte sedimentation rate* [ESR] and C-reactive protein [CRP]), and a global assessment of health. A DAS28 score of greater than 5.1 implies active disease, between 2.6 and 3.2 implies low disease activity, and less than 2.6 implies remission (5). The DAS28 score allows clinicians to use multiple indices to assess an overall level of disease activity and provides a useful measure to guide disease management following a TTT approach in the clinical setting.

Two systematic literature reviews (SLR) on RA were conducted by the Institute for Clinical and Economic Review (ICER). An evidence report was published by ICER in 2017 on the clinical and cost effectiveness of TIMs in patients with moderately-to-severely active RA, who experienced an inadequate response to or

intolerance of prior methotrexate or other cDMARDs (10). The SLR included all TIMs available as of 2016, including baricitinib and sarilumab, which were then under Food and Drug Administration (FDA) review for the treatment of RA. The report identified DAS28-ESR as the most frequently used measure of disease activity across clinical trials, reported in about 80% of the trials that included disease activity measures, with most studies using remission rates (defined as DAS28 score <2.6) as one of the study endpoints. However, the network meta-analysis (NMA) in the review assessed ACR20 response as it was the primary endpoint in the majority of the included randomized controlled trials (RCTs). ICER published an updated SLR and report in early 2020 focused on assessing the clinical and cost effectiveness of JAK inhibitors (upadacitinib, tofacitinib, and baricitinib) in patients with moderately-to-severely active RA, who experienced an inadequate response to or intolerance of prior methotrexate or other cDMARDs) (11). Similarly, an NMA was conducted for ACR response outcomes, but not for disease activity measures. In addition, no conclusions were made comparing JAK inhibitors to each other or other TIMs.

While these 2 reviews provided comprehensive assessments of the RA evidence base, disease activity measures were only evaluated descriptively in both reviews, and the comparative efficacy among TIMs for achieving DAS28 remission is unclear without quantitative synthesis. In addition, while the 2020 review included upadacitinib, which was the most recently approved TIM for RA, the review was limited to JAK inhibitors only, and did not involve a full analysis including all TIMs. As another new JAK inhibitor filgotinib is currently under FDA review and expected to be an additional treatment option, it becomes increasingly important to understand the comparative efficacy among TIMs in lowering disease activity. Clinical evidence of filgotinib is available from 2 recent phase III RCTs – FINCH-1 and FINCH-2 (12, 13). In order to inform the clinical community with comparative efficacy data for all TIMs including filgotinib, we developed an RA evidence base by utilizing evidence published in the 2 prior SLRs (10, 11), with additional clinical evidence from the FINCH-1 and FINCH-2 trials. An NMA was conducted using this evidence base, to evaluate the comparative efficacy of achieving DAS28 remission with RA treatments in patients with moderately-to-severely active disease who are TIM-naïve/mixed or TIM-experienced.

Materials And Methods

The primary objective of this NMA was to evaluate the comparative efficacy of TIM therapies for DAS28 remission. DAS28 is scored on a 0-10.0 continuous scale based on tender and/or swollen joint counts (up to 28 each), ESR or CRP findings, and patient global visual analog scale (VAS) score. The NMA included evidence from RCTs.

Data sources and searches

The details of the 2 previous SLRs have already been published by Ollendorf *et al* (10) and Tice *et al* (11). Briefly, both the SLRs were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news articles. All search strategies were generated utilizing the Population, Intervention,

Comparator, and Study Design elements (PICOS). The review of published studies was supplemented with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other gray literature including technical briefs and other online reports.

The literature yielded from the 2 previous evidence reports was complemented by 2 additional RCTs, FINCH-1 and FINCH-2, that compared the effects of filgotinib versus placebo on the signs and symptoms of RA patients who have an inadequate response to one or more prior DMARD treatment (12, 13).

In this NMA, evidence synthesis was performed using published study level summary data. No additional patient level data were used in this analysis.

Populations, interventions, comparators, outcomes, and study design

We included studies on patients with moderately-to-severely active RA who had an inadequate treatment response or intolerance to methotrexate or other cDMARD. Our research focused on 3 different patient populations. First, TIM-naïve/mixed population on combination therapy, where ≤ 20% of the study population had previous experience with TIM treatment and patients are currently receiving TIM therapies in combination with cDMARD. Second, TIM-naïve/mixed population on TIM monotherapy, where ≤ 20% of the study population had previous experience with TIM treatment and patients are currently receiving TIM treatment alone. And third, TIM-experienced population on combination therapy, where > 20% of the study population had previous treatment with TIMs and patients are currently receiving TIM treatment in combination with cDMARD.

All TIMs as specified in Ollendorf *et al* (10) and Tice *et al* (11) were included in this study, and only the FDA approved dosages were included in this NMA (see Supplementary Table 1, Additional File 2 for all TIMs and approved dosages included in this NMA). RCTs that compared TIMs to each other, cDMARD or placebo were included. Treatment groups evaluating dosages not approved by the FDA were excluded from this NMA. If multiple eligible dosages for the same treatment were reported in a study, results were pooled for the groups with FDA approved dosages. For filgotinib, which is currently under FDA review, both of the investigational dosages at 100 mg and 200 mg once daily were included for analysis. For studies where treatment switch or advancement were involved, only comparative results before the change of treatment were included for this NMA.

Our study focuses on DAS28 remission, which is defined by DAS28 score <2.6 at 12 weeks and 24 weeks. DAS28-ESR was used primarily and if not available, we used DAS28-CRP.

Data synthesis and network meta-analysis

As all the treatments of interest have not been directly compared, we developed quantitative, indirect comparisons among all TIM agents using a Bayesian NMA for the DAS28 remission outcome. The models used were based on those presented by Dias *et al* in the technical support document 2 developed by the National Institute for Health and Care Excellence Decision Support Unit (14). Posterior densities for the unknown parameters were estimated using Markov chain Monte Carlo (MCMC) simulations. The analyses were based on 60,000 iterations on 3 chains, with a burn-in of (at least) 20,000 iterations. Consistent with the 2 prior published reports, DAS28 remission was determined based on the DAS28 score at 12 weeks and 24 weeks, and proportion of patients achieving DAS28 remission was analyzed in the NMA among TIM-naïve/mixed and TIM-experienced patients. All statistical analyses were run within a Bayesian framework with WinBUGS version 3.2.3 via R Studio for both fixed effects (FE) and random effects (RE).

