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

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ABSTRACT

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

Methods: A fixed-effects Bayesian network meta-analysis (NMA) was performed using published study-level data from 41 randomized controlled trials (RCTs) identified from two recent systematic literature reviews conducted by the Institute for Clinical and Economic Review, and two additional phase III trials for filgotinib (FINCH-1, FINCH-2). RCTs that compared TIMs with each other, cDMARD therapy, or placebo were included. Treatments included Janus kinase (JAK) inhibitors, tumor necrosis factor α inhibitors (TNFi), and other non-TNFi therapies. 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-naive/mixed population, all TIMs combined with cDMARD therapy were significantly more likely to achieve remission compared with a cDMARD alone, 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 with cDMARD therapy. Similar trends were observed for the analyses on monotherapy or TIM-experienced population.

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

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**Keywords:** Disease activity score; Network meta-analysis; Remission; Rheumatoid arthritis; Targeted immune modulators

**Key Summary Points**

**Why carry out this study?**

This network meta-analysis (NMA) evaluated the comparative efficacy of targeted immune modulators (TIMs) for achieving DAS28 remission in patients with moderately to severely active rheumatoid arthritis (RA) with an inadequate response to or intolerance of conventional disease-modifying antirheumatic drugs (cDMARDs).

**What was learned from this study?**

The results showed consistently more favorable response for DAS28 remission with TIM therapies, as both monotherapy and combination therapy with cDMARDs, compared with a cDMARD alone at both 12 and 24 weeks.

In all analyses, tocilizumab had the highest probability of being ranked as the best treatment for DAS28 remission when compared with most other TIMs including new JAK inhibitors; intravenous tocilizumab had the highest odds ratio of achieving DAS28 remission among all TIMs compared with a cDMARD alone.

The results of this NMA have important clinical implications that coincide with the increasing use of the treat-to-target approach for patients with RA, as guidelines recommend frequent monitoring of disease activity to assess the likelihood of reaching the treatment target.

**INTRODUCTION**

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]) or prevent disease progression (disease-modifying antirheumatic drugs [DMARDs]) and, thus, tissue damage. Conventional synthetic DMARDs (cDMARDs) include older systemic agents such as methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide that decrease inflammation and slow radiographic progression. Methotrexate is the most frequently prescribed medication as an initial treatment, but only an estimated 30% of patients demonstrate...
low disease activity with methotrexate monotherapy, while combinations of cDMARDs and biologics are significantly more effective than methotrexate alone in such patients [7]. Therefore, in patients who 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 inhibitors, 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 nonbiologic 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 (T2T) 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 4–12 weeks after the start of treatment is recommended by guidelines following a T2T 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 > 5.1 implies active disease, between 2.6 and 3.2 implies low disease activity, and < 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 T2T approach in the clinical setting.

Two systematic literature reviews (SLRs) 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 because 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, a NMA was conducted for ACR response outcomes but not for disease activity measures. In addition, no conclusions were made comparing JAK inhibitors with each other or with other TIMs.

While these two 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 (e.g., a newer JAK inhibitor, filgotinib, was not included). Clinical evidence of filgotinib is available from two 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 using evidence published in the two prior SLRs [10, 11], with additional clinical evidence from the FINCH-1 and FINCH-2 trials. An NMA was conducted using this.
evidence base in order to evaluate the comparative efficacy of achieving DAS28 remission with RA treatments in populations with moderately to severely active disease that are TIM naïve/mixed or TIM experienced.

METHODS

The primary objective of this NMA was to evaluate the comparative efficacy of TIM therapies for DAS28 remission. DAS28 is scored on a continuous scale (0–10.0) 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 two previous SLRs, including search strategy and terms, 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. MEDLINE®, Embase®, and Cochrane-indexed publications from database inception to June 26, 2019, were searched. Each search was limited to English-language studies in humans and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news articles. All search strategies were generated using 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 two previous evidence reports was complemented by two additional RCTs, FINCH-1 and FINCH-2, that compared the effects of filgotinib vs. placebo on the signs and symptoms of patients with RA who had an inadequate response to one or more prior DMARD treatments [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 in patients with moderately to severely active RA who had an inadequate treatment response to or intolerance of methotrexate or another cDMARD. Our research focused on three different patient populations. First was a TIM-naïve/mixed population on combination therapy, in which ≤ 20% had previous TIM experience and were receiving TIM therapies in combination with a cDMARD. Second was a TIM-naïve/mixed population on TIM monotherapy, in which ≤ 20% had previous TIM experience and were receiving TIM monotherapy. Third was a TIM-experienced population on combination therapy, in which > 20% had previous treatment with TIMs and were receiving TIM treatment in combination with a cDMARD.

