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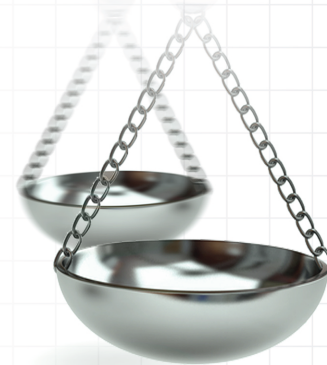
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Secukinumab for psoriatic arthritis: comparative effectiveness versus licensed biologics/apremilast: a network meta-analysis

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Aim: A network meta-analysis using randomized controlled trial data compared psoriatic arthritis (PsA) outcomes (American College of Rheumatology [ACR], Psoriasis Area Severity Index [PASI] and Psoriatic Arthritis Response Criteria [PsARC] response rates) at 12–16 weeks for secukinumab, adalimumab, apremilast, certolizumab, etanercept, golimumab, infliximab and ustekinumab. **Patients & methods:** Trials were identified by systematic review. Separate networks were developed for the full-study populations, biologic-naïve patients and biologic-experienced patients. **Results:** In the full populations, secukinumab, adalimumab, golimumab and infliximab demonstrated the highest ACR response rates. Secukinumab and infliximab demonstrated the highest PASI response rates, and infliximab and etanercept demonstrated the highest PsARC response rates. **Conclusion:** In the full populations, secukinumab demonstrated good efficacy across all outcomes. All treatments for active PsA included in this comprehensive network meta-analysis demonstrated superiority to placebo.

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Keywords: ACR • biologic therapy • network meta-analysis • PASI • PsARC • psoriatic arthritis • secukinumab

Psoriatic arthritis (PsA) is characterized by chronic inflammation, with musculoskeletal and dermatological issues, and other co-morbidities [1]. The pain, stiffness and swelling associated with PsA are often accompanied by structural damage to the joints, impairing patients' physical functioning and often resulting in severe disability [2]. The aim of treatment is to achieve sustained, low disease activity or remission, maximizing quality of life in the long term [2].

Current immune-modifying therapies, including biologics and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs), are recommended by several international guidelines for use if conventional DMARDs (cDMARDs), employed as first-line therapies, are not successful [3,4]. The earliest biologic therapies approved for the treatment of PsA targeted TNF. At present, five such agents (adalimumab, certolizumab, etanercept, golimumab and infliximab) have been approved, with biosimilars also now widely available. Two agents,

secukinumab and ustekinumab, which have been approved more recently, are directed against cytokines that are implicated in the pathophysiology of PsA and related disorders by genetic and tissue-based pathogenesis investigations [5]. Secukinumab is a fully human monoclonal antibody targeting IL-17A, which is involved in the pathogenesis of PsA as well as other autoimmune diseases in the spondyloarthritis family [6,7]. Ustekinumab is a fully human monoclonal antibody directed against the p40 subunit of IL-12 and IL-23. Like IL-17, IL-23 has been implicated in the pathogenesis of autoimmune diseases, including PsA [8]. In addition, the tsDMARD apremilast, a small-molecule inhibitor that modulates inflammatory cytokine production via inhibition of phosphodiesterase-4, has also been approved recently for the treatment of PsA.

The optimal treatment pathway to achieve the objectives set out in guidelines merits further investigation. In particular, there is an increasing need for comparative evidence on the efficacy of the foregoing treatments. Three randomized controlled trials (RCTs) have reported direct comparisons between biologic therapies employed in the treatment of patients with psoriasis: the CLEAR trial [9], which compared secukinumab and ustekinumab (NCT02074982); the FIXTURE trial [10] between secukinumab and etanercept (NCT01358578); and the ACCEPT study between ustekinumab and etanercept (NCT00454584) [11]. The CLEAR and FIXTURE trials included subpopulation analyses for patients with both psoriasis and PsA; however, these trials were conducted to compare the effects of these treatments in patients with psoriasis, and therefore had a focus on skin outcomes rather than articular inflammation. In the CLEAR trial, among patients with psoriasis and PsA, a significantly greater proportion receiving secukinumab 300 mg achieved a Psoriasis Area Severity Index 90 (PASI90) response (i.e., an improvement of at least 90% in PASI score) as early as week 8 compared with patients who received ustekinumab. This significant difference between treatment groups was sustained from week 16 onward: approximately 80% of patients receiving secukinumab achieved a PASI90 response at all time points through to week 52 [9]. In the FIXTURE trial, patients with psoriasis and PsA receiving secukinumab 300 mg were significantly more likely to achieve a PASI75 response at week 12 compared with patients receiving etanercept [10]. Comparatively higher rates of PASI75 and PASI90 response for patients receiving secukinumab 300 mg were sustained until week 52. The efficacy of biologics and tsDMARDs in patients with PsA has been demonstrated across many placebo-controlled trials; however, to our knowledge, only two trials directly comparing treatments for PsA and powered for superiority have been initiated and are currently ongoing. EXCEED 1 is intended to compare the efficacy of secukinumab and adalimumab [12], and SPIRIT-H2H will compare ixekizumab and adalimumab [13]. Unlike previous head-to-head trials, both of these studies will examine articular outcomes as well as skin outcomes. Currently, in the absence of findings from head-to-head trials, adjusted indirect comparisons provide the best available evidence allowing differentiation between treatments for PsA.

Network meta-analysis (NMA) is an extension of traditional pairwise meta-analysis. NMA compares outcomes across a number of treatments when relevant trials can be 'connected' into a network directly, or indirectly by use of common comparators, or both. NMA is increasingly used and accepted in comparative effectiveness research and healthcare decision-making [14,15]. Several analyses have used NMA to compare PsA treatments [16–20]; however, not all of them have compared the full range of approved therapies. Here, we have developed networks to compare all biologics and tsDMARDs for PsA approved at the time at which our study was conducted, with a focus on pairwise comparisons against secukinumab. The current study has been carried out in line with established standards [21,22] to meet health technology assessment requirements, and provides further comparative effectiveness data for PsA therapies.

Patients & methods

Systematic literature review

A systematic review of literature published up to 6 November 2015 identified trials of approved biologic therapies and tsDMARDs for patients with active PsA who had experienced an inadequate response to cDMARDs. The therapies of interest were adalimumab, certolizumab, etanercept, golimumab, infliximab, secukinumab and ustekinumab, and the non-biologic therapy apremilast. Relevant efficacy outcomes extracted from the trials identified included American College of Rheumatology 20 (ACR20), ACR50 and ACR70 responses (indicating at least a 20/50/70% improvement in the core set of ACR measures for assessing arthritis); PASI50, PASI75 and PASI90 responses (indicating at least a 50/75/90% reduction in PASI score); and Psoriatic Arthritis Response Criteria (PsARC) responses. Further details can be found in Supplementary Methods; trial inclusion criteria are given in [Supplementary Table 1](#).