Six networks were evaluated for feasibility of analysis. Binomial analyses were conducted separately for studies reporting on patients who were TIM-naïve/mixed on combination therapy, TIM-naïve/mixed on monotherapy, and TIM-experienced on combination therapy at 12 and 24 weeks each. The FE model was selected for all analyses, since lower deviance information criterion values were observed with the FE model compared with the RE model.

The surface under the cumulative ranking curve (SUCRA) was expressed as a probability of being ranked as the best treatment (e.g., a SUCRA value of 1 would suggest that a treatment was evaluated to be the best, while a value of 0 would suggest that a treatment was ranked to be the worst). The comparison of TIMs versus (vs.) cDMARD was presented in forest plots, with the treatments ranked according to their SUCRA value for the individual outcomes. League tables were used to present the pairwise comparison among all treatments in the network. We reported the posterior median odds ratio (OR) and the 95% credible interval (CrI). Results were considered to be statistically significant when the span of the 95% CrI did not include 1.

Results

Systematic literature review

The original literature search conducted by Ollendorf *et al* identified 4,042 potentially relevant references. After full-text review, 132 publications met the inclusion criteria (Supplementary methods in Additional File 1), which comprised of 67 RCTs and 17 observational studies. The original search focused on all TIM therapies in patients with moderately-to-severe active RA who experienced an inadequate response to previous methotrexate or other cDMARD therapy (10). The review by Tice *et al* yielded an additional 511 references after duplicates were removed and focused on identifying studies that use JAK inhibitors in which 40 references on 16 RCTs met the inclusion criteria (Supplementary methods in Additional File 1, (11)).

We included 41 trials that reported DAS28 remission at 12 or 24 weeks from the 2 previous SLRs, and 2 additional phase 3 RCTs reporting DAS28 remission for filgotinib. Among the 43 trials included in our evidence base, 35 had TIM-naïve/mixed patients, while 8 had TIM-experienced patients. Thirty-seven trials included patients on combination therapy while 6 trials included patients on monotherapy. Seventeen studies reported on JAK inhibitors, while 16 studies reported on TNF inhibitors (TNFi) and 20 reported on other non-TNFi TIMs.

Patient and study characteristics

Baseline characteristics for the study population of the 43 included studies are outlined in Table 1, with additional characteristics presented in Supplementary Table 2, Additional File 2. Treatment groups were generally comparable across all studies within each network. In the TIM-experienced group, all studies except ROSE had patients with approximately 100% prior TNF inhibitor use; the ROSE trial had approximately 38% of patients with prior TNF inhibitor use (15). Analysis methods were also comparable across the studies, except that in the ORAL Standard and ORAL Scan trials in the treatment-naïve/mixed population group on combination therapy, patients in the placebo groups were allowed to advance to tofacitinib treatment if they did not achieve a 20% reduction in the number of tender (68 joins examined) and swollen (66 joins examined) joints at 3 months (16, 17). Therefore, a non-responder imputation was used in these trials to account for these patients at 24 weeks.

Base case NMA results

DAS28 remission outcomes are presented in Supplementary Table 3, Additional File 2. Among the 43 included studies, 1 study (J-RAPID (18)) reported 0% of DAS28 remission in the cDMARD comparator group at 12 weeks and 24 weeks, and thus was not included in the NMA due to statistical considerations. The remaining 42 trials were included in the NMA. Six networks were evaluated for feasibility and all networks were deemed comparable (Fig. 1). NMA results are presented in Forest Plots with median ORs and associated SUCRA values (Fig. 2). Pairwise comparisons among all treatments are available in the supplementary appendix (Supplementary Table 4-9, Additional File 2).

TIM-naïve/mixed population—Combination therapy

A total of 17 and 24 studies of combination therapy with TIMs + cDMARD in TIM-naïve/mixed population evaluated DAS28 remission at 12 and 24 weeks, respectively. The network diagrams are presented in Fig. 1A-B. Results across both timepoints were similar. At 12 and 24 weeks, all TIMs in combination with cDMARD showed a statistically significantly higher odds of achieving DAS28 remission compared with cDMARD alone (Fig. 2A-B). Intravenous (IV) tocilizumab in combination with cDMARD showed the highest significant difference compared with cDMARD alone (OR 19.36, 95% CrI: 11.01, 38.16). Among all pairwise comparisons, results favored tocilizumab IV + cDMARD with the odds of achieving DAS28

remission statistically significantly better compared to 8 out of 12 comparisons and 11 out of 14 comparisons for 12 and 24 weeks respectively (Supplementary Table 4-5, Additional File 2). Based on the SUCRA probability, tocilizumab IV + cDMARD was ranked the highest at both 12 and 24 weeks, indicating it as likely the best treatment (Fig. 2A-B). cDMARD alone had the lowest SUCRA values for both 12 and 24 weeks, ranking as the worst treatment.

TIM-naïve/mixed population—Monotherapy

For patients on monotherapy in the TIM-naïve/mixed population, 5 and 4 studies were evaluated at 12 and 24 weeks, respectively (Fig. 1C-D). Although limited evidence resulted in a sparse network for both timepoints, treatment with TIM monotherapy demonstrated a statistically significantly higher odds of achieving DAS28 remission compared to cDMARD monotherapy (Forest Plots—Fig. 2C-D; League Tables — Supplementary Table 6-7, Additional File 2). The ranking probability based on SUCRA indicated that tocilizumab IV had the highest likelihood of being the best treatment for achieving DAS28 remission followed by sarilumab (SUCRA—Fig. 2C-D).

TIM-experienced population—Combination therapy

A sparse network with 5 studies and 7 studies were included in the evaluation of patients on combination TIM + cDMARD therapy in the TIM-experienced populations for DAS28 remission at 12 weeks and 24 weeks, respectively (Fig. 1E-F). At 12 weeks, all TIMs in combination with cDMARD were associated with a statistically significantly higher odds of achieving DAS28 remission compared to cDMARD alone. Similar results were seen at 24 weeks, except that baricitinib + cDMARD did not show a statistically significant difference compared to cDMARD alone (Forest Plots—Fig. 2E-F; League Tables— Supplementary Table 8-9, Additional File 2). Tocilizumab IV also had the highest SUCRA probability for best treatment followed by rituximab and abatacept IV.

