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Network Meta-Analysis of Tofacitinib, Biologic Disease-Modifying Antirheumatic Drugs, and Apremilast for the Treatment of Psoriatic Arthritis

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ABSTRACT

Background: Tofacitinib and other new treatments approved for use in psoriatic arthritis have only recently been included in psoriatic arthritis treatment guidelines, and studies evaluating the relative efficacy of available therapies are important to inform treatment decisions by healthcare professionals.
Objective: To perform a network meta-analysis to evaluate the efficacy and safety profiles of tofacitinib, biologic disease-modifying antirheumatic drugs (bDMARDs), and apremilast in patients with psoriatic arthritis naïve to tumor necrosis factor inhibitor therapy (TNFi-naïve) or with an inadequate response (TNFi-IR).
Methods: A systematic literature review used searches of MEDLINE, Embase, and The Cochrane Library on October 9, 2017. Randomized controlled trials including adult patients with psoriatic arthritis receiving treatment administered as monotherapy or with conventional synthetic DMARDs were selected. Efficacy outcomes included American College of Rheumatology 20 response, change from baseline in Health Assessment Questionnaire-Disability Index, ≥75% improvement in Psoriasis Area and Severity Index, and change from baseline in Dactylitis Severity Score and Leeds Enthesitis Index. Treatment effects were evaluated during placebo-controlled phases, using a binomial logit model for binary outcomes and a normal identify link model for other outcomes. Discontinuations due to adverse events and serious infection events were assessed as safety outcomes.
Results: The network meta-analysis included 24 published randomized controlled trials, of which 13 enrolled TNFi-naïve patients only, 3 enrolled TNFi-IR patients only, and 8 enrolled both TNFi-naïve and TNFi-IR patients. Placebo-controlled treatment durations ranged from 12 to 24 weeks. Indirect comparisons showed tofacitinib 5 and 10 mg BID to have similar efficacy compared with most bDMARDs and apremilast in improving joint symptoms (based on American College of Rheumatology 20 response), and with some bDMARDs in improving skin symptoms (based on Psoriasis Area and Severity Index) (tofacitinib 10 mg BID only in TNFi-IR) in patients with psoriatic arthritis who were TNFi-naïve or TNFi-IR. Results also showed that, compared with placebo, the improvement in physical functioning (based on Health Assessment Questionnaire-Disability Index) with tofacitinib 5 and 10 mg BID was similar to that

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observed with most bDMARDs and apremilast in TNFi-naïve patients, and similar to that observed with all bDMARDs with available data in the TNFi-IR population. Improvements in Dactylitis Severity Score and Leeds Enthesitis Index scores were comparable between treatments. Tofacitinib 5 and 10 mg BID were median-ranked 8 and 15, respectively, for discontinuation due to any adverse events, and 5 and 16, respectively, for a serious infection event out of a total of 20 treatments in the network (lower numbers are more favorable).

Conclusions: Tofacitinib provides an additional treatment option for patients with psoriatic arthritis, both in patients naïve to TNFi and in those with TNFi-IR. (*Curr Ther Res Clin Exp.* 2020; 81:XXX–XXX)

Introduction

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory musculoskeletal disease manifesting as peripheral arthritis, enthesitis, dactylitis, spondylitis, and skin and nail psoriasis.[1–3]

Recommended treatments for active PsA include nonsteroidal anti-inflammatory drugs, corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic (b)DMARDs, the targeted synthetic DMARD apremilast, or tofacitinib.[1,4,5] Despite being recommended as a first-line treatment for active PsA,[6] >50% of patients treated for ≥6 months with tumor necrosis factor inhibitor (TNFi) bDMARD therapy have been observed to fail to reach treatment targets.[7–10] It has also been reported that around 50% of patients from the United States with PsA temporarily or permanently discontinue or switch treatment within 12 months,[11] indicating an unmet need for therapies with novel mechanisms of action.

Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. The approved dose of tofacitinib for the treatment of active PsA is 5 mg BID.[12] The safety and efficacy of tofacitinib 5 and 10 mg BID have been demonstrated in Phase III trials of 6 and 12 months' duration in patients with active PsA and an inadequate response (IR) to csDMARDs or TNFi therapy.[13,14] OPAL Broaden (NCT01877668) was a 12-month randomized controlled trial (RCT) in a TNFi-naïve population with active PsA and an IR to ≥1 csDMARD; patients received tofacitinib 5 or 10 mg BID, adalimumab 40 mg q2w, or placebo advancing to tofacitinib 5 or 10 mg BID at Month 3.[13] OPAL Beyond (NCT01882439) was a 6-month RCT in patients with an IR to ≥1 TNFi; patients received tofacitinib 5 or 10 mg BID, or placebo advancing to tofacitinib 5 or 10 mg BID at Month 3.[14] In both OPAL Broaden and OPAL Beyond, patients were required to receive a stable dose of 1 csDMARD in addition to the study medication. Tofacitinib is also being investigated in an ongoing, long-term extension study in patients with PsA who participated in OPAL Broaden or OPAL Beyond (NCT01976364).

Tofacitinib and other new treatments approved for use in PsA (eg, secukinumab, ixekizumab, and abatacept) have only recently been included in PsA treatment guidelines,[6] and studies evaluating the relative efficacy of available therapies are important to inform treatment decisions by healthcare professionals. We performed a systematic literature review (SLR) and network meta-analysis (NMA) to evaluate the efficacy and safety profiles of tofacitinib 5 and 10 mg BID relative to bDMARDs or apremilast in patients with PsA who were TNFi-naïve or TNFi-IR.

Methods

SLR and study selection

Full details of the SLR methodology, including the search strategies and the population, interventions, comparators, outcomes, and study design criteria used to identify eligible studies, are reported in **Supplemental Tables 1** and **2** in the online version at doi:XXXXXXXXXX. Online literature searches were conducted to identify English language publications reporting RCTs evaluating tofacitinib, bDMARDs, or apremilast for the treatment of PsA. Searches were conducted of MEDLINE, Embase, and The Cochrane Library on October 9, 2017. Online searches were supplemented with searches of conference proceedings, clinical trial registries, previous health technology assessment submissions, and reference lists of included publications. Potentially relevant studies were reviewed by 2 independent analysts, in accordance with the guidelines presented by The Cochrane Collaboration.[15]

For publications to be included in the SLR, studies were required to be RCTs in adults with PsA who had not previously received a TNFi (TNFi-naïve) or had previously had an IR to TNFi. RCTs of any design, date, or location could be included, and patients could be csDMARD-naïve or csDMARD-IR; treatments could be administered as monotherapy or in combination with csDMARDs. Treatments included: placebo; tofacitinib 5 and 10 mg BID; bDMARDs (abatacept 125 mg subcutaneous [SC] once every week [q1w], abatacept 10 mg/kg IV on weeks 0, 2 and 4, then q4w, adalimumab 40 mg SC q2w, certolizumab pegol 400 mg SC at weeks 0, 2, and 4, then 200 mg q2w or 400 mg q4w, etanercept 25 mg SC twice weekly, golimumab 50 and 100 mg SC q4w, infliximab 5 mg/kg IV at weeks 0, 2, and 6, then q8w, ixekizumab 160 mg SC [loading dose], then 80 mg q2w and q4w, secukinumab 10 mg/kg IV at weeks 0, 2 and 4, then 150 mg SC q4w, secukinumab 150 or 300 mg SC q1w for 4 weeks, then q4w, and ustekinumab 45 and 90 mg SC at weeks 0 and 4, then q12w); apremilast 20 and 30 mg BID. Clinical efficacy outcomes assessed included the proportion of patients achieving ≥20% improvement in the American College of Rheumatology score (ACR20), the change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI), the proportion of patients achieving ≥75% improvement in Psoriasis Area and Severity Index (PASI75), and change from baseline in the Dactylitis Severity Score (DSS) and Leeds Enthesitis Index (LEI).

Quality assessment

A quality (risk of bias) assessment of eligible publications was conducted independently by 2 reviewers using the 7-criteria checklist from the UK National Institute for Health and Care Excellence's single technology appraisal user guide.[16] This approach is based on guidance provided by the UK Centre for Reviews and Disseminations for assessing the quality of studies included in SLRs, and assesses the likelihood of selection, performance, attrition, and detection bias.[17] Discrepancies between reviewers were resolved by discussion and/or additional referees.