Treatment networks

Three treatment networks were developed: one for ACR responses, one for PASI responses and one for PsARC responses. Principal networks were developed for the full study populations (termed the ‘mixed’ populations), which included all patients, regardless of whether they had received previous biologic therapy. Networks were also developed for trials reporting data from ‘biologic-naive’ patients at study entry as a separate subpopulation. A network was developed for ‘biologic-experienced’ patients for ACR responses only, as there was insufficient evidence reported for the other outcomes. Data used in the networks were those collected at time points up to week 16, the point at which many patients receiving placebo switched to active treatment, particularly in the major trials for apremilast, certolizumab, golimumab, infliximab, secukinumab and ustekinumab.

NMA & statistical methodology

ACR and PASI responses were modeled using a Bayesian NMA with probit link function and conditional multinomial likelihood [21]. This approach can be adopted in cases in which continuous data (e.g., PASI score) are interpreted using a prespecified cut-off point to generate binomial data for analyses (e.g., response or non-response). For PsARC, a dichotomous composite measure developed specifically for use in PsA, a generalized linear model with logit link function and binomial likelihood, was used. Where feasible, for each treatment network, both random-effect and fixed-effect models were conducted. Models with baseline adjustments for placebo response were conducted where needed and feasible. Several factors were examined in order to assess the fit of each model, including the deviance information criterion (see [Supplementary Methods](#)).

The output of the Bayesian NMA was a posterior distribution of relative treatment effects, represented as median relative risks with 95% credible intervals, which were constructed from the 2.5th and 97.5th percentiles of the posterior distribution, and can be interpreted in a similar way to CIs. There was considered to be statistical evidence of superiority for a treatment over a given comparator when the relative risk of an ACR, PASI or PsARC response was > 1 at both upper and lower 95% credible interval. This can be interpreted as analogous to testing a two-sided p-value at the 5% threshold.

Sensitivity analyses

When feasible, sensitivity analyses were used to examine the impact of including or excluding certain studies in each network. One sensitivity analysis examined the impact of adding adalimumab and placebo data from SPIRIT-P1 [23,24]. This study was excluded from the original network because it is a trial including ixekizumab, which was not approved at the time the analyses were carried out. Three different iterations of the analysis by time point were also performed:

- Inclusion of all trials that reported at 12–16 weeks
- Restriction of network to only those trials that reported at 12 weeks
- Restriction of network to only those trials that reported at 16 weeks

Results

Study selection

Following full-text screening of publications identified by systematic review, 20 trials were selected for potential inclusion in the NMA. Of these, 17 included ACR20/50/70 responses, 19 included PASI50/75/90 responses and 13 included PsARC responses ([Table 1](#)). A feasibility assessment determined the degree of heterogeneity across the different trials, examined the quality of the data and established that the selected trials could be used to develop a network. Subsequently, the SPIRIT-P1 trial [23,24] was identified separately for potential inclusion. This placebo-controlled study investigating the efficacy of ixekizumab contains adalimumab as an active control arm.

Details of included studies’ designs and populations are given in [Tables 1 & 2](#). For adalimumab, golimumab and infliximab, populations were entirely biologic-naive, whereas data for the remainder of the therapies came from mixed populations in which some patients were biologic-experienced. In trials that reported data from biologic-experienced populations, disparities in inclusion criteria meant that patients receiving certain agents might have experienced several previous anti-TNF therapy failures, whereas other populations were permitted to have received only one previous anti-TNF therapy. There were also differences between trials in terms of the methods used to

Table 1. Study details for trials included in sensitivity analyses.

Trial name [Ref.]	Relevant treatments (number of patients randomized)	Primary endpoint(s)	Use in ACR NMA (reason for exclusion)	Use in PASI NMA (reason for exclusion)	Use in PsARC NMA (reason for exclusion)	Imputation method	Population composition [†]
ADEPT [25]	Adalimumab 40 mg (153) Placebo (162)	ACR20 response at 12 weeks Modified Sharp score change from baseline at 24 weeks	Yes	Yes	Yes	NRI	Biologic-naive
CLEAR [9]	Secukinumab 300 mg (69) Ustekinumab 45 mg (54)	PASI90 response at 16 weeks	No (ACR data not collected)	Yes	No (PsARC data not reported)	NRI	Mixed
ERASURE [10]	Secukinumab 150 mg (46) Secukinumab 300 mg (57) Placebo (68)	PASI75 response at 12 weeks IGA Mod 2011 at 12 weeks	No (ACR data not collected)	Yes	No (PsARC data not reported)	NRI	Mixed
FIXTURE [10]	Etanercept 50 mg BIW (44) Secukinumab 150 mg (49) Secukinumab 300 mg (50) Placebo (49)	PASI75 response at 12 weeks IGA Mod 2011 at 12 weeks	No (ACR data not collected)	Yes	No (PsARC data not reported)	NRI	Mixed
FUTURE 1 [26]	Secukinumab 150 mg (202) Secukinumab 300 mg (202) Placebo (202)	ACR20 response at 24 weeks	No (excluded owing to intravenous loading doses, which do not reflect approved posology)	No (excluded owing to intravenous loading doses, which do not reflect approved posology)	No (excluded owing to intravenous loading doses, which do not reflect approved posology)	NRI	Mixed
FUTURE 2 [27]	Secukinumab 150 mg (100) Secukinumab 300 mg (100) Placebo (98)	ACR20 response at 24 weeks	Yes	Yes	Yes	NRI	Mixed
Genovese <i>et al.</i> [28]	Adalimumab 40 mg (51) Placebo (51)	ACR20 response at 12 weeks	No (excluded owing to lack of 16-week data)	No (no PASI data reported)	Yes	NRI	Biologic-naive
GO-REVEAL [29]	Golimumab 50 mg (146) Golimumab 100 mg (146) Placebo (113)	ACR20 response at 14 weeks	Yes	Yes	Yes	LOCF	Biologic-naive
IMPACT [30]	Infliximab 5 mg/kg (52) Placebo (52)	ACR20 response at 14 weeks	Yes	Yes	Yes	Unclear	Biologic-naive
IMPACT2 [31]	Infliximab 5 mg/kg (100) Placebo (100)	ACR20 response at 14 weeks	Yes	Yes	Yes	NRI/LOCF	Biologic-naive
Mease <i>et al.</i> [32]	Etanercept 25 mg BIW (30) Placebo (30)	PsARC response at 12 weeks	No (excluded owing to lack of 16-week data)	Yes	Yes	LOCF	Not reported
Mease <i>et al.</i> [33]	Etanercept 25 mg BIW (101) Placebo (104)	ACR20 response at 12 weeks	No (excluded owing to lack of 16-week data)	No	Yes	LOCF	Not reported
PALACE 1 [34]	Apremilast 20 mg (168) Apremilast 30 mg (168) Placebo (168)	ACR20 response at 16 weeks	Yes	Yes	Yes	NRI	Mixed
PALACE 2 [35,36]	Apremilast 20 mg (163) Apremilast 30 mg (162) Placebo (159)	ACR20 response at 16 weeks	Yes	Yes	Yes	Unclear	Mixed

[†] Study populations were either mixed (including both biologic-naive and biologic-experienced patients) or biologic-naive.

[‡] With a 400 mg loading dose.