All TIMs were included, as specified in Ollendorf et al. [10] and Tice et al. [11], and only the FDA-approved dosages were included in this NMA (see Supplementary Table 1, Supplement 2, for all included TIMs and dosages). RCTs that compared TIMs with each other, a cDMARD, or placebo were included. Treatment groups evaluating dosages not approved by the FDA were excluded. 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 was under FDA review at the time of this NMA, both investigational dosages (100 mg and 200 mg once daily) were included for analysis. For studies that involved treatment switch or advancement, only comparative results before the change of treatment were included in this NMA.

Our study focused on DAS28 remission, defined by DAS28 score < 2.6 at 12 weeks and 24 weeks. DAS28-ESR was used primarily; if not available, we used DAS28-CRP.
Data Synthesis and Network Meta-Analysis

Because not all treatments of interest have been directly compared, we developed quantitative, indirect comparisons among all TIM agents using a Bayesian NMA for the DAS28 remission outcome. The models 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 unknown parameters were estimated using Markov chain Monte Carlo (MCMC) simulations. The analyses were based on 60,000 iterations on three chains, with a burn-in of ≥ 20,000 iterations. Consistent with the two 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 among TIM-naive/mixed and TIM-experienced populations. All statistical analyses were run within a Bayesian framework with WinBUGS version 3.2.3 (RStudio; Boston, MA) 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 populations who were TIM naive/mixed on combination therapy, TIM naive/mixed on monotherapy, and TIM experienced on combination therapy at 12 and 24 weeks each. The FE model was selected for all analyses because 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 comparisons of TIMs with cDMARDs were 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 4042 potentially relevant references. After full-text review, 132 publications met the inclusion criteria (Supplementary methods in Supplement 1), comprising 67 RCTs and 17 observational studies. The original search focused on all TIM therapies in patients with moderately to severely 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 used JAK inhibitors, for which 40 references on 16 RCTs met the inclusion criteria (Supplementary methods in Supplement 1 [11]).