NMA

Some studies were excluded from the NMA as they did not meet the eligibility criteria (see **Supplemental Table 2** in the on-

line version at doi:XXXXXXXXXX), including: population (psoriasis study with a subpopulation of PsA patients), outcomes (outcomes were not reported at 12–24 weeks), and intervention (study only included unlicensed dose or did not have a common comparator treatment arm to be connected to the evidence network).

The type of model used in this analysis (fixed-effect [FE] vs random-effect [RE]) was chosen based on the deviance information criterion (DIC), with lower values indicating better fit. When possible, the consistency between indirect and direct estimates was compared and evaluated.[18,19] To test for inconsistency, FE and RE ACR20 and HAQ-DI results in the TNFi-naïve population were compared (direct log of odds ratios [ORs] to indirect log of ORs for each possible head-to-head comparison). Similarity was evaluated based on knowledge of the subject matter and with sensitivity (subgroup) analyses, along with the assessment of the consistency assumption whenever possible. The variation in the calculated ORs was evaluated by determining the heterogeneity of these values using tau-squared.

Efficacy analysis

Treatment effects were evaluated during the placebo-controlled phases of the included RCTs. The NMA was conducted using WinBUGs (Bayesian inference Using Gibbs Sampling) version 1.4 (MRC Biostatistics Unit, Cambridge, United Kingdom),[19,20] with noninformative prior distributions used for all models.[19]

A binomial logit model was used to model the binary outcomes ACR20 and PASI75, and a normal identify link model was used to analyze change from baseline in HAQ-DI, DSS, and LEI. Credible intervals (CrIs) were used to compare treatment effects. CrIs are the Bayesian equivalent of frequentist confidence intervals; when the CrI associated with a measure of relative treatment effect does not include the null value, it can be stated with a high degree of certainty that the results favor 1 treatment over the other. The width of the 95% CrI should also be considered when assessing the magnitude and precision of treatment effect. Information relating to treatment rankings from the NMAs is presented in the form of median treatment rankings (with 95% CrI), to aid in the interpretation of the NMA results. Median treatment rankings represent findings from each iteration of the model from which inferences are based.

Sensitivity analysis

Sensitivity analyses were conducted in the TNFi-naïve population for ACR20 and change from baseline in HAQ-DI, by evaluation of the following subgroups:

- TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab);
- Interleukin (IL) inhibitors (ixekizumab [IL-17A inhibitor], secukinumab [IL-17A inhibitor], ustekinumab [IL-12/23 inhibitor]);
- All TNFi and IL inhibitors together;
- Only RCTs with a primary end point time of 12 to 14 weeks;
- Only RCTs with a primary end point time of 12 to 16 weeks; and
- Without placebo adjustment to assess active treatment versus placebo for ACR20.

Sensitivity analyses were performed using data from the TNFi-naïve population only, owing to limited data in the TNFi-IR population.

Safety profile analysis

Safety outcomes were evaluated mostly during the placebo-controlled period (up to 24 weeks) from the included RCTs. The safety profile analysis also included data at 52 or 54 weeks, where data for safety outcomes during the placebo-controlled period were not available. The reporting of safety outcomes varied between trials. Following assessment of availability and feasibility of safety data from each clinical trial, two safety outcomes were included in the safety NMA: discontinuation due to any adverse event (AE) and serious infection events (SIEs). SIEs were defined as infections that required hospitalization or parenteral antimicrobial therapy.

In the base-case analysis, no restrictions on population were applied; both TNFi-naïve and TNFi-IR patient populations were therefore included, and the same methodology was applied as in the efficacy analyses.

Results

Studies identified in the SLR

The online literature searches identified 4084 citations, of which 3943 were excluded because they did not meet the criteria; 14 additional citations were identified via supplementary searches, leaving 155 citations (43 unique RCTs) included in the SLR. Of these, 75 citations (19 RCTs) were unsuitable for inclusion in the NMA because they did not report the outcomes in a comparable format. The complete SLR process is illustrated using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram (Figure 1), and the results of the quality assessment are reported in **Supplemental Table 3** in the online version at doi:XXXXXXXXXX.

The SLR identified 24 eligible RCTs to include in the NMA, including patients with PsA who were TNFi-naïve or TNFi-IR. Thirteen RCTs enrolled TNFi-naïve patients only, 8 enrolled both TNFi-naïve and TNFi-IR patients, and 3 enrolled patients who were TNFi-IR only.

The majority of included RCTs allowed the use of methotrexate; a stable dose of a single concomitant csDMARD as background medication was required in the 2 tofacitinib studies, OPAL Broaden and OPAL Beyond. All studies included in the analysis were placebo-controlled (treatment durations ranged from 12 to 24 weeks across RCTs), and there were no head-to-head studies (active comparator) included in the analysis; the only studies with an active comparator were OPAL Broaden and SPIRIT-P1, which included adalimumab as a reference arm. These studies were not powered to assess noninferiority or superiority between tofacitinib and adalimumab, or ixekizumab and adalimumab.[13,21] Dactylitis and/or enthesitis were assessed only in the 2 tofacitinib RCTs (OPAL Broaden and OPAL Beyond),[13,14] SPIRIT-P1,[21] and SPIRIT-P2 (both ixekizumab).[22] The clinical studies included in the SLR and NMA are shown in Table 1.

Patient characteristics

Patient characteristics at baseline across the included RCTs are summarized briefly here. The maximum reported mean age was 52.6 years.[22,23] The proportion of male patients ranged from 39%[14] to 71%,[36] with a notable imbalance between treatment arms of the IMPACT 2 trial (71% infliximab vs 51% placebo).[36] PsA duration of the RCT populations ranged from a mean 3.4[27] to 11.7[35] years, and baseline disease severities were assessed by tender joint counts (range of means from 17.1[13] to 29.3[25]), swollen joint counts (range of means from 9.2[28] to 18.4[25]), C-reactive protein levels (range of means from 0.8 mg/dL[27] to 17.0 mg/dL[22]), and patients with ≥3% psoriasis body surface area (range of means from 33% to 87%).[35,36] Baseline LEI scores were reported in OPAL Broaden, OPAL Beyond, SPIRIT-P1, and SPIRIT-P2 (range of means [SD] from 2.3 [1.2] to 3.4 [1.8][13,14,21,22]), and baseline DSS was reported in OPAL Broaden and OPAL Beyond (range of means [SD] from 6.8