Sensitivity analysis

We conducted a sensitivity analysis in the TIM-experienced population for both 12 and 24 weeks to assess the stability of results by removing the ROSE trial (tocilizumab). In this trial, only 38% of patients were anti-TNF experienced while other trials in this network were ≈100% TIM-experienced. Similar to the base case analysis, results at 12 weeks demonstrated that all TIMs in combination with cDMARD showed a statistically significantly higher odds of achieving DAS28 remission compared to cDMARD alone, except with wider credible intervals for tocilizumab IV (Forest Plots—Supplementary Fig. 1A; League Table — Supplementary Table 10, Additional File 2). At 24 weeks, all TIMs in combination with cDMARD showed a statistically significant higher odds of achieving DAS28 remission compared to cDMARD alone except for baricitinib + cDMARD, consistent with the base case analysis (Forest Plots—Fig. 1B; League Table— Supplementary Table 11, Additional File 2). However, in this sensitivity analysis rituximab had the

highest SUCRA probability (0.86) for best treatment followed closely by abatacept IV (0.83) and tocilizumab IV (0.83).

Discussion

The results of this NMA showed consistently more favorable response with TIM therapies, as both monotherapy and combination therapy with cDMARD, compared to cDMARD alone for DAS28 remission. Favorable results with TIM therapies were seen at 12 and 24 weeks, and in both TIM-naïve/mixed as well as TIM-experienced patients. JAK inhibitors, as a relatively new class of drugs for the treatment of moderately-to-severe RA, have similar efficacy to other approved TIM therapies in lowering disease activity and achieving DAS28 remission. In all of our analyses, tocilizumab had the highest probability of being ranked as the best treatment for DAS28 remission. Tocilizumab IV also had the highest odds ratio of achieving DAS28 remission among all TIMs when comparing to cDMARD alone.

Our results are consistent with previous NMAs in the evaluation of other measurements of treatment response (i.e. ACR). Ollendorf *et al* also analyzed ACR response criteria in patients with moderate-to-severe RA who are TIM-naïve/mixed and TIM-experienced (10). They reported that all TIMs produced statistically and clinically superior improvements in ACR response when compared to cDMARD alone. Their results were also consistent regardless of whether TIMs were used in combination with cDMARDs or as monotherapy. Ollendorf *et al* also reported that tocilizumab IV monotherapy had the highest likelihood of achieving ACR20 or better in the TIM-naïve/mixed population. When analyzing JAK inhibitors on ACR response in the same population, Tice *et al* reported that proportions of patients achieving low disease activity or remission at 12 weeks, 24 weeks, and 48 weeks, were substantially greater in the JAK inhibitor group, with or without combination cDMARD therapy, compared to those receiving cDMARDs alone (11). Lee *et al* evaluated the efficacy of biologics and tofacitinib in patients with inadequate response to TNFi and reported that tocilizumab was associated with the most favorable SUCRA for the ACR20 response rate and the tocilizumab 8mg group showed a significantly higher ACR20 response rate compared to abatacept and tofacitinib (19). However, Lee at al. acknowledged that remission rates in each group were too small to perform an NMA. In these previous NMAs, only ACR response was used for the quantitative synthesis while DAS28 remission was presented as descriptive findings. Using DAS28 remission as the NMA outcome, our study provided a comprehensive comparison of all the eligible TIM therapies for their disease activity lowering effects, which could be useful to guide disease management strategies in different populations.

This study has some limitations. First, we did not perform our own SLR for this study. Included studies in the analysis were based on previous reviews by Ollendorf et al., 2017 and Tice et al., 2020, therefore it was assumed that the screening process and study selection were accurate in the previous reviews. We did, however, evaluate the eligibility criteria and comparability of studies before conducting the NMA to ensure potential effect modifiers were balanced across studies. After review by a clinician, we concluded studies were similar. Second, due to the limited evidence base and lack of available treatment comparisons, weaker networks were seen in the evaluation of monotherapy in the TIM-naïve/mixed

population and combination therapy in the TIM-experienced population, with only one or two studies informing each comparison. Moreover, as also reported by Ollendorf *et al* and Tice *et al* our treatment efficacy estimates were limited to the moderate-to-severe RA population (10, 11). Therefore, the applicability of these results should be limited to a moderate-to-severe RA population. Lastly, there are inherent drawbacks with the DAS28-ESR and CRP measurements. If a patient has a high ESR blood result, or if RA is present in the feet (which are not included in the 28-joint count), the score may be misleadingly high or low. Agents inhibiting IL-6 and JAK signaling may also lead to a rapid reduction in CRP or ESR levels while not affecting the other to a similar extent (20, 21). As a result, using DAS28-CRP when DAS28-ESR was not available may overestimate treatment effect and remission rates. Although the effect on acute phase reactants (ESR or CRP) by these agents might have an impact on the disease activity measure by DAS28, DAS28 remission is still considered appropriate since there were composite eligibility criteria involving joint counts and acute phase reactant levels at trial entry, such that changes in ESR/CRP alone are not likely to drive remission at week 12 or week 24.

Conclusion

Our NMA presents a comprehensive and simultaneous evaluation of all FDA approved TIM therapies and those undergoing FDA review using direct and indirect evidence. Our results suggest that TIM therapies, particularly tocilizumab IV, are effective in achieving DAS28 remission as early as 12 weeks compared to cDMARD alone. These results have important clinical implications that coincide with the increasing utilization of the TTT approach for patients with RA. RA is heterogeneous in terms of clinical presentation and disease management. As guidelines recommend more frequent monitoring of disease activity to better assess the likelihood of reaching the treatment target, using the DAS28 as a measure of disease activity can guide patient treatment and optimize outcomes. The DAS28 has validated thresholds for high and low disease activity and shows a clear relationship between clinically inactive RA and remission. Thus, therapies demonstrating achievement of low disease activity or remission at early follow-up, such as 12 weeks after treatment initiation, may have a higher likelihood of achieving success and improving outcomes.

Abbreviations

ACR	American College of Rheumatology
CrI	Credible Interval
CRP	C-reactive Protein
DAS28	Disease Activity Score-28
DMARD	Disease-modifying Antirheumatic Drugs
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FE	Fixed Effects
ICER	Institute for Clinical and Economic Review
IV	Intravenous
JAK	Janus Kinase
MCMC	Markov Chain Monte Carlo
NMA	Network Meta-analysis
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OR	Odds Ratio
RA	Rheumatoid Arthritis
RCTs	Randomized Controlled Trials
RE	Random Effects
SLR	Systematic Literature Reviews
TIMs	Targeted Immune Modulators
TNF	Tumor Necrosis Factor
TTT	Treat-to-target
US	United States
VAS	Visual Analog Scale

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests: JB and WR are employees and stockholders of Genentech, Inc. JD was an employee of Genentech, Inc. at the time this study was conducted. YK, JU, YJ, AK, and RS are employees of IQVIA Inc., which provides consulting and other research services to biopharmaceutical companies. IQVIA received funding from Genentech, Inc. to conduct this study and prepare the manuscript.