We included 41 trials that reported DAS28 remission at 12 or 24 weeks from the two previous SLRs, as well as two additional phase 3 RCTs reporting DAS28 remission with filgotinib. Among the 43 trials included in our evidence base, 35 had TIM-naive/mixed populations, while eight had TIM-experienced patients. Thirty-seven trials included patients on combination therapy, while six 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, Supplement 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 TNFi use; in the ROSE trial, approximately 38%
| Author, year | Study abbreviation | Treatment arm | Total per arm, N | Age, mean, years | Female, % | Disease duration, years | Prior history of anti-TNF, % | DAS28, mean |
|-------------|-------------------|---------------|------------------|----------------|----------|------------------------|---------------------------|--------------|
| TIM-naïve/mixed population—combination therapy |
| Kremer, 2003 [23] | 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 [24] | ABTiv + cDMARD | 61 | 53.4 | 80.3 | 7.4 | 0 | 6 |
| cDMARD | 66 | 53.4 | 78.8 | 7.3 | 0 | 6 |
| Kremer, 2006 | ABTiv + cDMARD | 433 | 51.5 | 77.8 | 8.5 | 0.2 | 6.4 |
| AIM [25] | cDMARD | 219 | 50.4 | 81.7 | 8.9 | 0 | 6.4 |
| Schiff, 2008 | ABTiv + cDMARD | 156 | 49 | 83.3 | 7.9 | 0 | 6.9 |
| ATTEST [26] | 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 | ABTsc + cDMARD | 318 | 51.4 | 81.4 | 1.9 | 0 | 5.5 |
| AMPLE [27] | ADA + cDMARD | 328 | 51 | 82.3 | 1.7 | 0 | 5.5 |
| Taylor, 2017 | ADA + cDMARD | 330 | 53 | 76 | 10 | 0 | 5.8 |
| RA-BEAM [28] | cDMARD | 488 | 53 | 78 | 10 | 0 | 5.7 |
| Dougados, 2016 | BAR + cDMARD | 229 | 52 | 80 | 8 | 0 | 5.6 |
| RA-BUILD [29] | cDMARD | 228 | 51 | 83 | 7 | 0 | 5.5 |
| Keystone, 2015 | BAR + cDMARD | 52 | 51 | 85 | 5.5 | 0 | 6.2 |
| 14 V-MC-JADA [30] | cDMARD | 98 | 49 | 87 | 5.4 | 0 | 6.3 |
| Choy, 2012 [31] | CTZ + cDMARD | 126 | 53 | 72.2 | 9.4 | 0 | 6.2 |
| cDMARD | 121 | 55.6 | 66.1 | 9.9 | 0 | 6.3 |
| Smolen, 2009 | CTZ + cDMARD | 246 | 51.9 | 78 | 6.5 | 0.8 | 6.8 |
| RAPID2 [32] | cDMARD | 127 | 51.5 | 84.3 | 5.6 | 1.6 | 6.8 |
| Yamamoto, 2014 | CTZ + cDMARD | 82 | 50.6 | 84.1 | 5.6 | 13.4 | 6.2 |
| J-RAPID [18] | cDMARD | 77 | 51.9 | 85.7 | 5.8 | 19.5 | 6.5 |
| Combe, 2019 | FIL100 + cDMARD | 480 | NR | 83.1 | 8.5 | NR | 5.7 |
| FINCH-1 [13] | 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 | GOL + cDMARD | 86 | 50.4 | 84.9 | 8.8 | NR | 5.5 |
| GO-FORTH [33] | cDMARD | 88 | 51.1 | 83 | 8.7 | NR | 5.6 |
| Author, year | Study abbreviation | Treatment arm | Total per arm, N | Age, mean, years | Female, % | Disease duration, years | Prior history of anti-TNF, % | DAS28, mean |
|--------------|---------------------|---------------|------------------|-------------------|----------|------------------------|-----------------------------|-------------|
| Keyston, 2009 | GO-FORWARD [34] | GOL + cDMARD | 89 | 52.0 | 80.9 | 4.5 | 0 | 6.1 |
| | | cDMARD | 133 | 52.0 | 82 | 6.5 | 0 | 6.1 |
| Li, 2015 [35] | | 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 | | IFX + cDMARD | 360 | NR | 80.0 | 8.0 | 0 | NR |
| START [36] | | cDMARD | 363 | NR | 83.2 | 8.4 | 0 | NR |
| Emery, 2010 | | RTX + cDMARD | 172 | 51.3 | 81.2 | 6.6 | 0 | 6.5 |
| SERENE [37] | | cDMARD | 172 | 52.1 | 85.4 | 7.5 | 0 | 6.5 |
| Genovese, 2015 | | SAR200 + cDMARD | 399 | 50.8 | 85 | 8.6 | 19.5 | 6 |
| MOBILITY [38] | | cDMARD | 398 | 50.9 | 81 | 9.1 | 20.6 | 5.9 |
| Kremer, 2011 | | TCZiv + cDMARD | 797 | 52.4 | 83 | 9.4 | 11.6 | 6.5 |
| LITHE [39] | | cDMARD | 393 | 51.3 | 83 | 9.0 | 11.5 | 6.5 |
| Smolen, 2008 | | TCZiv + cDMARD | 419 | 51.1 | 83.5 | 7.4 | 7.6 | 6.8 |
| OPTION [40] | | cDMARD | 204 | 50.6 | 78 | 7.8 | 9.0 | 6.8 |
| Genovese, 2008 | | TCZiv + cDMARD | 803 | 53.0 | 81.0 | 9.8 | NR | 6.7 |
| TOWARD [41] | | cDMARD | 413 | 54.0 | 84.0 | 9.8 | NR | 6.6 |
| Kivitz, 2014 | | TCZsc + cDMARD | 437 | 52.1 | 85.8 | 11.1 | NR | 6.7 |
| BREVACTA [42] | | cDMARD | 219 | 52.0 | 82.6 | 11.1 | NR | 6.6 |
| Kremer, 2012 [43] | | TOF + cDMARD | 71 | 52.0 | 80.3 | 9 | NR | 6.1 |
| | | cDMARD | 69 | 53.0 | 81.2 | 9.2 | NR | 6.1 |
| Kremer, 2013 | | TOF + cDMARD | 315 | 52.7 | 83.8 | 8.1 | 7.3 | NR |
| ORAL Sync [44] | | cDMARD | 159 | 50.8 | 79.7 | 9.5 | 6.3 | NR |
| Van Vollenhoven, 2012 | | TOF + cDMARD | 204 | 53.0 | 85.3 | 7.6 | 5.9 | 6.6 |
| ORAL STANDARD [17] | | ADA + cDMARD | 204 | 52.5 | 79.4 | 8.1 | 7.8 | 6.6 |
| Van der Heijde, 2013 | | TOF + cDMARD | 321 | 53.7 | 83.8 | 8.9 | 19.3 | 6.3 |
| ORAL Scan [16] | | cDMARD | 81 | 53.2 | 80.2 | 8.8 | 9.9 | 6.3 |
| Fleischmann, 2017 | | TOF + cDMARD | 376 | 50 | 83 | 13.6 | 4 | 6.6 |
| ORAL Strategy [45] | | ADA + cDMARD | 386 | 50.7 | 83 | 13.8 | 5 | 6.5 |
Table 1 continued