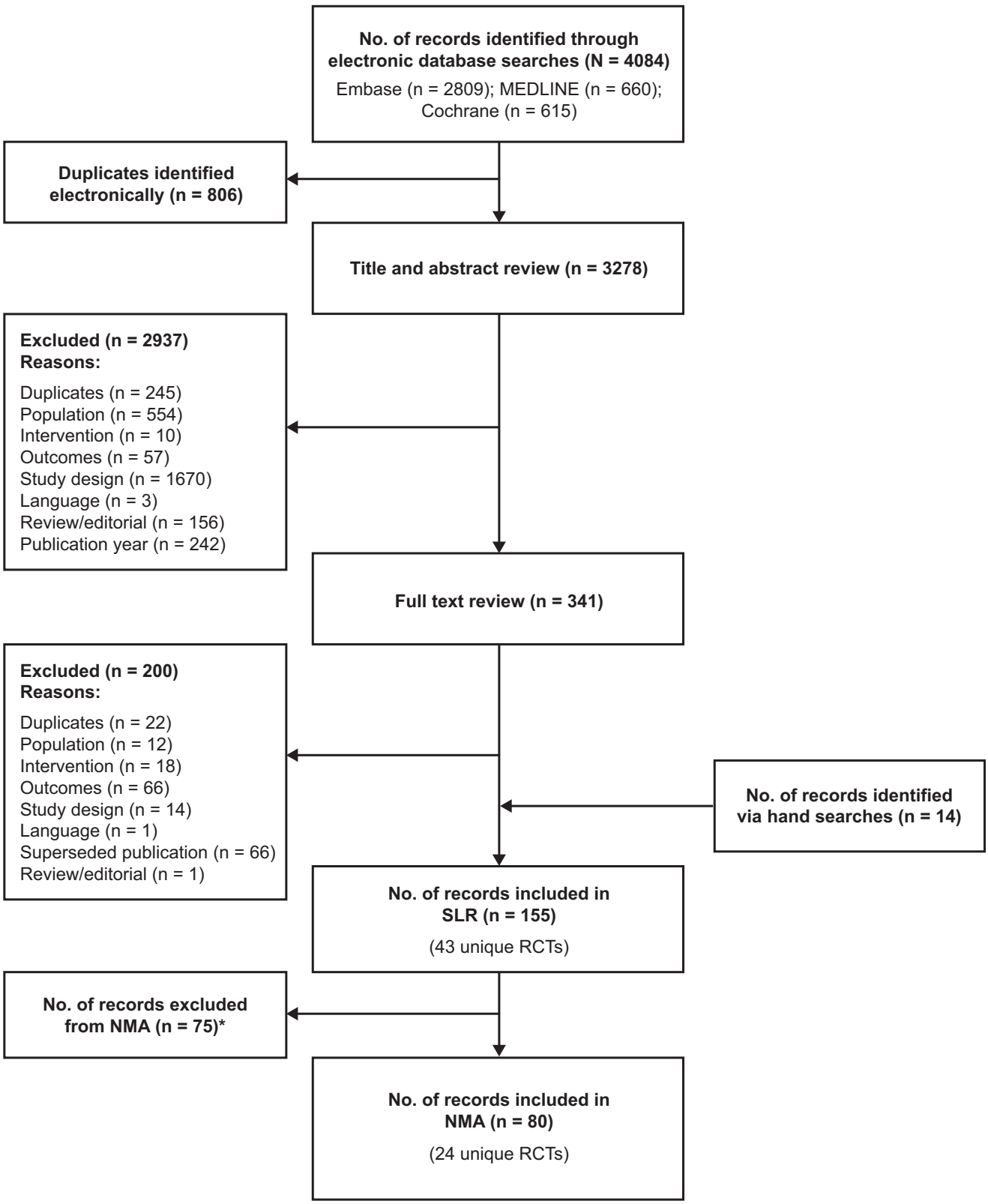

Figure 1. Systematic literature review Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram: identification of randomized controlled trials (RCTs) evaluating tofacitinib, biologic disease-modifying antirheumatic drugs (bDMARDs), or apremilast for the treatment of patients with active psoriatic arthritis (PsA). *Not all publications included in the SLR contributed to the analyses included in the evidence networks; 75 citations (19 RCTs) were excluded from the NMA, as they only included unlicensed doses, did not include a placebo arm, did not connect to the evidence networks, or only reported PsA results for a subgroup of patients in a psoriasis RCT. This resulted in 24 unique RCTs being included in the NMA. bDMARD = biologic disease-modifying antirheumatic drug; NMA = network meta-analysis; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; PsA = psoriatic arthritis; RCT = randomized controlled trial; SLR = systematic literature review.

Table 1
Clinical studies included in the systematic literature review (SLR) and network meta-analysis (NMA) in tumor necrosis factor inhibitor (TNFi)-naïve and TNFi-inadequate response (IR) populations with psoriatic arthritis (PsA).

Trial	Total no. of ITT patients	Population	Treatment arms and doses, ITT patient numbers	Duration of follow-up time, wk	Reference
NCT00534313	170	bDMARD-IR TNFi-IR	Abatacept 3 mg/kg IV at Week 0, 2, 4, then q4w (n = 45) Abatacept 10 mg/kg IV at Week 0, 2, 4, then q4w (n = 40) Abatacept 30 mg/kg IV at Week 0, 2, 4, then q4w (n = 43) Placebo IV at Day 1, 15, 29, then q4w (n = 42)	24	Mease, et al (2011)[23]
ASTRAEA (NCT01860976)	424	TNFi-naïve, TNFi-IR subpopulation	Abatacept 125 mg SC q1w (n = 213) Placebo (n = 211)	24	Mease, et al. (2017)[24]
ADEPT (NCT00195689)	313	TNFi-naïve	Adalimumab 40 mg SC q2w (n = 151) Placebo (n = 162)	12	Mease, et al (2005)[2]
NCT00646178	100	TNFi-naïve	Adalimumab 40 mg SC q2w (n = 51) Placebo (n = 49)	12	Genovese, et al (2007)[25]
ACTIVE (NCT01925768)	209	bDMARD-naïve	Apremilast 30 mg BID (n = 110) Placebo (n = 109)	16	Nash, et al (2018)[26]
PALACE 1 (NCT01172938)	504	bDMARD-naïve, bDMARD-IR subpopulation (≤10% of total population)	Apremilast 20 mg BID (n = 168) Apremilast 30 mg BID (n = 168) Placebo (n = 168)	16	Kavanaugh, et al (2014)[27]
PALACE 2 (NCT01212757)	484	bDMARD-naïve, bDMARD-IR subpopulations	Apremilast 20 mg BID (n = 163) Apremilast 30 mg BID (n = 162) Placebo (n = 159)	16	Cutolo, et al (2016)[28]
PALACE 3 (NCT01212770)	505	bDMARD-naïve, bDMARD-IR subpopulation (≤10% of total population)	Apremilast 20 mg BID (n = 169) Apremilast 30 mg BID (n = 167) Placebo (n = 169)	16	Edwards, et al (2016)[29]
PALACE 4 (NCT01307423)	527	TNFi-naïve	Apremilast 20 mg BID (n=175) Apremilast 30 mg BID (n = 176) Placebo (n = 176)	16	Wells, et al (2018)[30]
RAPID-PsA (NCT01087788)	409	TNFi-naïve, TNFi-IR subpopulation (limited to ≤40% of total population)	Certolizumab pegol 400 mg SC loading dose at Week 0, 2, 4 + 200 mg q2w (n = 138) Certolizumab pegol 400 mg SC loading dose at Week 0, 2, 4 + 400 mg q4w (n = 135) Placebo (n = 136)	24	Mease, et al (2014)[31]
Mease 2000	60	TNFi-naïve	Etanercept 25 mg SC twice weekly (n = 30) Placebo (n = 30)	12	Mease, et al (2000)[32]
NCT00317499	205	TNFi-naïve	Etanercept 25 mg SC twice weekly (n = 101) Placebo (n = 104)	12	Mease, et al (2004)[33]
GO-REVEAL (NCT00265096)	405	TNFi-naïve	Golimumab 50 mg SC q4w (n = 146) Golimumab 100 mg SC q4w (n = 146) Placebo (n = 113)	14	Kavanaugh, et al (2009)[34]
IMPACT	104	TNFi-naïve	Infliximab 5 mg/kg IV at 0, 2, 6, and 14 weeks (q8w) (n = 52) Placebo (n = 52)	16	Antoni, et al (2005)[35]
IMPACT 2 (NCT00051623)	200	TNFi-naïve	Infliximab 5 mg/kg IV at 0, 2, 6, 14, and 22 weeks (q8w) (n = 100) Placebo (n = 100)	14	Antoni, et al. (2005)[36]
RESPOND (NCT00367237)	110	bDMARD-naïve, methotrexate-naïve	Infliximab 5 mg/kg IV at 0, 2, 6, and 14 weeks + methotrexate 15 mg q1w (n = 56) Methotrexate 15 mg q1w (n = 54)	16	Baranauskaite, et al. (2012)[37]
SPIRIT-P1 (NCT01695239)	417	bDMARD-naïve	Adalimumab 40 mg q2w (n = 101) Ixekizumab 80 mg SC q2w (n = 103) Ixekizumab 80 mg SC q4w (n = 107) Placebo (n = 106)	12	Mease, et al (2017)[21]
SPIRIT-P2 (NCT02349295)	363	TNFi-IR	Ixekizumab 160 mg SC starting dose, then 80 mg q2w (n = 123) Ixekizumab 160 mg SC starting dose, then 80 mg q4w (n = 122) Placebo (n = 118)	12	Nash, et al (2017)[22]
FUTURE 1 (NCT01392326)	606	TNFi-naïve, TNFi-IR subpopulation	Secukinumab 10 mg/kg IV at Weeks 0, 2, and 4, then 75 mg SC q4w (n=202) Secukinumab 10 mg/kg IV at Weeks 0, 2, and 4, then 150 mg SC q4w (n = 202) Placebo (n = 202)	24	Mease, et al (2015)[38]