ACR20: At least a 20% improvement in the core set of American College of Rheumatology measures for assessing arthritis; BIW: Twice per week; IGA Mod 2011: Investigator's Global Assessment (modified in 2011); LOCF: Last observation carried forward; NMA: Network meta-analysis; NRI: Non-responder imputation; PASI75/90: At least a 75/90% reduction in Psoriasis Area Severity Index score; PsARC: Psoriatic Arthritis Response Criteria; QW: Once a week.

Table 1. Study details for trials included in sensitivity analyses (cont.).

Trial name [Ref.]	Relevant treatments (number of patients randomized)	Primary endpoint(s)	Use in ACR NMA (reason for exclusion)	Use in PASI NMA (reason for exclusion)	Use in PsARC NMA (reason for exclusion)	Imputation method	Population composition [†]
PALACE 3 [37]	Apremilast 20 mg (169) Apremilast 30 mg (167) Placebo (169)	ACR20 response at 16 weeks	Yes	Yes	Yes	NRI	Mixed
PRESTA [38]	Etanercept 50 mg BIW (379) Etanercept 50 mg QW (373)	Proportion of patients achieving 'clear' or 'almost clear' on the physician's global assessment of psoriasis at 12 weeks	No (reported ACR response data, but could not be linked to ACR treatment network via placebo or an active comparator)	Yes	No (PsARC data not reported)	LOCF	Biologic-naive
PSUMMIT1 [39]	Ustekinumab 45 mg (205) Ustekinumab 90 mg (204) Placebo (206)	ACR20 response at 24 weeks	Yes	No	No (PsARC data not reported)	LOCF	Biologic-naive
PSUMMIT2 [40]	Ustekinumab 45 mg (103) Ustekinumab 90 mg (105) Placebo (104)	ACR20 response at 24 weeks	Yes	No	No (PsARC data not reported)	LOCF	Mixed
RAPID-PsA [41]	Certolizumab 200 mg [‡] (138) Certolizumab 400 mg [‡] (135) Placebo (136)	ACR20 response at 12 weeks Modified total Sharp score change from baseline at 24 weeks	Yes	Yes	Yes	NRI	Mixed
Schett <i>et al.</i> [42]	Apremilast 20 mg (69) Apremilast 40 mg (67) Placebo (68)	ACR20 response at 12 weeks	No (excluded owing to lack of 16-week data)	No (no PASI data reported)	Yes	LOCF	Mixed
SPIRIT-P1 [23,24]	Adalimumab 40 mg (101) Placebo (106)	ACR20 response at 24 weeks	No (excluded following sensitivity analysis)	Yes	No	NRI	Biologic-naive

[†] Study populations were either mixed (including both biologic-naive and biologic-experienced patients) or biologic-naive.
[‡] With a 400 mg loading dose.
ACR20: At least a 20% improvement in the core set of American College of Rheumatology measures for assessing arthritis; BIW: Twice per week; IGA Mod 2011: Investigator's Global Assessment (modified in 2011); LOCF: Last observation carried forward; NMA: Network meta-analysis; NRI: Non-responder imputation; PASI75/90: At least a 75/90% reduction in Psoriasis Area Severity Index score; PsARC: Psoriatic Arthritis Response Criteria; QW: Once a week.

adjust for missing data; some used nonresponder imputation (NRI), whereas others employed the less conservative last observation carried forward imputation approach.

Treatment networks

The treatment networks selected for each outcome in the mixed population are shown in [Figure 1](#). For ACR responses, networks were limited to studies reporting data at week 16, meaning that the studies of *Genovese et al.* [28], *Mease et al.* [32,33] and *Schett et al.* [42] were excluded. SPIRIT-P1 [23,24] was not included. Thus, the final network contained 11 studies. For PASI responses, the evidence base was smaller when networks were restricted by time point. Therefore, available evidence was maximized by using data from 12–16-week time points, and including data from SPIRIT-P1 [23,24]; the final network contained 15 trials. For PsARC responses, data from 12–16-week time points were used. The treatment network contained 13 trials. Networks for the biologic-naive and biologic-experienced populations are shown in [Supplementary Figures 1 & 2](#).

Model selection

Values for the deviance information criterion were similar across models for ACR and PASI scores, regardless of adjustments for placebo response or other covariates. Thus, unadjusted models were selected for both networks. The leverage plots assessing model fit indicated that a model adjusted for placebo response was the best fit for PsARC responses in our study, and, consequently, this model was used for PsARC analyses in both mixed and biologic-naive populations. This approach has been recommended previously to avoid the introduction of bias when using data from studies in which placebo response improves over time [43]. For all mixed populations, random-effect models were selected to address the potential heterogeneity across trials identified in the feasibility assessment. The relatively

Table 2. Trial design details for studies including biologic-experienced patients.

Trial [Ref.]	Relevant treatments	Inclusion of patients with previous primary treatment failure [†]	Inclusion of patients with previous secondary treatment failure [‡]	Relevant inclusion criteria for biologic-experienced patients	Relevant exclusion criteria for biologic-experienced patients	
CLEAR [9]	Secukinumab 300 mg Ustekinumab 45 mg			Study publication did not differentiate between primary and secondary treatment failure	Patients were eligible if their psoriasis had been poorly controlled with biologic therapy	Patients who had received secukinumab, ustekinumab or other biologic drugs targeting IL-17A or IL-17RA were excluded
ERASURE [10]	Secukinumab 150 mg Secukinumab 300 mg Placebo			Study publication did not differentiate between primary and secondary treatment failure	Patients who had received previous biologic therapy were eligible; prestudy washout periods were 6 months for ustekinumab and 12 weeks for other biologics or etanercept	NA
FIXTURE [10]	Etanercept 50 mg BIW Secukinumab 150 mg Secukinumab 300 mg Placebo	–	–		Patients who had received previous biologic therapy were eligible; prestudy washout periods were 6 months for ustekinumab and 12 weeks for other biologics	Patients were not permitted to have received etanercept previously
FUTURE 2 [27]	Secukinumab 150 mg Secukinumab 300 mg Placebo	Yes	Yes		Patients who had previously received ≤ 3 anti-TNF agents were eligible for inclusion if they had not responded to treatment or had discontinued treatment for safety or tolerability reasons	Patients who had previously received any biologic agent other than anti-TNF agents were excluded
PALACE 1 [34,44]	Apremilast 20 mg Apremilast 30 mg Placebo	Yes	Yes		Patients who had previously received biologics, including patients who had not responded to biologic treatment, were eligible for inclusion. TNF efficacy failures were permitted in $\leq 10\%$ of included patients	Patients who had previously experienced treatment failure with >3 agents for PsA (small molecules and/or biologics) or >1 anti-TNF were excluded
PALACE 2 [35,44]	Apremilast 20 mg Apremilast 30 mg Placebo	Yes	Yes		Patients were permitted to have received biologics. TNF efficacy failures were permitted in $\leq 10\%$ of included patients. Washout periods were 12 weeks for adalimumab, certolizumab, etanercept, golimumab or infliximab, and 24 weeks for ustekinumab	Patients who had previously experienced treatment failure with >3 agents for PsA (small molecules and/or biologics) or >1 anti-TNF were excluded
PALACE 3 [37,44]	Apremilast 20 mg Apremilast 30 mg Placebo	Yes	Yes		Patients were permitted to have received biologics. TNF efficacy failures were permitted in $\leq 10\%$ of included patients	Patients who had previously experienced treatment failure with >3 agents for PsA (small molecules and/or biologics) or >1 anti-TNF were excluded
PSUMMIT2 [40]	Ustekinumab 45 mg Ustekinumab 90 mg Placebo	Yes	Yes		The protocol specified that 150–180 patients out of a total of 300 must have previously received anti-TNF agents, defined as adalimumab, certolizumab, etanercept or golimumab for at least 8 weeks, or infliximab for at least 14 weeks, or proven inability to tolerate anti-TNF therapy for 8–14 weeks	Patients who had received anti-IL-12/23 agents were excluded
RAPID-PsA [41]	Certolizumab 200 mg [§] Certolizumab 400 mg [§] Placebo	No	Yes		Up to 40% of patients included were permitted to have received one or more anti-TNF agent previously, with a washout period of >3 months before baseline visit (28 days for etanercept)	Patients who had had previous exposure to ≥ 2 biologics or >1 anti-TNF agent for the treatment of PsA or psoriasis, or primary failure of a previous anti-TNF agent, defined as no response within the first 12 weeks of treatment, were excluded
Schett <i>et al.</i> [42]	Apremilast 20 mg Apremilast 40 mg Placebo			Study publication did not differentiate between primary and secondary treatment failure	Patients were permitted to have received previous biologic therapy, with a washout period of ≥ 56 days for etanercept and ≥ 84 days for adalimumab or infliximab	NA

