Rheumatol Ther (2021) 8:693–710
https://doi.org/10.1007/s40744-021-00322-y

REVIEW

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

Jennie H. Best · Yuting Kuang · Yilin Jiang · Rajpal Singh · Andreas Karabis · Jennifer Uyei · Joseph Dang · William G. Reiss

Received: April 14, 2021 / Accepted: May 12, 2021 / Published online: May 26, 2021

ABSTRACT

Introduction: The objective of this study was to evaluate the relative efficacy of targeted immune modulators (TIMs) in TIM-naïve/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-naïve/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-naïve/mixed or TIM-experienced populations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-021-00322-y.

J. H. Best · J. Dang · W. G. Reiss
Genentech, Inc., South San Francisco, CA, USA

Y. Kuang (✉) · J. Uyei
IQVIA, Inc., 135 Main Street, San Francisco, CA 94105, USA
e-mail: yuting.kuang@iqvia.com

Y. Jiang · A. Karabis
IQVIA, Amsterdam, Netherlands

R. Singh
IQVIA, Mumbai, India

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.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14573544.

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 $\leq$ 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 $\leq$ 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 $\geq$ 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-naïve/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 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 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-naïve/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%

Table 1 Patient characteristics

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

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
Keystone, 2009	GOL + cDMARD	89	52.0	80.9	4.5	0	6.1
GO-FORWARD [34]	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
	ADA + cDMARD	204	52.5	79.4	8.1	7.8	6.6
ORAL STANDARD [17]	cDMARD	56	55.5	76.8	6.9	7.1	6.4
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	UPA15 + cDMARD	651	NR	NR	NR	NR	NR
SELECT-COMPARE [46]	ADA + cDMARD	327	NR	NR	NR	NR	NR
	cDMARD	651	NR	NR	NR	NR	NR
Burmester, 2018	UPA15 + cDMARD	221	55.3	82	7.3	12	5.7
SELECT-NEXT [47]	cDMARD	221	56	75	7.2	13	5.6
TIM-naïve/mixed population—monotherapy							
Burmester, 2016	SAR	184	50.9	85.3	8.1	0	6.8
MONARCH [48]	ADA	185	53.6	81.1	6.6	0	6.8
Gabay, 2013	TCZiv	163	54.4	79	7.3	0	6.7
ADACTA [49]	ADA	162	53.3	82	6.3	0	6.8
Nishimoto, 2007	TCZiv	145	53.1	82.1	2.4	NR	6.4
SAMURAI [50]	cDMARD	157	52.9	86.2	2.2	NR	6.5
Nishimoto, 2009	TCZiv	61	52.6	90.2	8.5	NR	6.1
SATORI [51]	cDMARD	64	50.8	75	8.7	NR	6.2
Fleischmann, 2012 [52]	TOF	49	54	87.8	8.1	NR	6.6
	ADA	53	54	84.9	7.7	NR	6.3
Smolen, 2018	UPA15	217	NR	NR	NR	0	NR
SELECT-MONOTHERAPY [53]	cDMARD	216	NR	NR	NR	0	NR
TIM-experienced population—combination therapy							
Genovese, 2005	ABTiv + cDMARD	258	53.4	77.1	12.2	100	6.5
ATTAIN [54]	cDMARD	133	52.7	79.7	11.4	100	6.5
Genovese, 2016	BAR + cDMARD	174	55	79	14	100	6.7
RA-BEACON [55]	cDMARD	176	56	82	14	100	6.6
Genovese, 2019	FIL100 + cDMARD	153	55	77.8	10.9	100	5.9
FINCH-2 [12]	FIL200 + cDMARD	147	56	81.6	11.1	100	5.9
	cDMARD	148	56	81.8	10.6	100	5.9
Cohen, 2006	RTX + cDMARD	308	52.2	81	12.1	100	6.9
REFLEX [56]	cDMARD	209	52.8	81	11.7	100	6.8

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, 2016	SAR200 + cDMARD	184	52.9	82.1	12.7	100	6.3
TARGET [57]	cDMARD	181	51.9	85.1	12	100	6.2
Emery, 2008	TCZiv + cDMARD	331	52.4	82.5	11.8	100	6.8
RADIATE [58]	cDMARD	158	53.4	79	11.4	100	6.8
Yazici, 2012	TCZiv + cDMARD	409	55.2	79.5	8.6	37.9	6.5
ROSE [15]	cDMARD	205	55.8	83.9	8.5	38	6.6
Burmester, 2013	TOF + cDMARD	133	55.4	85	13	99.2	6.5
ORAL Step [59]	cDMARD	132	54.4	80.3	11.3	100	6.4