(*continued on next page*)

Table 1 (*continued*)

Trial	Total no. of ITT patients	Population	Treatment arms and doses, ITT patient numbers	Duration of follow-up time, wk	Reference
FUTURE 2 (NCT01752634)	298	TNFi-naïve, TNFi-IR subpopulation	Secukinumab 75 mg SC q1w, then q4w Secukinumab 150 mg SC q1w, then q4w (n = 100) Secukinumab 300 mg SC q1w, then q4w (n = 100) Placebo (n = 98)	24	McInnes, et al (2015)[39]
OPAL Broaden (NCT01877668)	422	TNFi-naïve	Tofacitinib 5 mg BID (n = 107) Tofacitinib 10 mg BID (n = 104) Adalimumab 40 mg SC q2w (n = 106) Placebo (n = 105)	13	Mease, et al (2017)[13]
OPAL Beyond (NCT01882439)	394	TNFi-IR	Tofacitinib 5 mg BID (n = 131) Tofacitinib 10 mg BID (n = 132) Placebo (n = 131)	13	Gladman, et al (2017)[14]
PSUMMIT 1 (NCT01009086)	615	TNFi-naïve	Ustekinumab 45 mg SC at Week 0 and 4, then q12w (n = 205) Ustekinumab 90 mg SC at Week 0 and 4, then q12w (n = 204) Placebo (n = 206)	24	McInnes, et al (2013)[40]
PSUMMIT 2 (NCT01077362)	312	TNFi-naïve, TNFi-IR subpopulation (>50% of total population)	Ustekinumab 45 mg SC at Week 0 and 4, then q12w (n = 103) Ustekinumab 90 mg SC at Week 0 and 4, then q12w (n = 105) Placebo (n = 104)	24	Ritchlin, et al (2014)[41]

bDMARD = biologic disease-modifying antirheumatic drug; BID = twice daily; csDMARD = conventional synthetic disease-modifying antirheumatic drug; IR = inadequate response; ITT = intent-to-treat; IV = intravenous; NMA = network meta-analysis; NR = not reported; PsA = psoriatic arthritis; qXw = once every X weeks; SC = subcutaneous; SLR = systematic literature review; TNFi = tumor necrosis factor inhibitor.

[5.7] to 9.9 [8.4][13,14]). The mean duration of active psoriasis in the populations of the trials reporting this characteristic ranged from 11.3 years[41] to 19.7 years.[33]

NMA

In this analysis, the FE NMA model, which assumes a fixed or constant treatment effect, was favored over the RE model for the majority of study outcomes. This was based on the DIC values, which were lower for the FE model than for the corresponding RE model in most cases (**Supplemental Table 4** in the online version at doi:XXXXXXXXXX).

Exceptions were ACR20 and HAQ-DI outcomes in the TNFi-naïve population, where the RE model produced a smaller DIC and was preferred over the FE model (**Supplemental Table 4** in the online version at doi:XXXXXXXXXX). A comparison of the results from the FE and RE models for ACR20 and HAQ-DI outcomes in the TNFi-naïve population showed them to be largely similar and consistent with the direct trial-level data. However, in the FE model there were significant inconsistencies in the comparison of tofacitinib 5 and 10 mg BID versus placebo, and also adalimumab 40 mg q2w versus tofacitinib 5 and 10 mg BID (both comparisons $P < 0.05$), whereas there were no statistical inconsistencies in the same comparisons from the RE model for ACR20 and HAQ-DI outcomes. The inconsistency test was not feasible for ACR20 and HAQ-DI outcomes in the TNFi-IR population as there is no loop formed with direct and indirect evidence.

ACR20

Evidence networks for ACR20 are presented in Figure 2A (TNFi-naïve) and Figure 2B (TNFi-IR).

TNFi-naïve population

All treatments resulted in higher proportions of patients achieving ACR20 versus placebo in the TNFi-naïve population (Figure 3). ORs for ACR20 with tofacitinib 5 and 10 mg BID were comparable with the majority of bDMARDs/apremilast. Decreased ORs (less favorable response) were reported for tofacitinib 5 mg BID versus etanercept 25 mg twice weekly, golimumab 50 mg q4w, and infliximab 5 mg/kg q8w (**Supplemental Table 5** in the online version at doi:XXXXXXXXXX).

TNFi-IR population

All treatments resulted in higher proportions of patients achieving ACR20 versus placebo in the TNFi-IR population (Figure 4). ACR20 ORs for tofacitinib 5 and 10 mg BID were similar to other bDMARDs/apremilast, with the exception of decreased ORs (less favorable response) versus certolizumab pegol 200 mg q2w and 400 mg q4w (**Supplemental Table 5** in the online version at doi:XXXXXXXXXX).

Change from baseline in HAQ-DI

TNFi-naïve population

All treatments were associated with improvements in change from baseline (positive response) in HAQ-DI versus placebo in the TNFi-naïve population, with the exception of apremilast 30 mg BID and secukinumab 150 mg q4w. Tofacitinib 5 and 10 mg BID demonstrated similar changes from baseline in HAQ-DI to other agents, with the exception of etanercept 25 mg twice weekly (**Supplemental Table 6** in the online version at doi:XXXXXXXXXX). Heterogeneity, determined by median τ^2 was 0.000898 (95% CrI, 0.000001–0.03223).

TNFi-IR population

All treatments were associated with improvements in change from baseline in HAQ-DI versus placebo in the TNFi-IR population. There were no substantial differences in change from baseline in HAQ-DI for tofacitinib versus any analyzed treatment (**Supplemental Table 6** in the online version at doi:XXXXXXXXXX).

Figure 2. Evidence network for American College of Rheumatology 20 response (ACR20) in A) tumor necrosis factor inhibitor (TNFi)-naïve and B) TNFi-inadequate response (IR) patients with psoriatic arthritis (PsA). Each circle represents a treatment; connecting lines indicate pairs of treatments that have been directly compared in randomized controlled trials (RCTs). The line thickness is proportional to the number of RCTs making that comparison. Circle diameters are proportional to the number of patients randomized to that treatment. ACR20 = American College of Rheumatology 20 response; BID = twice daily; IR = inadequate response; PsA = psoriatic arthritis; qXw = once every X weeks; RCT = randomized controlled trial; TNFi = tumor necrosis factor inhibitor.