[†]Primary treatment failure was defined as non-response to treatment.
[‡]Secondary treatment failure was defined as loss of response to treatment over time.
[§]With a 400 mg loading dose.
 Bold text indicates studies that were included in the biologic-experienced network for American College of Rheumatology responses.
 BIW: Twice per week; NA: Not applicable; PsA: Psoriatic arthritis.

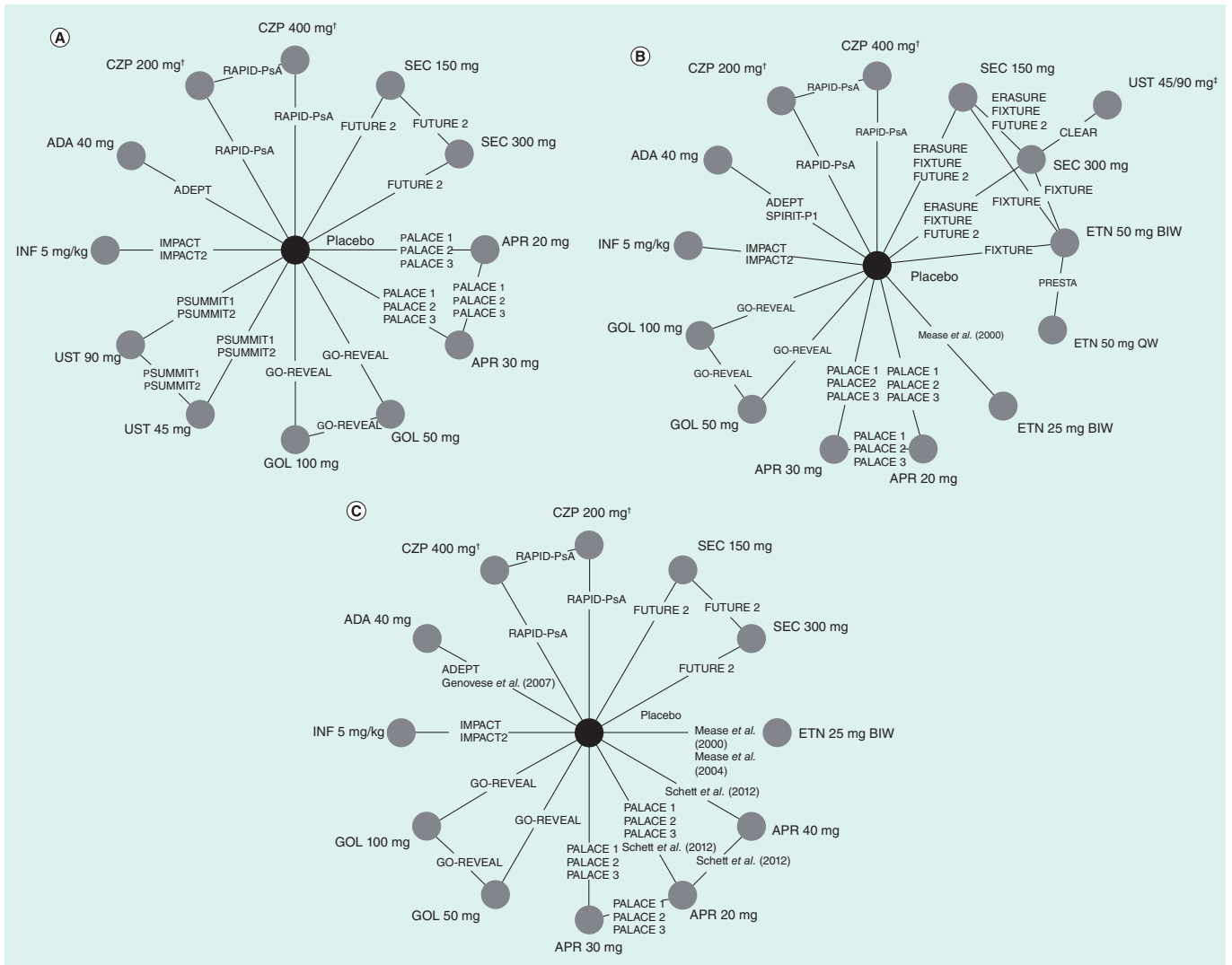


Figure 1. Treatment networks for the mixed populations of patients with PsA. (A) ACR responses at 16 weeks, **(B)** PASI responses at 12–16 weeks and **(C)** PsARC responses at 12–16 weeks. Populations containing biologic-naive and biologic-experienced patients: apremilast, certolizumab, etanercept (for PASI data; population composition for PsARC data not reported), secukinumab, ustekinumab. Populations containing biologic-naive patients only: adalimumab, golimumab, infliximab.

†With a 400 mg loading dose.

‡Patients received ustekinumab 45 or 90 mg in the CLEAR trial, depending upon bodyweight; therefore, patients receiving either dose were treated as a single treatment group.

ACR: American College of Rheumatology; ADA: Adalimumab; APR: Apremilast; BIW: Twice per week; CZP: Certolizumab; ETN: Etanercept; GOL: Golimumab; INF: Infliximab; PASI: Psoriasis Area Severity Index; PsARC: Psoriatic Arthritis Response Criteria; QW: Once weekly; SEC: Secukinumab; UST: Ustekinumab.

smaller sizes of the biologic-naive and biologic-experienced patient populations meant that use of a random-effects model was not feasible, because there were either insufficient degrees of freedom to conduct the analysis or so few degrees of freedom that the posterior distribution of the between-study heterogeneity remained large, leading to nonsensical, posterior distributions for the efficacy parameters. Therefore, fixed-effects models were used in these populations.