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

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

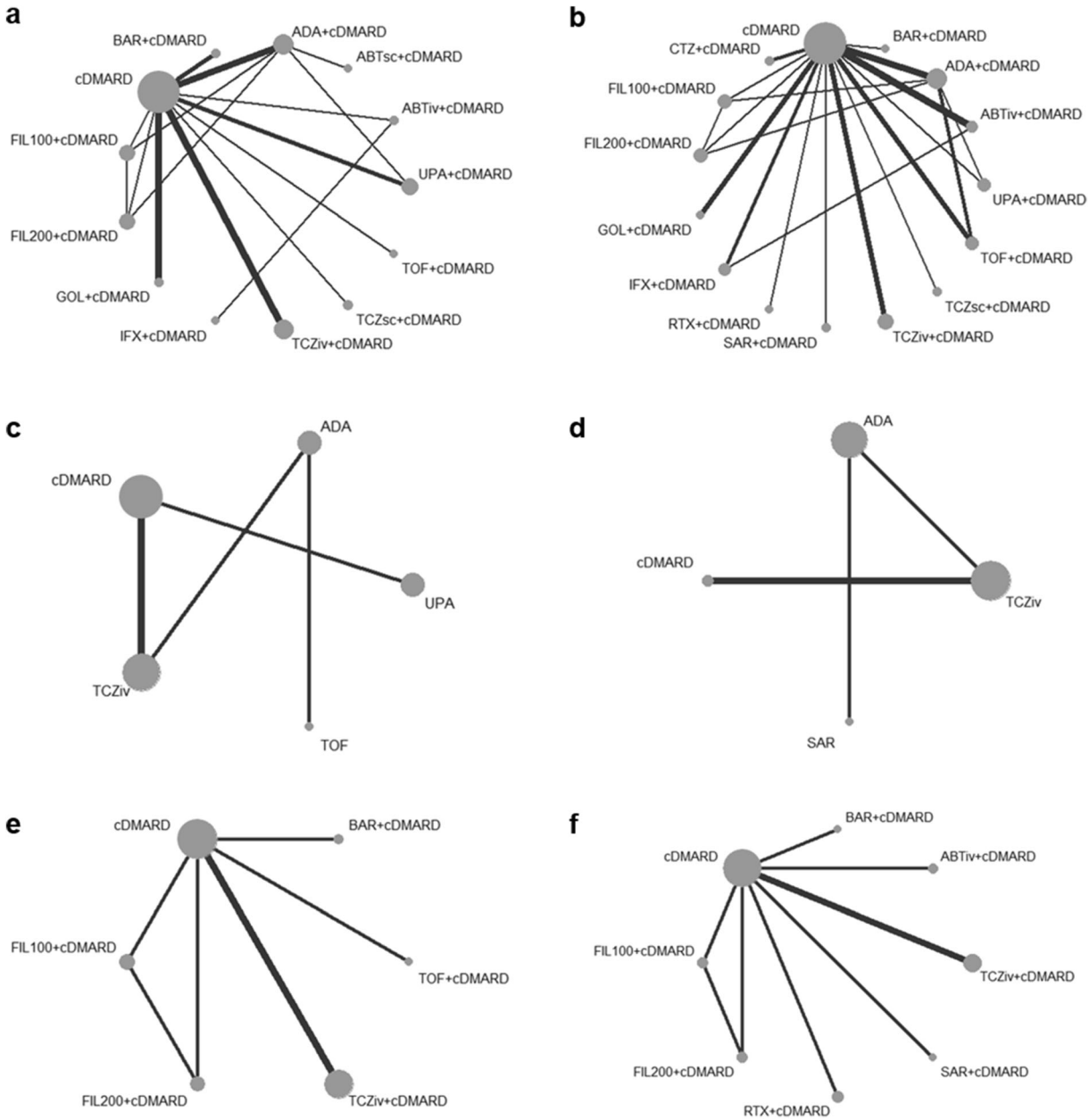


Fig. 1 Network diagrams of studies evaluating DAS28 remission with TIM treatment. **a** TIM-naïve/mixed population receiving combination therapy at 12 weeks. **b** TIM-naïve/mixed population receiving combination therapy at 24 weeks. **c** TIM-naïve/mixed population receiving monotherapy at 12 weeks. **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: Fig. 2e, f; league tables: 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).