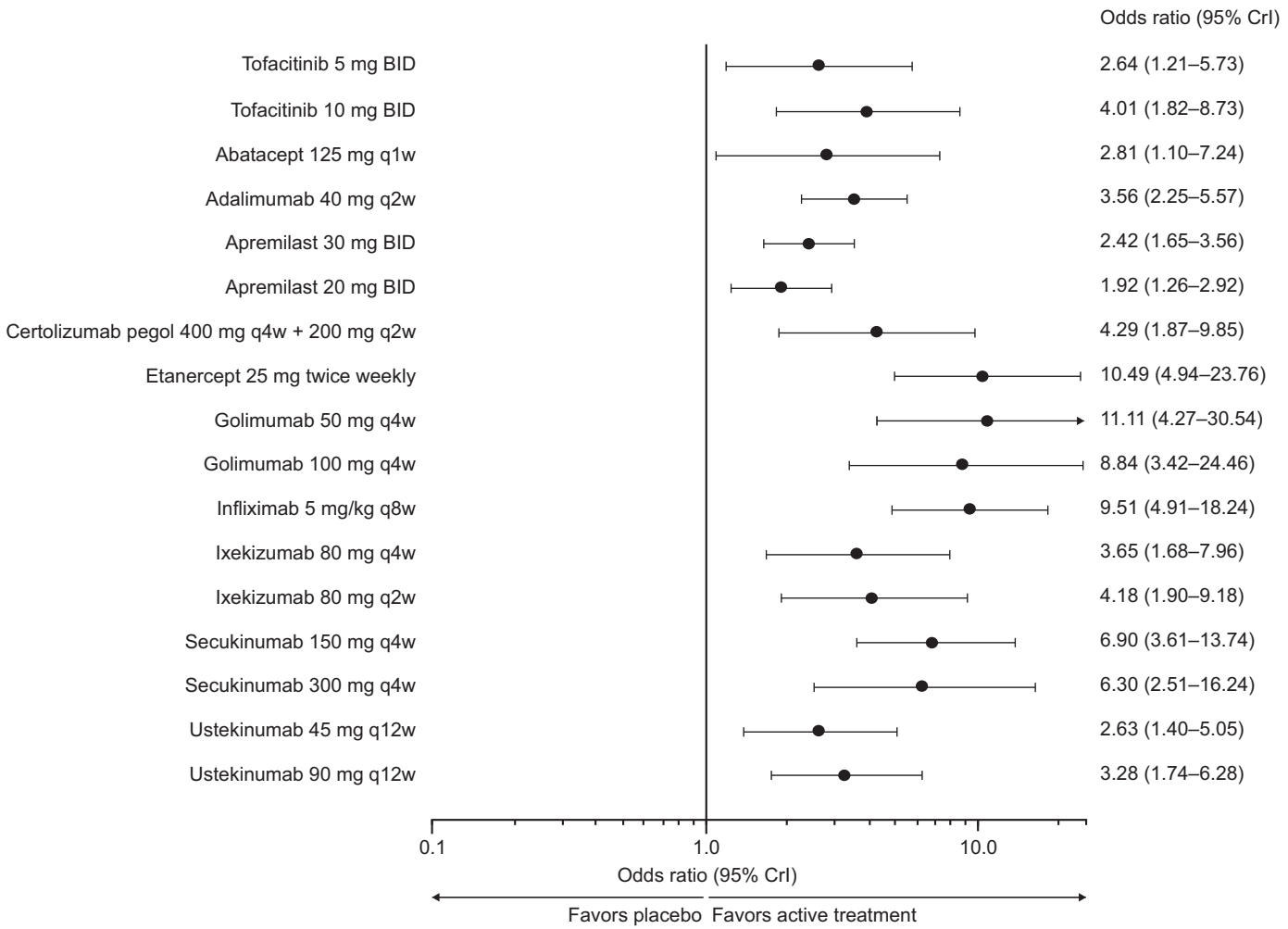

Figure 3. Forest plot of random-effect (RE) network meta-analysis (NMA) for American College of Rheumatology 20 response (ACR20): tofacitinib, biologic disease-modifying antirheumatic drugs (bDMARDs), and apremilast versus placebo in the tumor necrosis factor inhibitor (TNFi)-naïve psoriatic arthritis (PsA) population. Heterogeneity: median τ^2 (95% credible interval [CrI]) = 0.08319 (0.003030.34200). Arrowheads indicate that the upper CrI exceeds the visible scale of the x-axis. ACR20 = American College of Rheumatology 20 response; bDMARD = biologic disease-modifying antirheumatic drug; BID = twice daily; CrI = credible interval; NMA = network meta-analysis; PsA = psoriatic arthritis; qXw = once every X weeks; RE = random-effect; TNFi = tumor necrosis factor inhibitor.

PASI75

TNFi-naïve population

All treatments resulted in higher odds of PASI75 versus placebo in the TNFi-naïve population, except for abatacept 125 mg q1w (Figure 5).

Tofacitinib 5 and 10 mg BID were associated with lower odds of PASI75 (less favorable response) compared with golimumab 100 mg q4w, infliximab 5 mg/kg q8w, and ixekizumab 80 mg q4w and 80 mg q2w. Tofacitinib 5 mg BID was also associated with substantially decreased ORs for PASI75 versus golimumab 50 mg q4w. All remaining relative treatment comparisons of tofacitinib 5 mg and 10 mg with active comparators include the null value within the 95% CrIs (**Supplemental Table 7** in the online version at doi:XXXXXXXXXX).

TNFi-IR population

All treatments resulted in higher odds of PASI75 versus placebo in the TNFi-IR population, except for tofacitinib 5 mg BID, abatacept 125 mg q1w, and abatacept 10 mg/kg q4w (Figure 6).

Tofacitinib 5 mg BID was associated with decreased ORs of PASI75 versus tofacitinib 10 mg BID, ixekizumab 80 mg q4w, ixekizumab 80 mg q2w, secukinumab 300 mg q4w, ustekinumab 45 mg q12w, and ustekinumab 90 mg q12w. ORs for PASI75 with tofacitinib 10 mg BID were comparable with most bDMARDs (ie, 95% CrIs did not include the null value), with the exception of decreased ORs versus ustekinumab 45 mg q12w and ustekinumab 90 mg q12w (**Supplemental Table 7** in the online version at doi:XXXXXXXXXX).

Change from baseline in DSS and LEI

TNFi-naïve population

Two RCTs evaluated change from baseline in DSS and LEI in the TNFi-naïve patient population: OPAL Broaden assessed response to tofacitinib treatment[13] and SPIRIT-P1 assessed response to ixekizumab and adalimumab treatment.[21] There were no substantial differences in change from baseline in DSS and LEI for tofacitinib 5 and 10 mg BID versus adalimumab 40 mg q2w and ixekizumab 80 mg q2w and q4w.

TNFi-IR population

Two RCTs evaluated change from baseline in LEI in the TNFi-IR population: OPAL Beyond assessed response to tofacitinib treatment[14] and SPIRIT-P2 assessed response to ixekizumab treatment.[22] There were no substantial differences in change from baseline in LEI for tofacitinib 5 and 10 mg BID versus ixekizumab 80 mg q2w and q4w.

No comparator RCT evaluated DSS in this population.