| Author, year | Study abbreviation | Treatment arm | Total per arm, N | Age, mean, years | Female, % | Disease duration, years | Prior history of anti-TNF, % | DAS28, mean |
|--------------|--------------------|---------------|------------------|------------------|-----------|------------------------|----------------------------|-------------|
| Fleischmann, 2018 | SELECT-COMPARE [46] | 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 [47] | 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

| Author, year | Study abbreviation | Treatment arm | Total per arm, N | Age, mean, years | Female, % | Disease duration, years | Prior history of anti-TNF, % | DAS28, mean |
|--------------|--------------------|---------------|------------------|------------------|-----------|------------------------|----------------------------|-------------|
| Burmester, 2016 | MONARCH [48] | 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 [49] | TCZiv | 163 | 54.4 | 79 | 7.3 | 0 | 6.7 |
| Nishimoto, 2007 | SAMURAI [50] | TCZiv | 145 | 53.1 | 82.1 | 2.4 | NR | 6.4 |
| | | cDMARD | 157 | 52.9 | 86.2 | 2.2 | NR | 6.5 |
| Nishimoto, 2009 | SATORI [51] | TCZiv | 61 | 52.6 | 90.2 | 8.5 | NR | 6.1 |
| | | cDMARD | 64 | 50.8 | 75 | 8.7 | NR | 6.2 |
| Fleischmann, 2012 | TOF [52] | ADA | 49 | 54 | 87.8 | 8.1 | NR | 6.6 |
| | | cDMARD | 53 | 54 | 84.9 | 7.7 | NR | 6.2 |
| Smolen, 2018 | SELECT-MONOTHERAPY [53] | UPA15 | 217 | NR | NR | NR | 0 | NR |
| | | cDMARD | 216 | NR | NR | NR | 0 | NR |

TIM-experienced population—combination therapy

| Author, year | Study abbreviation | Treatment arm | Total per arm, N | Age, mean, years | Female, % | Disease duration, years | Prior history of anti-TNF, % | DAS28, mean |
|--------------|--------------------|---------------|------------------|------------------|-----------|------------------------|----------------------------|-------------|
| Genovese, 2005 | ATTAIN [54] | 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 [55] | 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 [56] | RTX + cDMARD | 308 | 52.2 | 81 | 12.1 | 100 | 6.9 |
| | | cDMARD | 209 | 52.8 | 81 | 11.7 | 100 | 6.8 |
of patients had prior TNFi 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 joints examined) and swollen (66 joints examined) joints at 3 months [16, 17]. Therefore, a nonresponder 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, Supplement 2. Among the 43 included studies, one 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 Tables 4–9, Supplement 2).

**TIM-Naïve/Mixed Population: Combination Therapy**

A total of 17 and 24 studies of combination therapy with TIMs + a cDMARD in TIM-naïve/mixed populations evaluated DAS28 remission at 12 and 24 weeks, respectively. The network diagrams are presented in Fig. 1a and b. Results across both time points were similar. At 12 and 24 weeks, all TIMs in combination with a cDMARD showed significantly higher odds of achieving DAS28 remission compared with a cDMARD alone (Fig. 2a, b). Intravenous (IV) tocilizumab in combination with a cDMARD showed the highest significant difference compared with a cDMARD alone (OR 19.36; 95% Crl 11.01–38.16). Among all pairwise comparisons, results favored tocilizumab IV + a cDMARD, with the odds of achieving DAS28 remission significantly better compared with 8 of 12 comparisons and 11 of 14 comparisons for 12 and 24 weeks, respectively (Supplementary Tables 4–5, Supplement 2). Based on the SUCRA
Fig. 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. 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 drug, CTZ certolizumab pegol, FIL filgotinib, GOL golimumab, IFX infliximab, IV intravenous, RTX rituximab, SAR sarilumab, SC subcutaneous, TCZ tocilizumab, TIM targeted immune modulator, TNF tumor necrosis factor, TOF tofacitinib, UPA upadacitinib
probability, tocilizumab IV + a cDMARD was ranked highest at both 12 and 24 weeks, designating it as likely the best treatment (Fig. 2a, b). A cDMARD alone had the lowest SUCRA values for both 12 and 24 weeks, ranking cDMARD therapy as the worst treatment.