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Authors' contributions: JB, YK, JU, WR, JD contributed to the design of the study, interpretation of data, and manuscript drafting. YK, RS, and JU contributed to the data acquisition. YJ and AK performed data analysis. All authors read, revised, and approved the final manuscript.

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Tables

Table 1 Patient characteristics

Author, Year Study Acronym	Treatment Arm	Total N per Arm	Mean Age (years)	% Female	Disease Duration (years)	% Prior history of anti-TNF	DAS28 (mean)
TIM-naïve/mixed population—combination therapy							
Kremer, 2003 (22)	ABTiv+cDMARD	115	55.8	74.8	9.7	2.6	NR
	cDMARD	119	54.7	66.4	8.9	2.5	NR
Takeuchi, 2013 (23)	ABTiv+cDMARD	61	53.4	80.3	7.4	0	6
	cDMARD	66	53.4	78.8	7.3	0	6
Kremer, 2006 **AIM (24)**	ABTiv+cDMARD	433	51.5	77.8	8.5	0.2	6.4
	cDMARD	219	50.4	81.7	8.9	0	6.4
Schiff, 2008 **ATTEST (25)**	ABTiv+cDMARD	156	49	83.3	7.9	0	6.9
	IFX+cDMARD	165	49.1	82.4	7.3	0	6.8
	cDMARD	110	49.4	87.3	8.4	0	6.8
Weinblatt, 2013 **AMPLE (26)**	ABTsc+cDMARD	318	51.4	81.4	1.9	0	5.5
	ADA+cDMARD	328	51	82.3	1.7	0	5.5
Taylor, 2017 **RA-BEAM (27)**	ADA+cDMARD	330	53	76	10	0	5.8
	cDMARD	488	53	78	10	0	5.7
Dougados, 2016 **RA-BUILD (28)**	BAR+cDMARD	229	52	80	8	0	5.6
	cDMARD	228	51	83	7	0	5.5
Keystone, 2015 **14V-MC-JADA (29)**	BAR+cDMARD	52	51	85	5.5	0	6.2
	cDMARD	98	49	87	5.4	0	6.3
Choy, 2012 (30)	CTZ+cDMARD	126	53	72.2	9.4	0	6.2
	cDMARD	121	55.6	66.1	9.9	0	6.3
Smolen, 2009 **RAPID2 (31)**	CTZ+cDMARD	246	51.9	78	6.5	0.8	6.8
	cDMARD	127	51.5	84.3	5.6	1.6	6.8
Yamamoto, 2014 **J-RAPID (18)**	CTZ+cDMARD	82	50.6	84.1	5.6	13.4	6.2
	cDMARD	77	51.9	85.7	5.8	19.5	6.5

Author, Year Study Acronym	Treatment Arm	Total N per Arm	Mean Age (years)	% Female	Disease Duration (years)	% Prior history of anti-TNF	DAS28 (mean)
Combe, 2019 FINCH-1 (13)	FIL100+cDMARD	480	NR	83.1	8.5	NR	5.7
	FIL200+cDMARD	475	NR	79.8	7.3	NR	5.8
	ADA+cDMARD	325	NR	81.8	8.0	NR	5.7
	cDMARD	475	NR	82.3	7.3	NR	5.7
Tanaka, 2012 GO-FORTH (32)	GOL+cDMARD	86	50.4	84.9	8.8	NR	5.5
	cDMARD	88	51.1	83	8.7	NR	5.6
Keystone, 2009 GO-FORWARD (33)	GOL+cDMARD	89	52.0	80.9	4.5	0	6.1
	cDMARD	133	52.0	82	6.5	0	6.1
Li, 2015 (34)	GOL+cDMARD	132	47.7	83.3	7.6	0	5.4
	cDMARD	132	46.7	78.8	8.0	0	5.5
Westhovens, 2006 START (35)	IFX+cDMARD	360	NR	80.0	8.0	0	NR
	cDMARD	363	NR	83.2	8.4	0	NR
Emery, 2010 SERENE (36)	RTX+cDMARD	172	51.3	81.2	6.6	0	6.5
	cDMARD	172	52.1	85.4	7.5	0	6.5
Genovese, 2015 MOBILITY (37)	SAR200+cDMARD	399	50.8	85	8.6	19.5	6
	cDMARD	398	50.9	81	9.1	20.6	5.9
Kremer, 2011 LITHE (38)	TCZiv+cDMARD	797	52.4	83	9.4	11.6	6.5
	cDMARD	393	51.3	83	9.0	11.5	6.5
Smolen, 2008 OPTION (39)	TCZiv+cDMARD	419	51.1	83.5	7.4	7.6	6.8
	cDMARD	204	50.6	78	7.8	9.0	6.8
Genovese, 2008 TOWARD (40)	TCZiv+cDMARD	803	53.0	81.0	9.8	NR	6.7
	cDMARD	413	54.0	84.0	9.8	NR	6.6
Kivitz, 2014 BREVACTA (41)	TCZsc+cDMARD	437	52.1	85.8	11.1	NR	6.7
	cDMARD	219	52.0	82.6	11.1	NR	6.6

Author, Year Study Acronym	Treatment Arm	Total N per Arm	Mean Age (years)	% Female	Disease Duration (years)	% Prior history of anti-TNF	DAS28 (mean)
Kremer, 2012 (42)	TOF+cDMARD	71	52.0	80.3	9	NR	6.1
	cDMARD	69	53.0	81.2	9.2	NR	6.1
Kremer, 2013 ORAL Sync (43)	TOF+cDMARD	315	52.7	83.8	8.1	7.3	NR
	cDMARD	159	50.8	79.7	9.5	6.3	NR
Van Vollenhoven, 2012 ORAL STANDARD (17)	TOF+cDMARD	204	53.0	85.3	7.6	5.9	6.6
	ADA+cDMARD	204	52.5	79.4	8.1	7.8	6.6
	cDMARD	56	55.5	76.8	6.9	7.1	6.4
Van der Heijde, 2013 ORAL Scan (16)	TOF+cDMARD	321	53.7	83.8	8.9	19.3	6.3
	cDMARD	81	53.2	80.2	8.8	9.9	6.3
Fleischmann, 2017 ORAL Strategy (44)	TOF+cDMARD	376	50	83	13.6	4	6.6
	ADA+cDMARD	386	50.7	83	13.8	5	6.5
Fleischmann, 2018 SELECT-COMPARE (45)	UPA15+cDMARD	651	NR	NR	NR	NR	NR
	ADA+cDMARD	327	NR	NR	NR	NR	NR
	cDMARD	651	NR	NR	NR	NR	NR
Burmester, 2018 SELECT-NEXT (46)	UPA15+cDMARD	221	55.3	82	7.3	12	5.7
	cDMARD	221	56	75	7.2	13	5.6
TIM-naïve/mixed population—monotherapy							
Burmester, 2016 MONARCH (47)	SAR	184	50.9	85.3	8.1	0	6.8
	ADA	185	53.6	81.1	6.6	0	6.8
Gabay, 2013 ADACTA (48)	TCZiv	163	54.4	79	7.3	0	6.7
	ADA	162	53.3	82	6.3	0	6.8
Nishimoto, 2007 SAMURAI (49)	TCZiv	145	53.1	82.1	2.4	NR	6.4
	cDMARD	157	52.9	86.2	2.2	NR	6.5