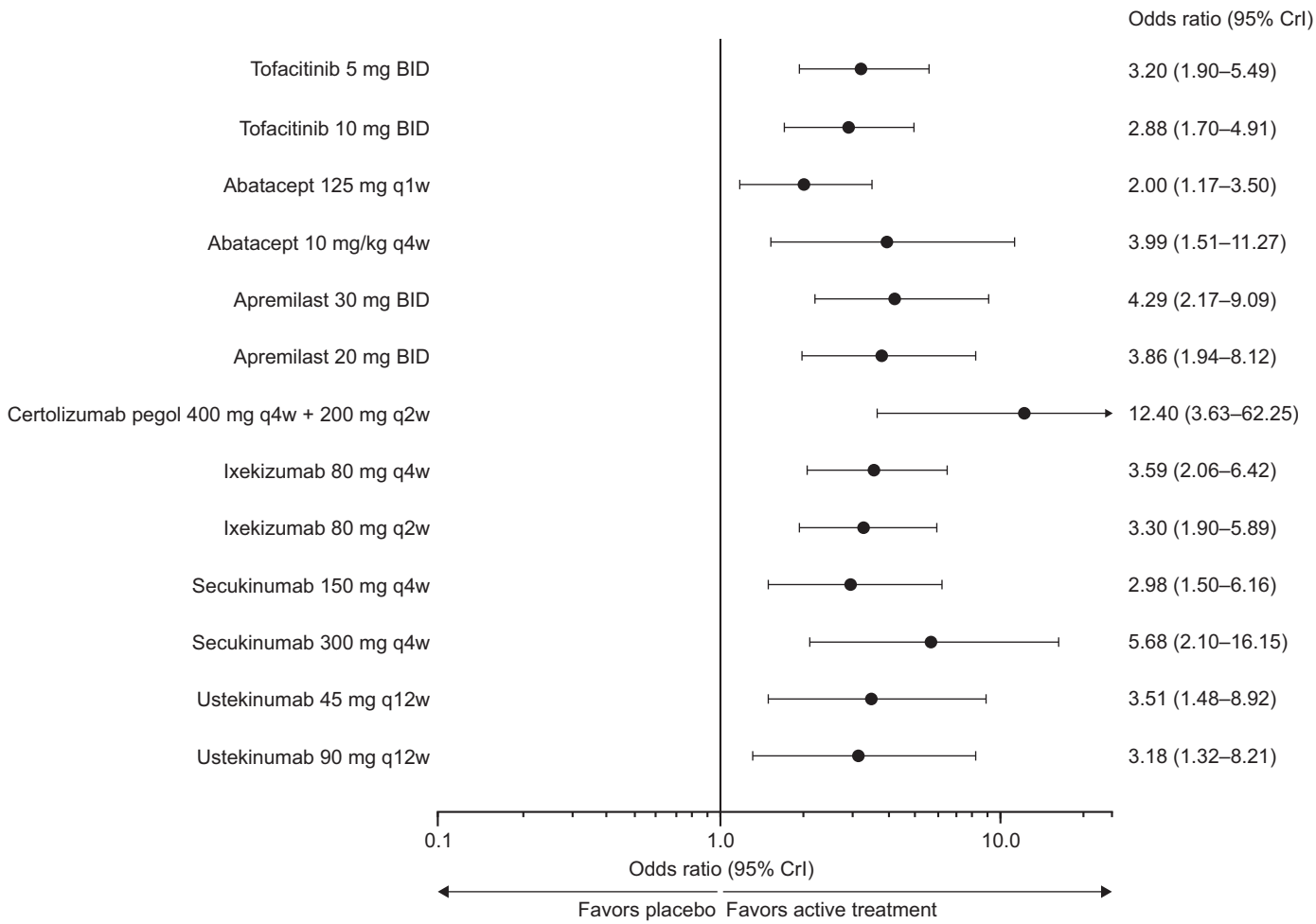

Figure 4. Forest plot of fixed-effect (FE) network meta-analysis (NMA) for American College of Rheumatology 20 response (ACR20): tofacitinib, biologic disease-modifying antirheumatic drugs (bDMARDs), and apremilast versus placebo in the tumor necrosis factor inhibitor (TNFi)-naïve psoriatic arthritis (PsA) population. Arrowheads indicate that the upper credible interval (CrI) exceeds the visible scale of the x-axis. ACR20 = American College of Rheumatology 20 response; bDMARD = biologic disease-modifying antirheumatic drug; BID = twice daily; CrI = credible interval; FE = fixed-effect; NMA = network meta-analysis; PsA = psoriatic arthritis; qXw = once every X weeks; TNFi = tumor necrosis factor inhibitor.

Median treatment rankings

TNFi-naïve population

Median treatment rankings in the TNFi-naïve patient population for the treatments included in the NMA are shown in **Supplemental Table 8** in the online version at doi:XXXXXXXXXX. Median rankings (95% CrI) for tofacitinib 5 and 10 mg BID were 14 (95% CrI, 8–17) and 9 (95% CrI, 5–14), respectively, for ACR20 among 18 comparators; 11 (95% CrI, 7–13) and 10 (95% CrI, 6–13), respectively, for PASI75 among 15 comparators; 11 (95% CrI, 4–13) and 8 (95% CrI, 2–13), respectively, for change from baseline in HAQ-DI among 14 comparators; 4 (95% CrI, 1–6) and 1 (95% CrI, 1–4), respectively, for change from baseline in DSS among 6 comparators; and 5 (95% CrI, 2–6) and 2 (95% CrI, 1–4), respectively, for change from baseline in LEI among 6 comparators.

TNFi-IR population

Median treatment rankings in the TNFi-IR patient population for the treatments included in the NMA are shown in **Supplemental Table 9** in the online version at doi:XXXXXXXXXX. Median rankings (95% CrI) for tofacitinib 5 and 10 mg BID were 8 (95% CrI, 3–13) and 9 (95% CrI, 3–13), respectively, for ACR20 among 14 comparators; 9 (95% CrI, 8–11) and 7 (95% CrI, 5–8), respectively, for PASI75 among 11 comparators; 4 (95% CrI, 1–8) and 5 (95% CrI, 1–9), respectively, for change from baseline in HAQ-DI among 10 comparators; and 2 (95% CrI, 1–4) and 2 (95% CrI, 1–4), respectively, for change from baseline in LEI among 5 comparators.

Sensitivity analyses in the TNFi-naïve population

The results of the sensitivity analyses confirmed the results of the primary analysis. For ACR20, golimumab 50 mg q4w remained the highest median-ranked treatment in all sensitivity analyses, except when grouping golimumab with other TNFi; only secukinumab 150 mg q4w ranked higher when TNFi were grouped together as 1 treatment. For change from baseline in HAQ-DI, etanercept 25 mg twice weekly remained the highest median-ranked treatment in all sensitivity analyses, except when grouping etanercept with other TNFi; only ixekizumab 80 mg q2w ranked higher than the TNFi grouping.

Safety profile analysis

For the safety profile analysis, data were included for patients regardless of prior TNFi experience. A median ranking of 1 was associated with the lowest chance of a safety event occuring (discontinuation due to any AE, or having an SIE), and a median ranking of 20 was associated with the highest chance of any of these events. The lowest chance of discontinuation due to any AE of the 20 treatments ranked was observed with ustekinumab

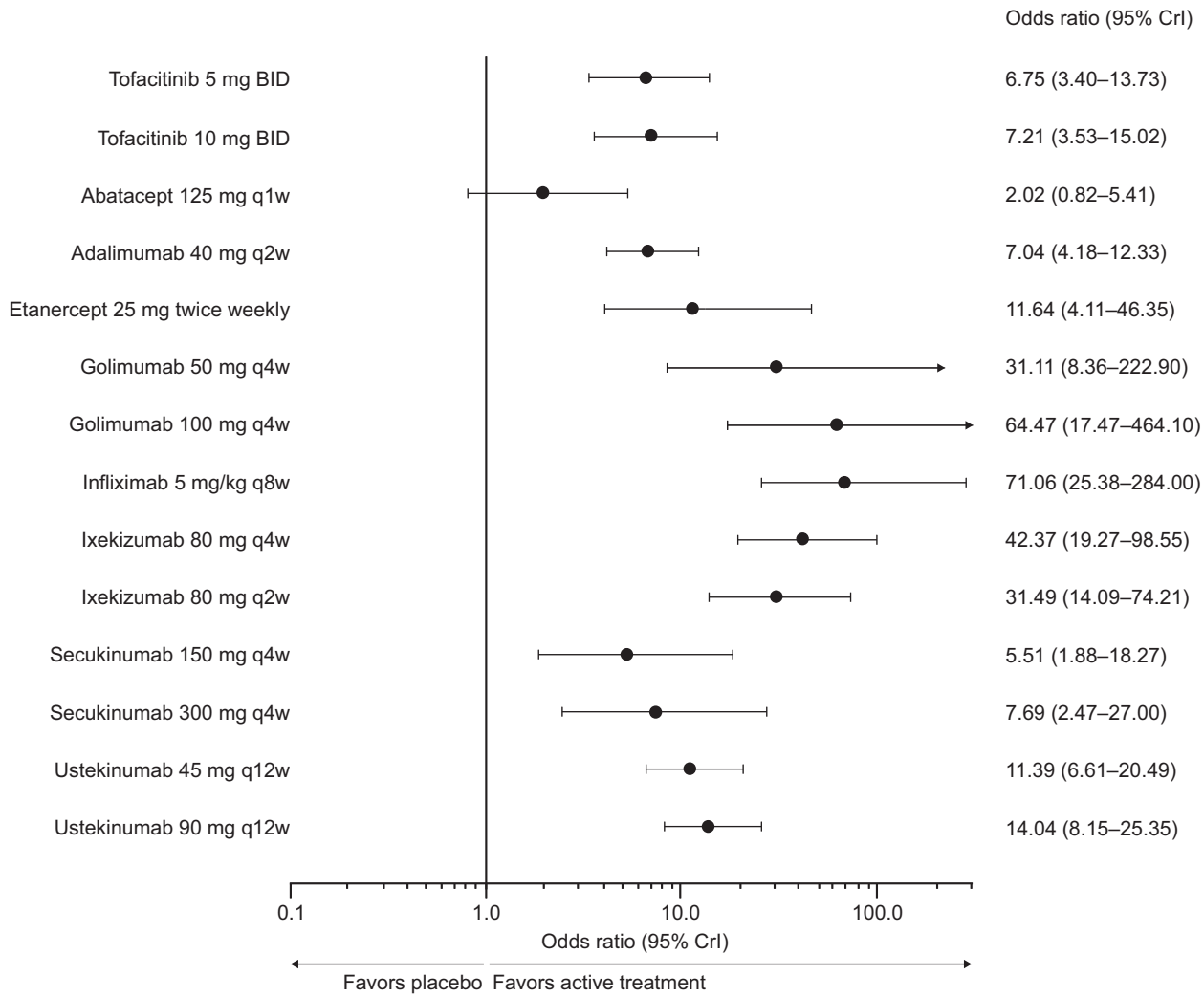

Figure 5. Forest plot of fixed-effect (FE) network meta-analysis (NMA) for ≥75% improvement in Psoriasis Area and Severity Index (PASI75): tofacitinib and biologic disease-modifying antirheumatic drugs (bDMARDs) versus placebo in the tumor necrosis factor inhibitor (TNFi)-naïve psoriatic arthritis (PsA) population. Arrowheads indicate that the upper credible interval (CrI) exceeds the visible scale of the x-axis. bDMARD = biologic disease-modifying antirheumatic drug; BID = twice daily; CrI = credible interval; FE = fixed-effect; NMA = network meta-analysis; PASI75 = ≥75% improvement in Psoriasis Area and Severity Index; PsA = psoriatic arthritis; qXw = once every X weeks; TNFi = tumor necrosis factor inhibitor.