**TIM-Naïve/Mixed Population: Monotherapy**
For patients on monotherapy in the TIM-naïve/mixed population, five and four studies were evaluated at 12 and 24 weeks, respectively (Fig. 1c, d). Although limited evidence resulted in a sparse network for both time points, treatment with TIM monotherapy demonstrated significantly higher odds of achieving DAS28 remission compared with cDMARD monotherapy (forest plots: Fig. 2c, d; league tables: Supplementary Tables 6–7, Supplement 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 (Fig. 2c, d).

**TIM-Experienced Population: Combination Therapy**
A sparse network with five studies and seven studies was included in the evaluation of patients on combination TIM + cDMARD therapy in the TIM-experienced populations for DAS28 remission at 12 and 24 weeks, respectively (Fig. 1e, f). At 12 weeks, all TIMs in combination with cDMARDs were associated with significantly higher odds of achieving DAS28 remission compared with a cDMARD alone. Similar results were seen at 24 weeks, except that baricitinib + a cDMARD did not show a significant difference compared with a cDMARD alone (forest plots: Supplementary Tables 8, 9, Supplement 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 at both 12 and 24 weeks to assess the stability of results by removing the ROSE trial (tocilizumab). In this trial, only 38% of patients had prior anti-TNF experience, while rates of TIM experience in other trials in this network were approximately 100%. Similar to the base case analysis, results at 12 weeks demonstrated that all TIMs in combination with cDMARDs showed significantly higher odds of achieving DAS28 remission compared with a cDMARD alone except with wider CrIs for tocilizumab IV (forest plots: Supplementary Fig. 1a; league table: Supplementary Table 10, Supplement 2). At 24 weeks, all TIMs in combination with cDMARDs showed significantly higher odds of achieving DAS28 remission compared with a cDMARD alone except for baricitinib + a cDMARD, consistent with the base case analysis (forest plots: Fig. 1b; league table: Supplementary Table 11, Supplement 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 for DAS28 remission with TIM therapies, as both monotherapy and combination therapy with cDMARDs, compared with a cDMARD alone. Favorable results with TIM therapies were seen at 12 and 24 weeks, and in both TIM-naïve/mixed populations as well as TIM-experienced patients. JAK inhibitors, as a relatively new class of drugs for the treatment of moderate 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 compared with a cDMARD alone.