ACR networks (16 weeks)

Mixed population

In the mixed population, the treatment network permitted comparisons for all therapies, with the exception of etanercept (Figure 1A). Populations for adalimumab, golimumab and infliximab were biologic-naive, whereas those

for other therapies were mixed. For all treatments, there was statistical evidence of superior ACR20 response rates at 16 weeks, compared with placebo. Secukinumab 150 and 300 mg both demonstrated statistical superiority over apremilast 20 or 30 mg and ustekinumab 45 mg (Figure 2A & B). Furthermore, infliximab 5 mg/kg, golimumab 50 and 100 mg and adalimumab 40 mg demonstrated statistical superiority in terms of ACR20 response rates over apremilast 20 or 30 mg and ustekinumab 45 or 90 mg (Supplementary Table 2). These treatments were associated with similar or slightly higher response rates when compared with secukinumab, but without statistical evidence of superiority. ACR50 and ACR70 responses showed similar trends to ACR20 (Supplementary Tables 3 & 4).

Biologic-naïve subpopulation

Eight trials were included in the treatment network for this subpopulation. In terms of ACR20, ACR50 and ACR70 response rates, all treatments demonstrated superiority over placebo. Adalimumab and secukinumab 150 mg demonstrated superiority over both doses of apremilast and both doses of ustekinumab. Secukinumab 300 mg demonstrated statistical superiority over apremilast 20 mg and ustekinumab 45 mg only; pairwise comparisons against apremilast 30 mg (RR [95% CI]: 1.62 [1.00–2.60]) and ustekinumab 90 mg (RR [95% CI]: 1.44 [0.96–2.07]) fell just short of statistical superiority in favor of secukinumab 300 mg (Figure 2C & D; Supplementary Tables 5–7). Infliximab and both doses of golimumab demonstrated statistical superiority over all treatments in the network, with the exception of adalimumab and secukinumab.

Biologic-experienced subpopulation

The NMA for ACR responses in the biologic-experienced population included four trials (see Table 2 for patient inclusion criteria). All treatments except ustekinumab 45 and 90 mg showed evidence of superiority to placebo. No therapy demonstrated statistical superiority over other treatments, except for certolizumab (200 and 400 mg doses considered as a single treatment group), which showed statistical superiority over either dose of ustekinumab (Supplementary Figure 3; Supplementary Tables 8–10).

PASI networks (12–16 weeks)

Mixed population

The treatment network for the mixed population allowed comparisons between all therapies included in this study (Figure 1B). In CLEAR, patients received ustekinumab 45 or 90 mg, depending upon bodyweight, in line with the licensed dosing scheme [9,45]; the doses were considered as a single treatment group for this analysis. Patient populations for adalimumab, golimumab and infliximab were biologic-naïve; populations for all other therapies were mixed.

In terms of response rates for PASI50, PASI75 and PASI90, all treatments demonstrated superiority over placebo. Secukinumab 150 or 300 mg demonstrated statistical superiority to apremilast 20 and 30 mg, certolizumab 200 and 400 mg, adalimumab 40 mg and etanercept 25 and 50 mg twice per week and 50 mg weekly. Furthermore, there was evidence of superiority for secukinumab 300 mg compared with golimumab 50 mg (Figure 3; Supplementary Tables 11–13). Similarly, infliximab demonstrated statistical superiority to all treatments apart from secukinumab, golimumab 100 mg and ustekinumab 45/90 mg. Infliximab was associated with slightly higher response rates than secukinumab, but without evidence of statistical superiority.

Biologic-naïve subpopulation

The treatment network for the biologic-naïve population included only five trials, and compared secukinumab 150 and 300 mg with adalimumab 40 mg, golimumab 50 and 100 mg and infliximab 5 mg/kg. All treatments demonstrated superiority over placebo in terms of PASI50, PASI75 and PASI90 responses. There was statistical evidence of superiority for infliximab over golimumab 50 mg and adalimumab 40 mg, and for golimumab 100 mg over golimumab 50 mg. All analyses marginally favored either dose of secukinumab over golimumab 50 mg or adalimumab 40 mg; however, none of these pairwise comparisons demonstrated evidence of statistical superiority (Supplementary Figure 4; Supplementary Tables 14–16).

PsARC responses (12–16 weeks)

Mixed population

The treatment network for PsARC in the mixed population included all therapies in this study except ustekinumab (Figure 1C). As in the other networks, patient populations were biologic-naïve for some treatments and mixed for