45 mg q12w. Tofacitinib 5 mg BID was median-ranked 8, which was similar to—or associated with a lower chance of discontinuation due to any AE than—abatacept, adalimumab, etanercept, certolizumab pegol, infliximab, ixekizumab, secukinumab 300 mg q4w, and apremilast; tofacitinib 10 mg BID was median-ranked 15 (Table 2). Of the 20 treatments assessed, golimumab (50 and 100 mg q4w) was median-ranked as the treatment with the lowest chance of having an SIE, with ustekinumab 45 mg q12w ranked second lowest, followed by tofacitinib 5 mg BID; tofacitinib 10 mg BID was median-ranked 16 (Table 2).

Discussion

Indirect comparisons in this NMA of published RCTs showed tofacitinib 5 and 10 mg BID to have similar efficacy to most bDMARDs and apremilast in improving joint symptoms (as assessed by achievement of ACR20) and to some bDMARDs in improving skin symptoms (as assessed by achievement of PASI75; tofacitinib 10 mg BID only in TNFi-IR) in patients with PsA who were TNFi-naïve, and in patients with PsA who were TNFi-IR.

The NMA also showed improvements in physical functioning (as assessed by HAQ-DI) with tofacitinib 5 and 10 mg BID, similar to that observed with most bDMARDs and apremilast in TNFi-naïve patients with PsA, and similar to that observed with all bDMARDs with available data in the TNFi-IR population with PsA. There was no substantial difference in the reduction of HAQ-DI scores in TNFi-naïve patients with PsA receiving tofacitinib 5 or 10 mg BID or adalimumab 40 mg q2w in OPAL Broaden, although the study design was not powered for this comparison.[13] HAQ-DI was reported by most of the trials included in the NMA, making it a preferable/more reliable outcome for assessing physical functioning than the SF-36[42] Physical Component Summary and the physical functioning domain (for which data were sparse and are therefore not reported here).

Our analyses also suggest that tofacitinib 5 and 10 mg BID have similar efficacy to adalimumab 40 mg q2w and ixekizumab 80 mg q2w or q4w in reducing DSS and LEI from baseline in TNFi-naïve patients with PsA, and similar efficacy to ixekizumab 80 mg q2w or q4w in reducing LEI from baseline in the TNFi-IR population (no studies evaluated DSS). There was also no substantial difference between tofacitinib 5 or 10 mg BID or adalimumab 40 mg

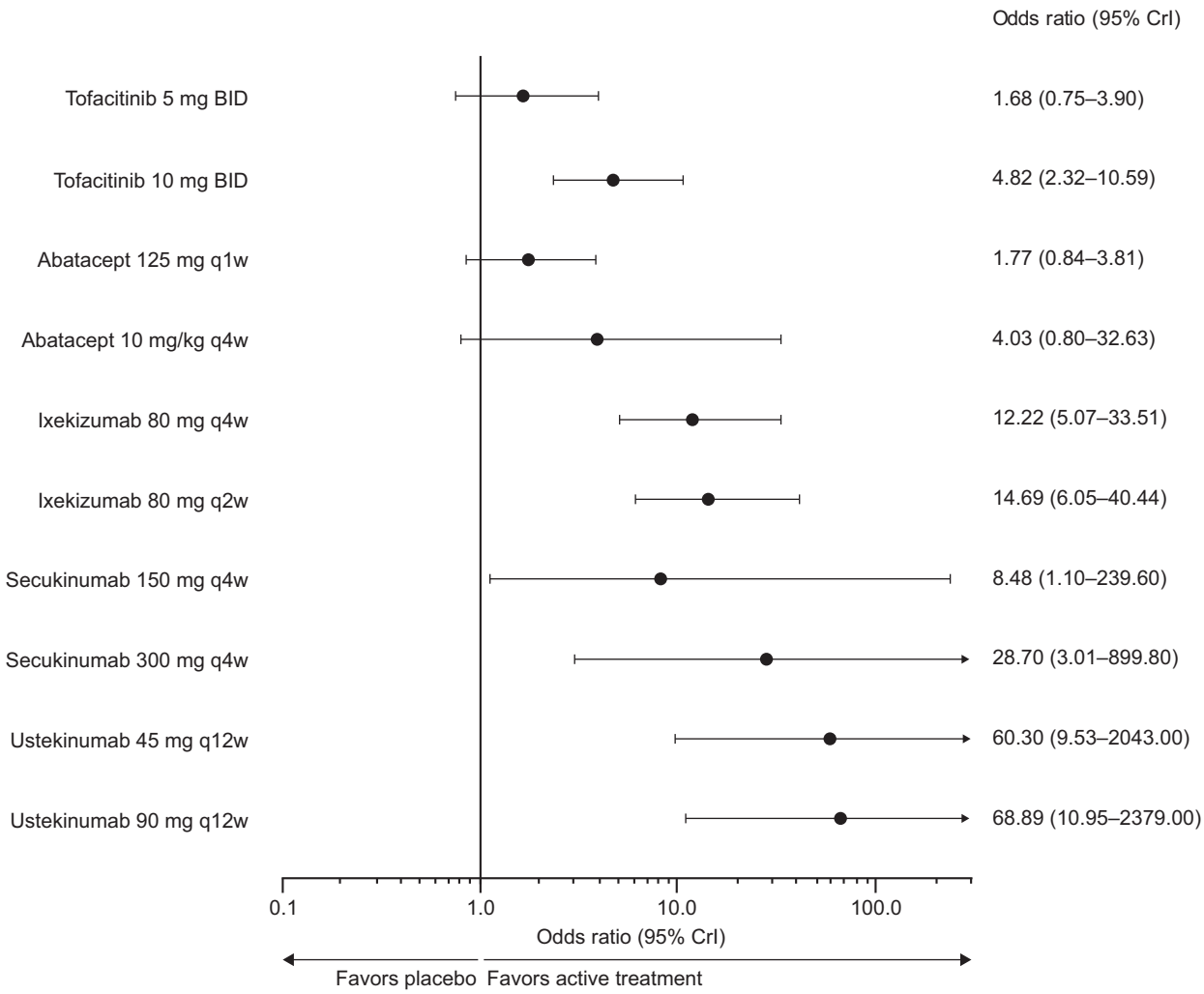

Figure 6. Forest plot of fixed-effect (FE) network meta-analysis (NMA) for ≥75% improvement in Psoriasis Area and Severity Index (PASI75): tofacitinib and biologic disease-modifying antirheumatic drugs (bDMARDs) versus placebo in the tumor necrosis factor inhibitor (TNFi)-naïve psoriatic arthritis (PsA) population. Arrowheads indicate that the upper credible interval (CrI) exceeds the visible scale of the x-axis. bDMARD = biologic disease-modifying antirheumatic drug; BID = twice daily; CrI = credible interval; FE = fixed-effect; IR = inadequate response; NMA = network meta-analysis; PASI75 = ≥75% improvement in Psoriasis Area and Severity Index; PsA = psoriatic arthritis; qXw = once every X weeks; TNFi = tumor necrosis factor inhibitor.

q2w in their influence on change from baseline in DSS and LEI in TNFi-naïve patients with PsA in OPAL Broaden.[13]

An NMA published after the current study was performed assessed the relative efficacy and safety profiles of tofacitinib and aprelimast at different doses in patients with active PsA. Similar to the current analysis, the authors compared tofacitinib efficacy and safety profile results from OPAL Broaden and OPAL Beyond with those from 6 RCTs of apremilast (5 of these RCTs were also included in the current analysis). The authors reported that tofacitinib 10 mg BID and aprelimast 30 mg BID ranked higher than tofacitinib 5 mg BID and aprelimast 20 mg BID in terms of ACR20 response, while no significant differences in serious AEs were observed.[43] Although these results support our findings for ACR20, a strength of the current NMA is that it assessed the relative efficacy of multiple active treatments across several end points.