Our results are consistent with previous NMAs in the evaluation of other measures of treatment response (i.e., ACR). Ollendorf et al. also analyzed ACR response criteria in populations with moderate to severe RA who are TIM-naïve/mixed and TIM-experienced [10]. They
| Intervention (vs. cDMARD) | Median OR [95% CI] | SUCRA |
|--------------------------|---------------------|-------|
| a                        |                     |       |
| TCZiv+cDMARD             | 19.36 [11.01, 38.16] | 0.99  |
| GOL+cDMARD               | 12.12 [5.36, 33.05]  | 0.85  |
| TCZsc+cDMARD             | 8.65 [3.94, 22.94]   | 0.75  |
| IFX+cDMARD               | 8.69 [2.14, 42.53]   | 0.71  |
| BAR+cDMARD               | 6.15 [2.65, 16.94]   | 0.60  |
| UPA+cDMARD               | 5.80 [4.45, 7.61]    | 0.60  |
| FIL200+cDMARD            | 5.50 [4.07, 7.54]    | 0.57  |
| ABTc+cDMARD              | 4.18 [2.48, 7.08]    | 0.40  |
| TOF+cDMARD               | 3.52 [1.11, 13.62]   | 0.35  |
| ADA+cDMARD               | 3.52 [2.76, 4.49]    | 0.28  |
| FIL100+cDMARD            | 3.34 [2.41, 4.63]    | 0.25  |
| ABTv+cDMARD              | 2.63 [1.17, 6.43]    | 0.19  |
| b                        |                     |       |
| TCZiv+cDMARD             | 12.10 [8.05, 19.16]  | 0.95  |
| TCZsc+cDMARD             | 11.94 [5.12, 35.61]  | 0.93  |
| UPA+cDMARD               | 6.65 [5.13, 8.69]    | 0.78  |
| FIL200+cDMARD            | 5.39 [4.11, 7.09]    | 0.65  |
| CTZ+cDMARD               | 5.28 [2.15, 16.10]   | 0.59  |
| GOL+cDMARD               | 4.76 [2.74, 8.60]    | 0.55  |
| SAR+cDMARD               | 4.66 [3.19, 6.93]    | 0.54  |
| RTX+cDMARD               | 4.67 [1.63, 17.18]   | 0.52  |
| ABTv+cDMARD              | 4.41 [2.86, 6.67]    | 0.50  |
| BAR+cDMARD               | 4.07 [1.97, 9.35]    | 0.44  |
| TOF+cDMARD               | 3.46 [2.34, 5.15]    | 0.30  |
| ADA+cDMARD               | 3.46 [2.81, 4.32]    | 0.30  |
| IFX+cDMARD               | 3.21 [2.34, 4.45]    | 0.23  |
| FIL100+cDMARD            | 3.12 [2.36, 4.12]    | 0.20  |
| c                        |                     |       |
| TCZiv                    | 35.92 [12.56, 165.60] | 0.89 |
| TOF                      | 33.26 [4.02, 412.60]  | 0.84 |
| ADA                      | 7.80 [2.21, 38.12]    | 0.46 |
| UPA                      | 4.37 [2.53, 7.95]     | 0.31 |
| d                        |                     |       |
| TCZiv                    | 22.88 [10.85, 56.87]  | 0.88 |
| SAR                      | 19.75 [6.11, 69.28]   | 0.79 |
| ADA                      | 3.99 [1.51, 11.61]    | 0.33 |
| e                        |                     |       |
| TCZiv+cDMARD             | 12.68 [5.64, 37.47]  | 0.92  |
| BAR+cDMARD               | 6.12 [1.49, 46.45]   | 0.65  |
| TOF+cDMARD               | 4.85 [1.11, 17.22]   | 0.57  |
| FIL100+cDMARD            | 3.95 [2.52, 8.32]    | 0.49  |
| FIL200+cDMARD            | 3.34 [1.68, 7.10]    | 0.37  |
| f                        |                     |       |
| TCZiv+cDMARD             | 31.93 [11.43, 140.96] | 0.88 |
| RTX+cDMARD               | 26.83 [4.75, 712.81]  | 0.85 |
| ABTv+cDMARD              | 21.05 [6.68, 626.30]  | 0.81 |
| SAR                      | 5.33 [2.87, 10.70]    | 0.56 |
| FIL200+cDMARD            | 3.71 [1.70, 8.16]    | 0.39  |
| FIL100+cDMARD            | 2.53 [1.35, 4.96]     | 0.28 |
| BAR+cDMARD               | 1.93 [0.63, 5.55]     | 0.22 |
reported that all TIMs produced statistically and clinically superior improvements in ACR response compared with a cDMARD alone. Their results were also consistent regardless of whether TIMs were used in combination with a cDMARD 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. and Pope et al. reported that proportions of patients achieving low disease activity or remission at 12 weeks and 24 weeks were substantially greater in the JAK inhibitor group, with or without combination cDMARD therapy, compared with those receiving cDMARDs alone [11, 19]. Similar to our findings, Pope et al. also quantitatively assessed DAS28 remission rates through a Bayesian NMA and reported that the JAK inhibitor + cDMARD groups had a higher odds ratio of achieving DAS28 remission compared to cDMARD alone. However, this analysis only quantitatively compared JAK inhibitors and cDMARDs, indicating that further studies comparing other treatments (i.e., biologic therapy) is necessary. 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 that the tocilizumab 8-mg group showed a significantly higher ACR20 response rate compared with abatacept and tofacitinib [20]. However, Lee et al. acknowledged that remission rates in each group were too small to allow an NMA. In the previous NMAs that included both biologics and JAK inhibitors, 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.

Fig. 2 Forest plots for median odds ratio (95% CrI) of achieving DAS28 remission in TIM treatment vs. 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. 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 drug, 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 modulator, TNF tumor necrosis factor, TOF tofacitinib, UPA upadacitinib
similar extent [21, 22]. 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 composite eligibility criteria involving joint counts and acute phase reactant levels were applied at trial entry, such that changes in ESR or CRP alone were not likely to drive remission at week 12 or week 24.

CONCLUSIONS

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 with a cDMARD alone. These results have important clinical implications that coincide with the increasing use of the T2T 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.

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