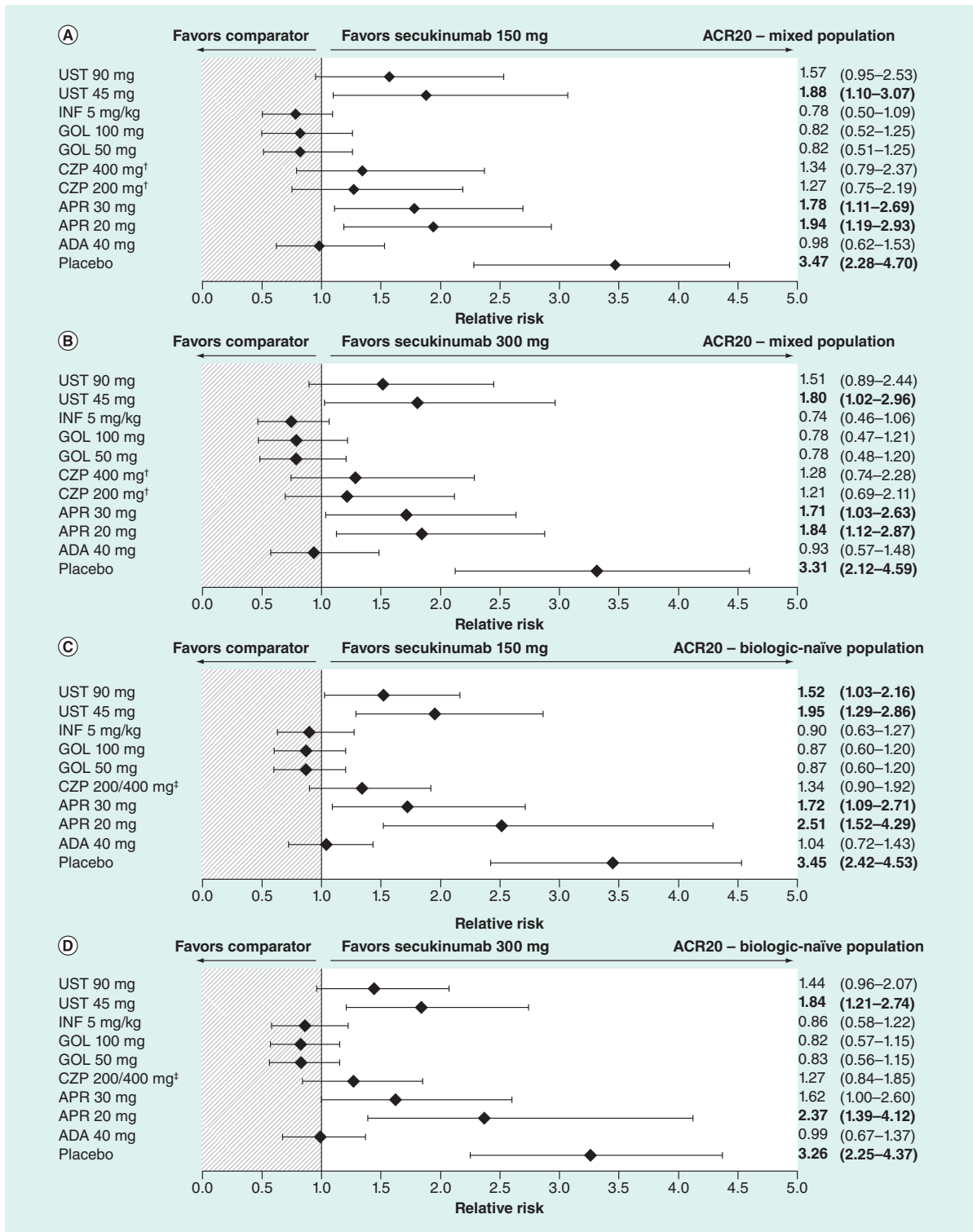


Figure 2. Relative risks of achieving an ACR20 response at 16 weeks. (A) Secukinumab 150 mg in the mixed population; **(B)** secukinumab 300 mg in the mixed population; **(C)** secukinumab 150 mg in the biologic-naïve population; and **(D)** secukinumab 300 mg in the biologic-naïve population.

Data shown are the estimated comparative effect (relative risk [and 95% credible interval, which can be interpreted as a confidence interval]) of secukinumab versus the treatments indicated in the left-hand column. Values in bold text indicate comparisons with evidence of superiority for secukinumab. Populations containing biologic-naïve and biologic-experienced patients: apremilast, certolizumab, secukinumab, ustekinumab. Populations containing biologic-naïve patients only: adalimumab, golimumab, infliximab.

[†]With a 400 mg loading dose.

[‡]Results for both doses of CZP (200 and 400 mg) were combined in the biologic-naïve subpopulation.

ACR20: At least a 20% improvement in the core set of American College of Rheumatology measures for assessing arthritis; ADA: Adalimumab; APR: Apremilast; CZP: Certolizumab; GOL: Golimumab; INF: Infliximab; UST: Ustekinumab.

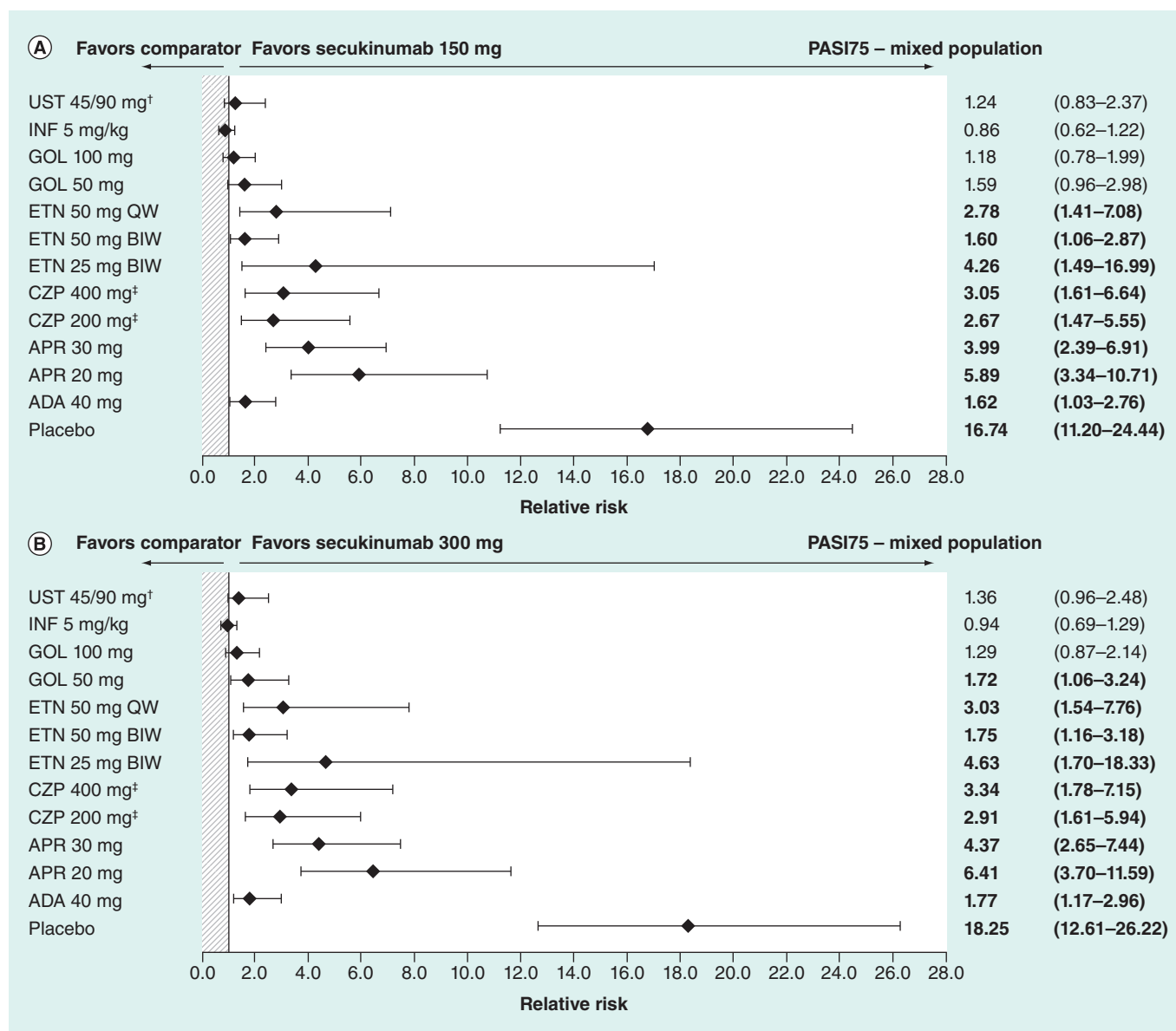


Figure 3. Relative risks of achieving at least a 75% reduction in Psoriasis Area Severity Index score responses at 12–16 weeks in the mixed population (SPIRIT-P1 trial [23,24] included). Data shown are the estimated comparative effect (relative risk [and 95% credible interval, which can be interpreted as a CI]) of secukinumab versus the treatment indicated in the left-hand column. Values in bold text indicate comparisons with evidence of superiority for secukinumab. Populations containing biologic-naïve and biologic-experienced patients: apremilast, certolizumab, secukinumab, ustekinumab. Populations containing biologic-naïve patients only: adalimumab, golimumab, infliximab.

[†]Patients received ustekinumab 45 or 90 mg in the CLEAR trial, depending upon bodyweight; therefore, patients receiving either dose were treated as a single treatment group.

[‡]With a 400 mg loading dose.