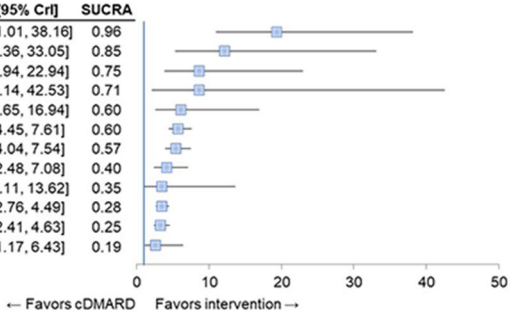
DISCUSSION

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

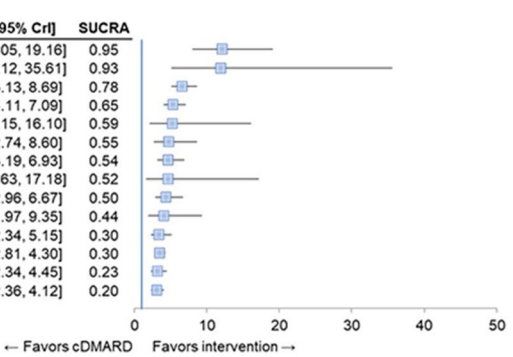
a

Intervention (vs. cDMARD)	Median OR	[95% CrI]	SUCRA
TCZiv+cDMARD	19.36	[11.01, 38.16]	0.96
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	[4.04, 7.54]	0.57
ABTsc+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
ABTiv+cDMARD	2.63	[1.17, 6.43]	0.19



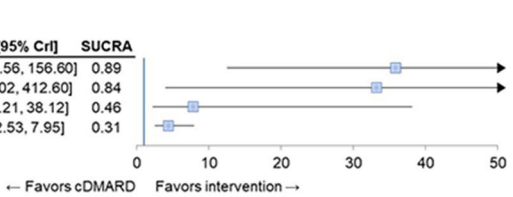
b

Intervention (vs. cDMARD)	Median OR	[95% CrI]	SUCRA
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	5.26	[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
ABTiv+cDMARD	4.41	[2.96, 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, 4.30]	0.30
IFX+cDMARD	3.21	[2.34, 4.45]	0.23
FIL100+cDMARD	3.12	[2.36, 4.12]	0.20



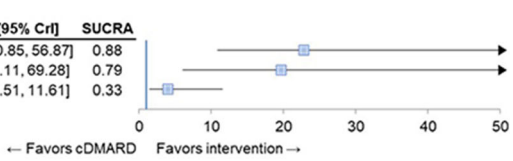
c

Intervention (vs. cDMARD)	Median OR	[95% CrI]	SUCRA
TCZiv	35.92	[12.56, 156.60]	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



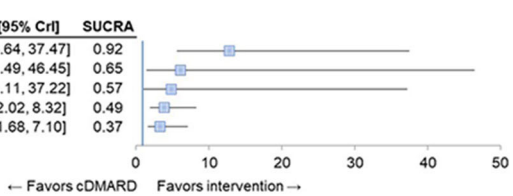
d

Intervention (vs. cDMARD)	Median OR	[95% CrI]	SUCRA
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



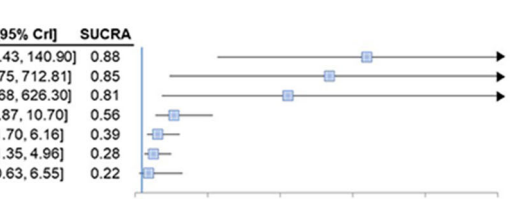
e

Intervention (vs. cDMARD)	Median OR	[95% CrI]	SUCRA
TCZiv+cDMARD	12.88	[5.64, 37.47]	0.92
BAR+cDMARD	6.12	[1.49, 46.45]	0.65
TOF+cDMARD	4.85	[1.11, 37.22]	0.57
FIL100+cDMARD	3.95	[2.02, 8.32]	0.49
FIL200+cDMARD	3.34	[1.68, 7.10]	0.37



f

Intervention (vs. cDMARD)	Median OR	[95% CrI]	SUCRA
TCZiv+cDMARD	31.93	[11.43, 140.90]	0.88
RTX+cDMARD	26.83	[4.75, 712.81]	0.85
ABTiv+cDMARD	21.05	[3.68, 626.30]	0.81
SAR+cDMARD	5.33	[2.87, 10.70]	0.56
FIL200+cDMARD	3.17	[1.70, 6.16]	0.39
FIL100+cDMARD	2.53	[1.35, 4.96]	0.28
BAR+cDMARD	1.93	[0.63, 6.55]	0.22



◀**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

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.