Author, Year Study Acronym	Treatment Arm	Total N per Arm	Mean Age (years)	% Female	Disease Duration (years)	% Prior history of anti-TNF	DAS28 (mean)
Nishimoto, 2009 SATORI (50)	TCZiv	61	52.6	90.2	8.5	NR	6.1
	cDMARD	64	50.8	75	8.7	NR	6.2
Fleischmann, 2012 (51)	TOF	49	54	87.8	8.1	NR	6.6
	ADA	53	54	84.9	7.7	NR	6.3
Smolen, 2018 SELECT-MONOTHERAPY (52)	UPA15	217	NR	NR	NR	0	NR
	cDMARD	216	NR	NR	NR	0	NR
TIM-experienced population—combination therapy							
Genovese, 2005 ATTAIN (53)	ABTiv+cDMARD	258	53.4	77.1	12.2	100	6.5
	cDMARD	133	52.7	79.7	11.4	100	6.5
Genovese, 2016 RA-BEACON (54)	BAR+cDMARD	174	55	79	14	100	6.7
	cDMARD	176	56	82	14	100	6.6
Genovese, 2019 FINCH-2 (12)	FIL100+cDMARD	153	55	77.8	10.9	100	5.9
	FIL200+cDMARD	147	56	81.6	11.1	100	5.9
	cDMARD	148	56	81.8	10.6	100	5.9
Cohen, 2006 REFLEX (55)	RTX+cDMARD	308	52.2	81	12.1	100	6.9
	cDMARD	209	52.8	81	11.7	100	6.8
Fleischmann, 2016 TARGET (56)	SAR200+cDMARD	184	52.9	82.1	12.7	100	6.3
	cDMARD	181	51.9	85.1	12	100	6.2
Emery, 2008 RADIATE (57)	TCZiv+cDMARD	331	52.4	82.5	11.8	100	6.8
	cDMARD	158	53.4	79	11.4	100	6.8
Yazici, 2012 ROSE (15)	TCZiv+cDMARD	409	55.2	79.5	8.6	37.9	6.5
	cDMARD	205	55.8	83.9	8.5	38	6.6
Burmester, 2013 ORAL Step (58)	TOF+cDMARD	133	55.4	85	13	99.2	6.5

Author, Year Study Acronym	Treatment Arm	Total N per Arm	Mean Age (years)	% Female	Disease Duration (years)	% Prior history of anti-TNF	DAS28 (mean)
	cDMARD	132	54.4	80.3	11.3	100	6.4

ABT Abatacept, *ADA* Adalimumab, *BAR* Baricitinib, *cDMARD* Conventional disease-modifying antirheumatic drugs, *CTZ* Certolizumab pegol, *FIL* Filgotinib, *GOL* Golimumab, *IFX* Infliximab, *iv* Intravenous, *RTX* Rituximab, *SAR* Sarilumab, *sc* Subcutaneous, *TCZ* Tocilizumab, *TIM* Targeted immune modulators, *TNF* Tumor necrosis factor, *TOF* Tofacitinib, *UPA* Upadacitinib

Additional Files

File name - Additional File 1, Additional File 2

File format: Word document; .docx

Title of data:

Additional File 1 includes

Supplementary methods:

- PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) eligibility criteria for Ollendorf et al, 2017
- PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) eligibility criteria for Tice et al, 2020

Additional File 2 includes

Supplementary tables:

- Supplementary Table 1. Targeted immune modulators: dosage forms and administration schedules
- Supplementary Table 2. Patient characteristics
- Supplementary Table 3. DAS28 remission (<2.6)
- Supplementary Table 4. Median odds ratio (95% CrI) of achieving DAS28 remission at 12 weeks, in TIM-naïve/mixed population receiving combination therapy, for pairwise comparison among included treatments
- Supplementary Table 5. Median odds ratio (95% CrI) of achieving DAS28 remission at 24 weeks, in TIM-naïve/mixed population receiving combination therapy, for pairwise comparison among included treatments
- Supplementary Table 6. Median odds ratio (95% CrI) of achieving DAS28 remission at 12 weeks, in TIM-naïve/mixed population receiving monotherapy, for pairwise comparison among included

treatments

- Supplementary Table 7. Median odds ratio (95% CrI) of achieving DAS28 remission at 24 weeks, in TIM-naïve/mixed population receiving monotherapy, for pairwise comparison among included treatments
- Supplementary Table 8. Median odds ratio (95% CrI) of achieving DAS28 remission at 12 weeks, in TIM-experienced population receiving combination therapy, for pairwise comparison among included treatments
- Supplementary Table 9. Median odds ratio (95% CrI) of achieving DAS28 remission at 24 weeks, in TIM-experienced population receiving combination therapy, for pairwise comparison among included treatments
- Supplementary Table 10. Median odds ratio (95% CrI) of achieving DAS28 remission at 12 weeks, in TIM-experienced population receiving combination therapy, for pairwise comparison among included treatments, in sensitivity analysis excluding the ROSE trial
- Supplementary Table 11. Median odds ratio (95% CrI) of achieving DAS28 remission at 24 weeks, in TIM-experienced population receiving combination therapy, for pairwise comparison among included treatments, in sensitivity analysis excluding the ROSE trial

Supplementary figure:

- Supplementary Fig. 1. Sensitivity analysis excluding the ROSE trial - forest plots for median odds ratio (95% credible interval) of achieving DAS28 remission in TIM treatment versus cDMARD treatment groups in TIM-experienced population receiving combination therapy, at A) 12 weeks and B) 24 weeks.

Description of data:

Additional File 1 includes supplementary methods presenting the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) eligibility criteria for Ollendorf et al, 2017 and Tice et al, 2020.