ADA: Adalimumab; APR: Apremilast; BIW: Twice per week; CZP: Certolizumab; ETN: Etanercept; GOL: Golimumab; INF: Infliximab; PASI75: At least a 75% reduction in Psoriasis Area Severity Index score; QW: Once weekly; UST: Ustekinumab.

others, including secukinumab. Data for etanercept in this analysis were derived from the studies [32,33], which did not report whether included patients had received previous biologic therapy. All treatments demonstrated superiority to placebo. Etanercept 25 mg twice per week and infliximab were associated with statistical superiority over adalimumab, and apremilast 20, 30 and 40 mg. Certolizumab 200 mg and secukinumab 150 mg demonstrated superiority to all doses of apremilast, whereas certolizumab 400 mg and secukinumab 300 mg were superior only to apremilast 20 and 30 mg. Golimumab 100 mg was superior to apremilast 20 and 40 mg (Figure 4; Supplementary

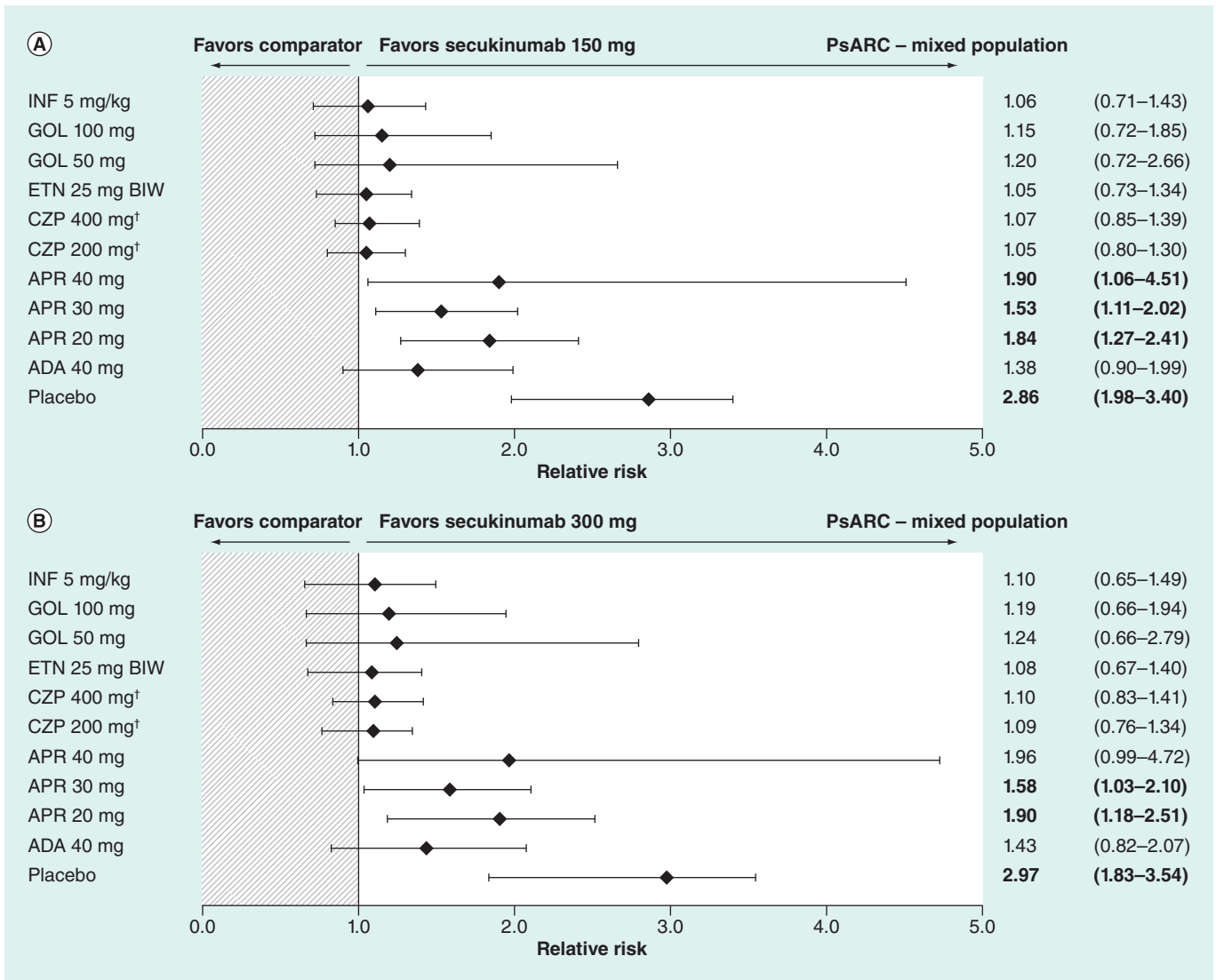


Figure 4. Relative risks of achieving Psoriatic Arthritis Response Criteria responses at 12–16 weeks in the mixed population. Data shown are the estimated comparative effect (relative risk [and 95% credible interval, which can be interpreted as a confidence interval]) of secukinumab versus the treatment indicated in the left-hand column. Values in bold text indicate comparisons with evidence of superiority for secukinumab. Populations containing biologic-naïve and biologic-experienced patients: apremilast, certolizumab, secukinumab. Populations containing biologic-naïve patients only: adalimumab, golimumab, infliximab. Population composition for etanercept not reported.

†With a 400 mg loading dose.

ADA: Adalimumab; APR: Apremilast; BIW: Twice per week; CZP: Certolizumab; ETN: Etanercept; GOL: Golimumab; INF: Infliximab; PsARC: Psoriatic Arthritis Response Criteria.

Table 17).

Biologic-naïve subpopulation

The treatment network for PsARC in the biologic-naïve population included only six trials and compared five treatments. Adalimumab 40 mg, etanercept 25 mg twice per week and infliximab 5 mg/kg demonstrated statistical superiority over placebo. Infliximab 5 mg/kg, golimumab 50 and 100 mg and etanercept 25 mg twice per week were all associated with slightly higher response rates than secukinumab 150 and 300 mg; adalimumab 40 mg was associated with slightly higher response rates than secukinumab 300 mg only. There was, however, no statistical evidence of superiority for any treatment over an active comparator (Supplementary Figure 5; Supplementary Table 18).

Discussion

This study used NMA to assess the relative efficacy of secukinumab and all other non-cDMARD PsA therapies (biologics and tsDMARDs) approved at the time the analysis was conducted, with placebo as the common comparator arm. Both articular and dermatologic manifestations of disease were examined in the analyses, via the inclusion of ACR and PASI responses, respectively. An analysis of PsARC responses was also included. Although this composite measure is included more frequently as a secondary endpoint in RCTs, rather than a primary endpoint [46], it has been included in several health technology assessment submissions for biologic therapies for the treatment of PsA. A recent NICE assessment recommended adjustment for placebo response when modeling PsARC outcomes, which is reflected in the approach adopted in our analysis [47].

Disparities in inclusion criteria and patient recruitment between studies meant that ‘mixed’ networks contained some patient populations that were biologic-naïve, whereas patients in other trial populations were permitted to have received one or several previous biologic therapies. Data for adalimumab, golimumab and infliximab were derived exclusively from biologic-naïve populations, whereas patients receiving apremilast, certolizumab, etanercept, secukinumab or ustekinumab could have experienced previous failure of a biologic treatment.