Additionally, a published meta-analysis has shown that indirect comparisons of the TNFi agents etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol with apremilast, ustekinumab, and secukinumab demonstrated that patients with PsA have a higher probability of achieving ACR20 with etanercept, infliximab, adalimumab, golimumab, and secukinumab than other agents.[44] Another meta-analysis conducted indirect comparisons of 4 non-TNFi bDMARDs (ie, abatacept, apremilast, secukinumab, and ustekinumab) and reported that the likelihood of achieving ACR20 in the TNFi-IR population with PsA did not differ significantly between these agents.[45] A descriptive review of the efficacy of a comprehensive list of bDMARDs and targeted synthetic DMARDs (including tofacitinib) in treating the range of clinical manifestations of PsA concluded that there are new treatments that could be effective for some patients with PsA.[46]

In OPAL Broaden, tofacitinib 5 and 10 mg BID did not differ substantially from adalimumab 40 mg q2w in their effects on ACR20 in a TNFi-naïve population, although this finding must be interpreted with caution because the study was not powered for a statistical comparison of these 2 treatment groups.[13] The findings from the NMA reported here are comparable with those from OPAL Broaden; ORs for ACR20 for adalimumab 40 mg q2w did not differ substantially from those for tofacitinib 5 and 10 mg BID, and median treatment rankings for ACR20 were similar for adalimumab and tofacitinib 10 mg BID.

Interpretation of the findings reported here should consider the differences between tofacitinib trials and other RCTs in terms of

Table 2
Median treatment rankings for safety outcomes for tofacitinib, biologic disease-modifying antirheumatic drugs (bDMARDs), and apremilast in patients with psoriatic arthritis (PsA).

Treatment	Discontinuations due to an AE[†]	Serious infections[†]
Placebo	10 (7–14)	8 (5–12)
Tofacitinib 5 mg BID	8 (3–17)	5 (1–18)
Tofacitinib 10 mg BID	15 (8–20)	16 (5–20)
Abatacept 125 mg q1w	8 (1–19)	17 (3–20)
Abatacept 10 mg/kg 4w	7 (1–19)	17 (3–20)
Adalimumab 40 mg q2w	11 (5–17)	13 (5–19)
Apremilast 30 mg BID	16 (12–19)	11 (4–19)
Apremilast 20 mg BID	14 (8–18)	7 (2–17)
Certolizumab pegol 200 mg q2w	17 (5–20)	14 (3–20)
Certolizumab pegol 400 mg q4w	19 (8–20)	14 (3–20)
Etanercept 25 mg twice weekly	11 (1–20)	8 (1–20)
Golimumab 50 mg q4w	4 (1–16)	2 (1–9)[*]
Golimumab 100 mg q4w	4 (1–16)	2 (1–9)[*]
Infliximab 5 mg/kg q8w	19 (12–20)	14 (5–20)
Ixekizumab 80 mg q4w	9 (3–17)	9 (2–18)
Ixekizumab 80 mg q2w	15 (7–19)	16 (8–20)
Secukinumab 150 mg q4w	5 (1–13)	12 (5–18)
Secukinumab 300 mg q4w	9 (1–19)	11 (3–19)
Ustekinumab 45 mg q12w	3 (1–9)[*]	4 (1–16)
Ustekinumab 90 mg q12w	4 (1–9)	11 (3–19)

AE = adverse event; bDMARD = biologic disease-modifying antirheumatic drug; BID = twice daily; CrI = credible interval; PsA = psoriatic arthritis; qXw = once every X weeks.
[*] Highest median rank.
[†] Values are presented as rank (95% CrI).

patient population, baseline characteristics, concomitant therapy, outcomes assessed, and the duration of the placebo-controlled period, all of which might have led to variability in the findings. Results of an exploratory meta-epidemiologic study suggested that certain eligibility criteria have an impact on response to targeted therapies.[47] Prior therapy, disease duration, rheumatoid factor, and use of Classification Criteria for Psoriatic Arthritis criteria for study entry were identified as important contextual factors that may influence the odds of achieving an ACR20 response in PsA trials.[47] As such, the odds of achieving ACR20 response were lower in trials in which a minimum disease duration of 6 months was required, compared with trials in which disease duration was not in the inclusion criteria.[47]

In the safety profile analysis reported here, the chance of an AE-related discontinuation with tofacitinib 5 mg BID was similar to—or less likely than—that with abatacept, adalimumab, etanercept, certolizumab pegol, infliximab, ixekizumab, secukinumab 300 mg q4w, and apremilast. The chance of having an SIE with tofacitinib 5 mg BID was lower than with all other treatments except golimumab (50 and 100 mg q4w) and ustekinumab 45 mg q12w. Wide CrIs were observed in the analysis of SIEs, which may reflect the limited number of events in some studies, and is consistent with the wide CrIs observed in an SLR and meta-analysis that evaluated the risk of serious infection with bDMARDs in patients with rheumatoid arthritis.[48]

Although direct comparisons cannot be made across trials, it should be noted that relatively high placebo response rates were observed in OPAL Broaden and OPAL Beyond (OPAL Broaden: ACR20, 33% and ACR70, 5%; OPAL Beyond: ACR20, 24% and ACR70, 10%), which were generally greater than the placebo response rates observed in other RCTs in patients with PsA.[13,14] Placebo response rates in PsA RCTs appear to have increased recently, with the PSUMMIT and SPIRIT-1 trials being notable examples.[21,40,41] Possible reasons for this placebo response may be increased patient confidence and optimism about beneficial clinical outcomes.[49]

Some limitations of this study must be acknowledged. Although the search criteria were carefully constructed, it is possible that some relevant RCTs were not identified if they were not listed in the electronic databases or congress proceedings used for the SLR. Additionally, the data in the network are too sparse for a full statistical examination of consistency between direct and indirect estimates; detection of inconsistency requires more data than is needed to establish the presence of a treatment effect, and failure to reject the null hypothesis of consistency does not indicate that there is no inconsistency.[19] Differing criteria for the use of concomitant csDMARDs across studies might also have resulted in variability; for example, RCTs for certolizumab pegol[31] and apremilast[30] did not mandate use of concomitant csDMARDs, whereas OPAL Broaden and OPAL Beyond did require concomitant use of csDMARDs.[13,14] Only 2 RCTs evaluated change from baseline in DSS and LEI with treatments other than tofacitinib (efficacy of ixekizumab in SPIRIT-P1 and SPIRIT-P2), limiting the number of treatment comparisons versus tofacitinib for these end points and the conclusions that can be made with regard to differences in efficacy for improving dactylitis and enthesitis. The availability of comparable safety data between clinical trials at the time of this analysis limited the safety outcomes reported in this NMA to discontinuations due to AEs and serious infections. For this reason, other safety events of interest, including herpes zoster, major adverse cardiovascular events, malignancies, nonmelanoma skin cancer, and venous thromboembolism, were not evaluated, and this is an area that warrants further research.

Conclusions

Despite these limitations, the robust methodology followed in selecting RCTs for inclusion and in completing the NMA allows us to conclude that tofacitinib represents an additional treatment option for patients with PsA, including those naïve to treatment with TNFi or with an IR to TNFi. In the absence of RCTs involving a direct comparison of treatments, this NMA provides useful evidence for comparing efficacy and safety profiles across various treatment options.

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Conflicts of interest statement

This study was sponsored by Pfizer Inc. Pfizer authors were involved in the conception and design of the study/analyses, as well as performing the data and statistical analyses. All authors were

involved in data interpretation and manuscript drafting, reviewing, and final approval to submit. The views and opinions expressed within this manuscript are those of all authors and do not necessarily represent those of the sponsor.

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or the European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2020.100601.

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