Additional File 2 includes supplementary tables and figure presenting the following: dosage forms and administration schedules of the targeted immune modulators; patient characteristics of individual studies included in the network meta-analysis; DAS28 remission (<2.6) outcomes of individual studies included in the network meta-analysis; summary tables of odds ratios (95% CrI) of achieving DAS28 remission at 12 weeks/24 weeks, for pairwise comparison among included treatments; summary tables and forest plots of odds ratios (95% CrI) of achieving DAS28 remission at 12 weeks/24 weeks determined in sensitivity analysis excluding the ROSE trial.

Figures

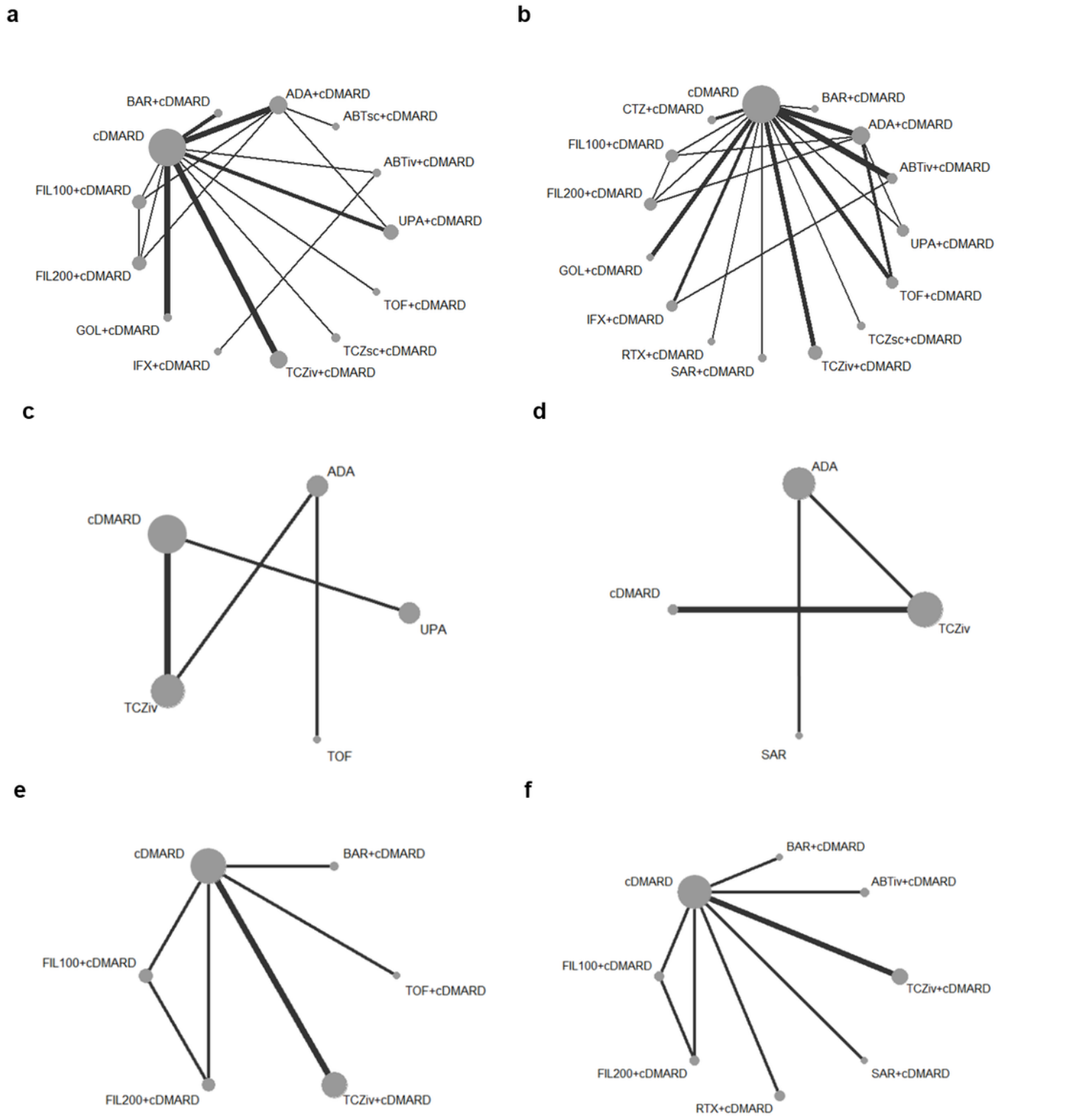


Figure 1

Network diagrams of studies evaluating DAS28 remission with TIM treatment. a TIM-naïve/mixed population receiving combination therapy at 12 weeks. b TIM-naïve/mixed population receiving combination therapy at 24 weeks. c TIM-naïve/mixed population receiving monotherapy at 12 weeks. d TIM-naïve/mixed population receiving monotherapy at 24 weeks. e TIM-experienced population receiving combination therapy at 12 weeks. f TIM-experienced population receiving combination therapy at 24

weeks. Legend: The size of the nodes corresponds to the number of participants assigned to each treatment, and the thickness of the edges corresponds to the number of trials evaluating the comparison. ABT Abatacept, ADA Adalimumab, BAR Baricitinib, cDMARD Conventional disease-modifying antirheumatic drugs, CTZ Certolizumab pegol, FIL Filgotinib, GOL Golimumab, IFX Infliximab, iv Intravenous, RTX Rituximab, SAR Sarilumab, sc Subcutaneous, TCZ Tocilizumab, TIM Targeted immune modulators, TOF Tofacitinib, UPA Upadacitinib.