This study has some limitations. First, the studies included in the analysis were based on previous reviews by Ollendorf et al., and Tice et al., therefore, it was assumed that the screening process and study selection were accurate in the previous reviews [10, 11]. We evaluated 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 population with moderate to severe RA [10, 11]. Therefore, the applicability of these results should be limited to that population. Lastly, the DAS28-ESR and CRP measurements have inherent drawbacks. 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 either CRP or ESR levels while not affecting the other to a

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.

ACKNOWLEDGEMENTS

Funding. This study was sponsored and funded by Genentech, Inc., South San Francisco, CA, USA. The Rapid Service Fee was funded by Genentech, Inc.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. Jennie H. Best, Yuting Kuang, Jennifer Uyei, Joseph Dang, and William G. Reiss contributed to the design of the study, interpretation of data, and drafting of the manuscript. Yuting Kuang, Rajpal Singh, and Jennifer Uyei contributed to the data acquisition. Yilin Jiang and Andreas Karabis performed data analysis. All authors read, revised, and approved the final manuscript.

Disclosures. Jennie H. Best and William G. Reiss are employees and stockholders of Genentech, Inc. Joseph Dang was an employee of Genentech, Inc., at the time of this study. Yuting Kuang, Jennifer Uyei, Yilin Jiang, Rajpal Singh and Andreas Karabis 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.

Medical Writing/Editorial Assistance. Arianna Nevo, Sukanya Ghildiyal, and Paranjoy Saharia of IQVIA, Inc. provided writing assistance, which was funded by Genentech, Inc.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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

REFERENCES

1. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheumatol. 2008;58(1):15–25.

2. Hunter TM, Boytsov NN, Zhang X, Schroeder K, Michaud K, Araujo AB. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004–2014. Rheumatol Int. 2017;37(9):1551–7.

3. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955–2007. Arthritis Rheumatol. 2010;62(6):1576–82.

4. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet (London, England). 2001;358(9285):903–11.

5. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res. 2016;68(1):1–25.

6. Smolen JS, Landewe RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79(6):685–99.

7. O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369(4):307–18.

8. Solomon DH, Bitton A, Katz JN, Radner H, Brown EM, Fraenkel L. Review: treat to target in rheumatoid arthritis: fact, fiction, or hypothesis? Arthritis Rheumatol. 2014;66(4):775–82.

9. Anderson J, Caplan L, Yazdany J, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res. 2012;64(5):640–7.

10. Ollendorf D, Chapman R, Pearson S, et al. Institute for Clinical and Economic Review. Targeted immune modulators for rheumatoid arthritis: effectiveness and value. https://icer.org/wp-content/uploads/2020/10/NE_CEPAC_RA_Evidence_Report_FINAL_040717.pdf. Accessed Mar 30, 2021.

11. Tice JA, Kuman VM, Chapman R, et al. Institute for Clinical and Economic Review. Janus kinase inhibitors and biosimilars for rheumatoid arthritis: effectiveness and value. https://icer.org/wp-content/uploads/2020/10/ICER_RA_Evidence_Report_112619-2.pdf. Accessed Mar 30, 2021.

12. Genovese MC, Kalunian K, Gottenberg JE, et al. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. JAMA. 2019;322(4):315–25.

13. Walker D, Combe BG, Kivitiz AJ, et al. P210. Efficacy and safety of filgotinib for patients with RA with inadequate response to methotrexate: FINCH1 primary outcome results. Rheumatology. 2020;59(Suppl_2):keaa111.205.

14. Dias S, Welton NJ, Sutton AJ, Ades AE. National Institute for Health and Care Excellence (NICE). NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. https://www.ncbi.nlm.nih.gov/books/NBK310366/pdf/Bookshelf_NBK310366.pdf. Accessed Mar 30, 2021.