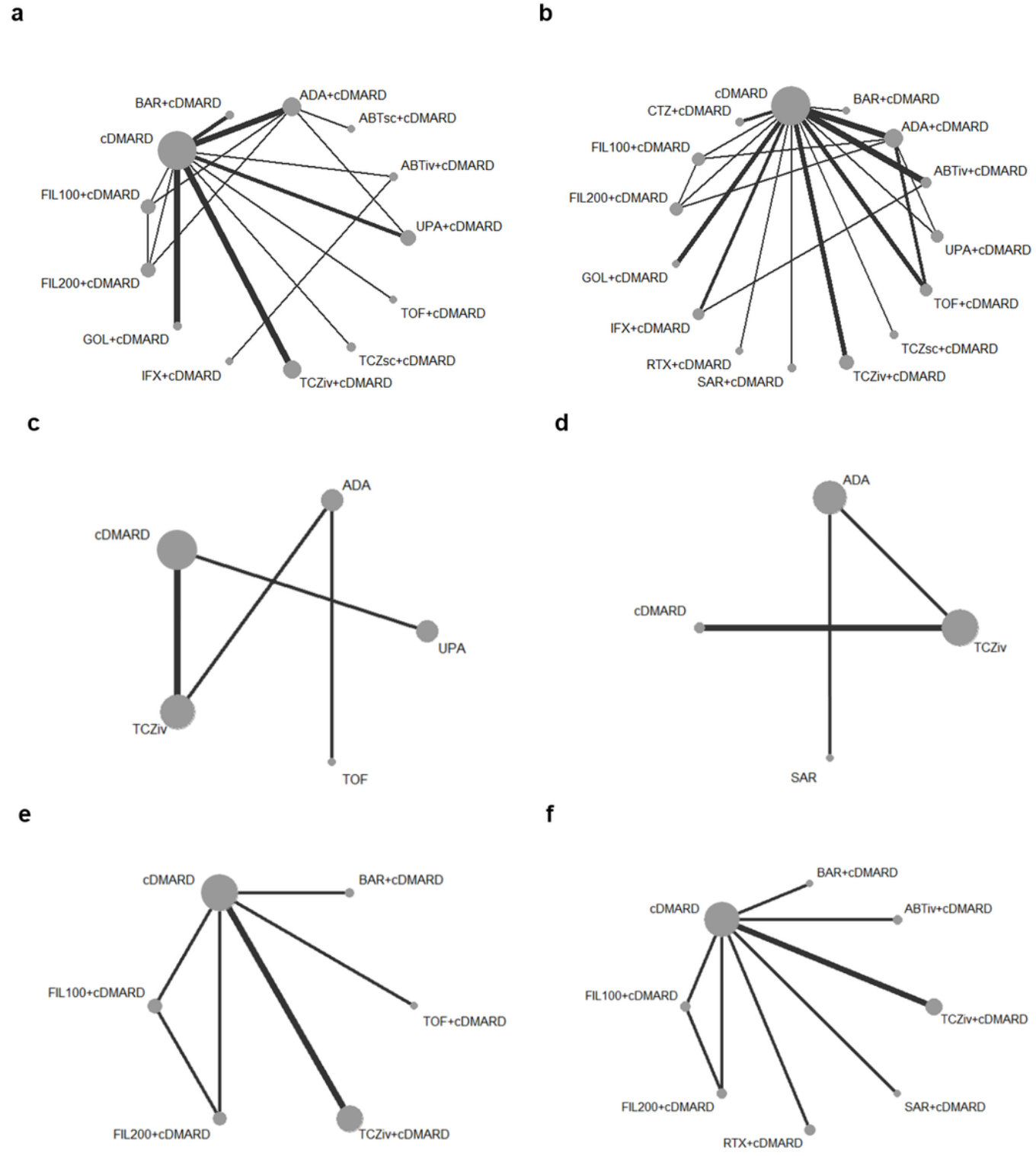


Figure 1

Network diagrams of studies evaluating DAS28 remission with TIM treatment. a TIM-naïve/mixed population receiving combination therapy at 12 weeks. b TIM-naïve/mixed population receiving combination therapy at 24 weeks. c TIM-naïve/mixed population receiving monotherapy at 12 weeks. d TIM-naïve/mixed population receiving monotherapy at 24 weeks. e TIM-experienced population receiving combination therapy at 12 weeks. f TIM-experienced population receiving combination therapy at 24 weeks. Legend: The size of the nodes corresponds to the number of participants assigned to each treatment, and the thickness of the edges corresponds to the number of trials evaluating the comparison. ABT Abatacept, ADA Adalimumab, BAR Baricitinib, cDMARD Conventional disease-modifying antirheumatic drugs, CTZ Certolizumab pegol, FIL Filgotinib, GOL Golimumab, IFX Infliximab, iv Intravenous, RTX Rituximab, SAR Sarilumab, sc Subcutaneous, TCZ Tocilizumab, TIM Targeted immune modulators, TOF Tofacitinib, UPA Upadacitinib.