15. Yazici Y, Curtis JR, Ince A, et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. Ann Rheum Dis. 2012;71(2):198–205.

16. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheumatol. 2013;65(3):559–70.

17. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in

rheumatoid arthritis. N Engl J Med. 2012;367(6): 508–19.

18. Yamamoto K, Takeuchi T, Yamanaka H, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(5): 715–24.

19. Pope J, Sawant R, Tundia N, et al. Comparative efficacy of JAK inhibitors for moderate-to-severe rheumatoid arthritis: a network meta-analysis. Adv Ther. 2020;37(5):2356–72.

20. Lee YH, Bae SC. Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled trials. Int J Rheum Dis. 2016;19(11):1103–11.

21. Smolen JS, Aletaha D. Interleukin-6 receptor inhibition with tocilizumab and attainment of disease remission in rheumatoid arthritis: the role of acute-phase reactants. Arthritis Rheumatol. 2011;63(1): 43–52.

22. Smolen JS, Aletaha D, Gruben D, Zwillich SH, Krishnaswami S, Mebus C. Brief report: remission rates with tofacitinib treatment in rheumatoid arthritis: a comparison of various remission criteria. Arthritis Rheumatol. 2017;69(4):728–34.

23. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med. 2003;349(20):1907–15.

24. Takeuchi T, Matsubara T, Nitobe T, et al. Phase II dose-response study of abatacept in Japanese patients with active rheumatoid arthritis with an inadequate response to methotrexate. Mod Rheumatol. 2013;23(2):226–35.

25. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006;144(12):865–76.

26. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67(8):1096–103.

27. Weinblatt ME, Schiff M, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheumatol. 2013;65(1):28–38.

28. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017;376(7): 652–62.

29. Dougados M, van der Heijde D, Chen Y-C, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017;76(1):88–95.

30. Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis. 2015;74(2):333–40.

31. Choy E, McKenna F, Vencovsky J, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. Rheumatology (Oxford). 2012;51(7):1226–34.

32. Smolen J, Landewé RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009;68(6):797–804.

33. Tanaka Y, Harigai M, Takeuchi T, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Ann Rheum Dis. 2012;71(6): 817.

34. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor alpha given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009;68(6):789–96.

35. Li Z, Zhang F, Kay J, et al. Efficacy and safety results from a Phase 3, randomized, placebo-controlled trial of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy. Int J Rheum Dis. 2016;19(11):1143–56.

36. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheumatol. 2006;54(4): 1075–86.

37. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of

rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis. 2010;69(9):1629–35.

38. Genovese MC, Fleischmann R, Kivitz AJ, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. Arthritis Rheumatol. 2015;67(6):1424–37.

39. Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheumatol. 2011;63(3):609–21.

40. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet (London, England). 2008;371(9617):987–97.

41. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheumatol. 2008;58(10):2968–80.

42. Kivitz A, Olech E, Borofsky M, et al. Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Arthritis Care Res. 2014;66(11):1653–61.

43. Kremer JM, Cohen S, Wilkinson BE, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheumatol. 2012;64(4):970–81.

44. Kremer J, Li ZG, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013;159(4):253–61.

45. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet (London, England). 2017;390(10093):457–68.

46. Fleischmann R, Pangan AL, Mysler E, et al. A phase 3, randomized, double-blind study comparing upadacitinib to placebo and to adalimumab, in patients with active rheumatoid arthritis with inadequate response to methotrexate. Arthritis Rheumatol. 2018;70:988–90.

47. Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying antirheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet (London, England). 2018;391(10139):2503–12.

48. Burmester GR, Lin Y, Patel R, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis. 2017;76(5):840–7.

49. Gabay C, Emery P, van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet (London, England). 2013;381(9877):1541–50.

50. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66(9):1162–7.

51. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12–9.

52. Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheumatol. 2012;64(3):617–29.

53. Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate

(SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. Lancet (London, England). 2019;393(10188):2303–11.

54. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353(11):1114–23.

55. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med. 2016;374(13):1243–52.

56. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheumatol. 2006;54(9):2793–806.

57. Fleischmann R, van Adelsberg J, Lin Y, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. Arthritis Rheumatol. 2017;69(2):277–90.

58. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516–23.

59. Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet (London, England). 2013;381(9865):451–60.