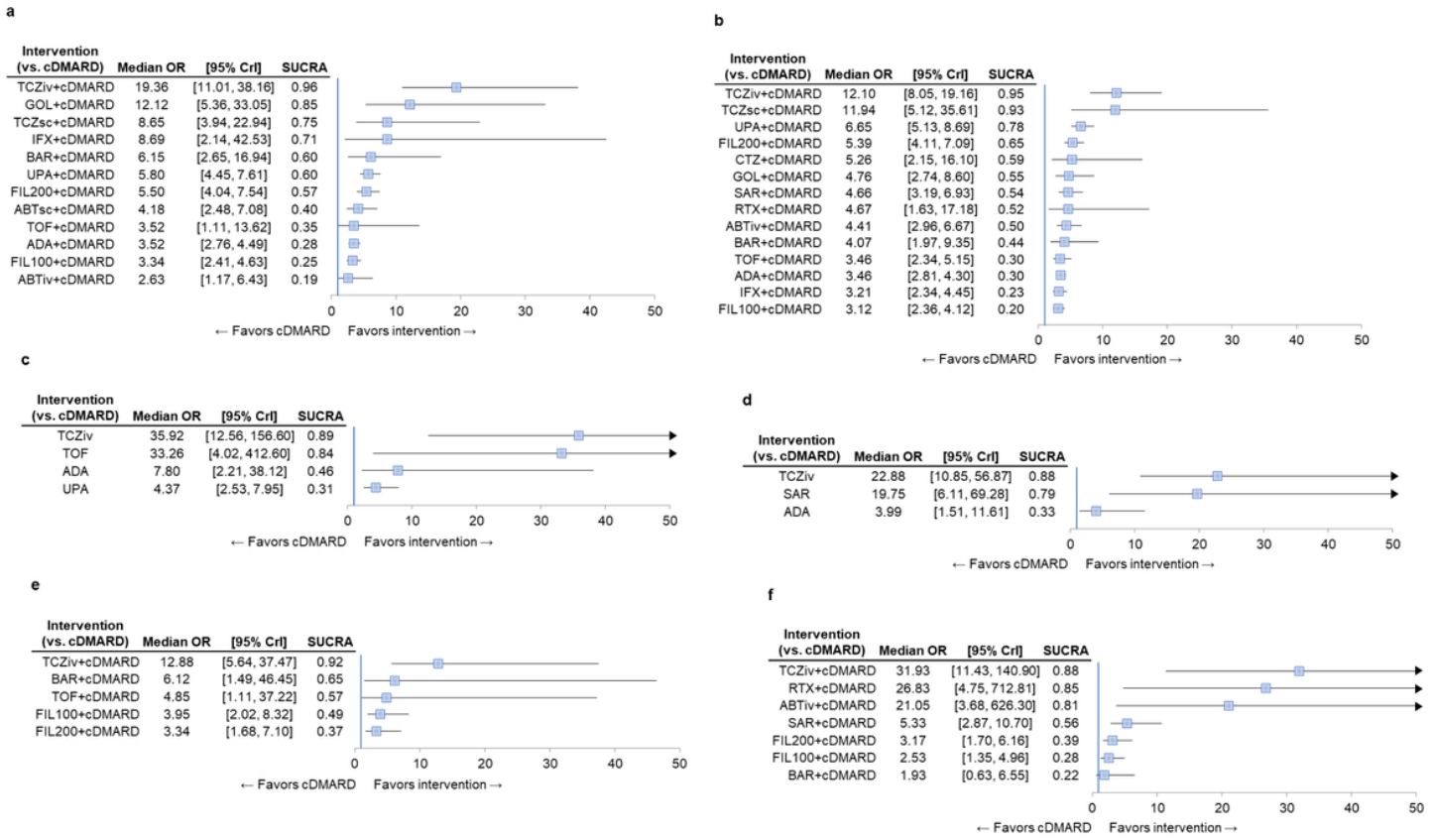
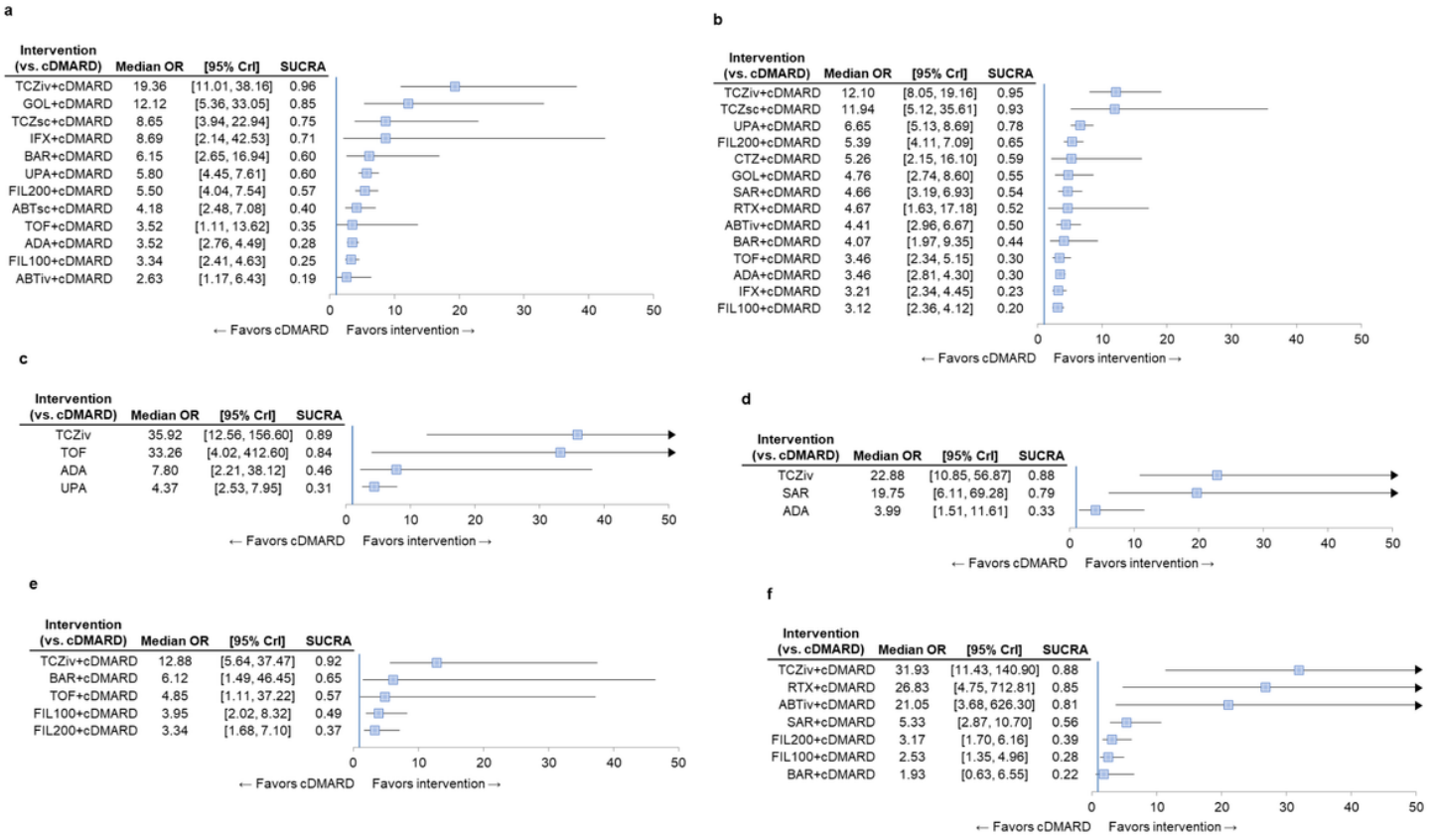


Figure 2

Forest plots for median odds ratio (95% credible interval) of achieving DAS28 remission in TIM treatment versus cDMARD treatment groups. a TIM-naïve/mixed population receiving combination therapy at 12 weeks. b TIM-naïve/mixed population receiving combination therapy at 24 weeks. c TIM-naïve/mixed population receiving monotherapy at 12 weeks. d TIM-naïve/mixed population receiving monotherapy at 24 weeks. e TIM-experienced population receiving combination therapy at 12 weeks. f TIM-experienced population receiving combination therapy at 24 weeks. Legend: The results were considered to be statistically significant when the span of the 95% CrI did not include 1. ABT Abatacept, ADA Adalimumab, BAR Baricitinib, cDMARD Conventional disease-modifying antirheumatic drugs, CrI Credible interval, CTZ

Certolizumab pegol, FIL Filgotinib, GOL Golimumab, IFX Infliximab, iv Intravenous, OR Odds ratio, RTX Rituximab, SAR Sarilumab, sc Subcutaneous, SUCRA Surface under the cumulative ranking curve, TCZ Tocilizumab, TIM Targeted immune modulators, TOF Tofacitinib, UPA Upadacitinib.



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