In the mixed population, secukinumab, infliximab, golimumab and adalimumab demonstrated good efficacy in terms of ACR20, ACR50 and ACR90 responses, in some cases showing statistical superiority over comparators. Similarly, for PASI50, PASI75 and PASI90 responses, both doses of secukinumab and infliximab demonstrated superiority over most other treatments in the analysis. The analysis assessing PsARC outcomes in the mixed population favored infliximab and etanercept at dosages of 25 mg twice per week. Most treatments included in this analysis demonstrated statistical superiority to some or all of the included doses of apremilast.

When treatment effects in biologic-naïve patients were assessed separately, trends were similar to those in the analyses of mixed populations for ACR outcomes, but differed slightly for PASI and PsARC outcomes; in particular, fewer pairwise comparisons showed statistical superiority for a treatment over an active comparator in these analyses. This may be due to the comparatively smaller evidence base for the biologic-naïve networks, which used data from 8, 5 and 6 trials for ACR, PASI and PsARC outcomes, respectively, in some cases using data only from a subset of the included patients. In contrast, the networks for the mixed populations used data from 11, 15 and 13 full trial populations, respectively. Therefore, the statistical power of the analysis for biologic-naïve populations is likely to have been lower. This lack of statistical power may explain the fact that, in the biologic-naïve population, secukinumab 150 mg demonstrated statistical superiority to both doses of apremilast and both doses of ustekinumab, whereas secukinumab 300 mg was superior to apremilast 20 mg and ustekinumab 45 mg, but fell short of statistical superiority to apremilast 30 mg and ustekinumab 90 mg. Differences in dose response, for example, a smaller difference in response between the two doses of secukinumab relative to apremilast or ustekinumab, may also have had an impact upon this analysis.

ACR outcomes only were assessed in the biologic-experienced population. At present, no ACR efficacy data from RCTs are available for adalimumab, etanercept, golimumab or infliximab in biologic-experienced populations; thus, the analysis was limited to apremilast, certolizumab, secukinumab and ustekinumab. Certolizumab 200/400 mg demonstrated superiority over either dose of ustekinumab, but there was no other evidence of statistical superiority. It is likely that bias was introduced into the mixed- and biologic-experienced networks by disparities in inclusion criteria across trials of PsA treatments (Table 2). For example, patients entering the RAPID-PsA trial for certolizumab were permitted to have received no more than one previous anti-TNF treatment [41] and were excluded if they had experienced primary failure of an anti-TNF therapy, which was defined as no response within the first 12 weeks of treatment. In contrast, the FUTURE 2 trial for secukinumab permitted inclusion of patients with primary or secondary treatment failure, and patients who had previously received up to three anti-TNF treatments could be included in the study [27]. These differences meant that patients receiving secukinumab may have been more difficult to treat than those receiving apremilast or certolizumab. In addition, the relatively small numbers of patients in the overall study populations who had received previous biologic therapy meant that analyses using the biologic-experienced networks had limited statistical power and, consequently, their results should be interpreted with caution. Restriction of networks by time point also limited patient numbers in some cases; in the ACR network, restriction of trials to those reporting week 16 data meant that a number of studies were not included.

NMA, when not adjusted using meta-regression, is not able to adjust for differences in study designs or patients’ baseline characteristics that are effect modifiers. In this analysis, patient populations are likely to have differed in terms of background exposure to methotrexate or corticosteroids, disease activity, and baseline PASI scores.

Consequently, heterogeneity across trials was a general limitation of this analysis, although several meta-regression models were fitted where possible (see [Supplementary Methods](#)). Meta-regression adjustment for differences in patient populations was not possible, because many of the trials in the analysis did not include biologic-experienced patients. This disparity was addressed by the development of different networks depending on patients' previous treatment use. In biologic-naïve networks, however, this introduced bias against treatments for which only a subset of trial data could be used; despite the predefined sub-analyses for biologic-naïve patients in these trials, they lack the statistical power of trials containing exclusively biologic-naïve patients. Some of the trials included in the networks, such as SPIRIT-P1, were not powered for noninferiority comparisons or, in the case of the CLEAR, ERASURE and FIXTURE trials, were designed to assess treatment effects in psoriasis, not PsA.

Overall, nine trials used NRI exclusively to account for missing data, whereas eight trials (for apremilast, etanercept, golimumab, infliximab and ustekinumab) used last observation carried forward ([Table 1](#)), which can bias analyses in favor of active treatment. Therefore, the NMA results may be biased against treatments for which the more conservative NRI method had been employed. For PASI and PsARC outcomes, the combination of 12- and 16-week time points may have introduced additional variation, biasing the analyses in favor of treatments for which 16-week data were used.

The short 12–16-week timeframe is a limitation of this analysis, imposed by the need to make comparisons only within the placebo-controlled phase of the trials. Although rapid treatment response is important following treatment initialization, long-term sustained control of disease is the major aim of PsA therapy due to the chronic nature of the condition [2]. For chronic conditions, meaningful treatment benefits, particularly in terms of quality of life and social functioning, are most likely to be detected in the long term. Furthermore, for some treatments, such as apremilast, maximum efficacy may not be reached until after the 12–16-week timeframe, meaning that treatment effect may not be captured by a short-term analysis. Therefore, treatment comparisons with a longer time horizon are a vital means of informing therapeutic decisions. This could be addressed by the use of an alternative method for generating comparative data, such as matching-adjusted indirect comparison (MAIC). Although MAIC can be used to compare only two treatments at the same time, whereas NMA allows for multiple pairwise comparisons, MAIC permits the included trials to be matched in terms of patient populations, disparities in imputation methods, and study design or reporting differences. Furthermore, because a common comparator is not required, MAIC allows the time horizon of analysis to be extended beyond the placebo-controlled phase. MAICs have been developed examining secukinumab and relevant comparators [48,49].

Of the five published NMAs in PsA identified by the authors, three did not include secukinumab [16,17,20] and the two that did include secukinumab had methodological limitations that impact the clinical relevance of the results [18,19]. We therefore contend that the current NMA is the most robust analysis in PsA to date. The first NMA to include secukinumab was published as a congress abstract in 2015, and compared all approved treatments using data from 14 trials [18]. The results were similar to those of the current NMA, showing adalimumab, golimumab, secukinumab (150 and 300 mg), and infliximab to be associated with the lowest numbers needed to treat for ACR20 responses at week 24 in both the mixed and biologic-naïve population. For PASI75 response at week 24 in the mixed population, adalimumab, golimumab, secukinumab 300 mg and infliximab had lower numbers needed to treat than the other treatments. However, this analysis did not account for the time at which patients switched from placebo to active treatment, which was earlier than 24 weeks in most trials. This limits the validity of the results. The second NMA to include secukinumab was published in 2016 and compared all PsA treatments approved at the time of the study. This showed secukinumab to be associated with numerically greater ACR20 responses at weeks 12–24 than apremilast, certolizumab and ustekinumab, although findings were not classically statistically significant. However, the authors used pooled data for etanercept, infliximab, adalimumab and golimumab and compared this grouping (older TNF inhibitors) against the newer therapies [19]. Thus, this study did not permit pairwise comparisons between all individual treatments, and the validity of the results is compromised by this limitation in the study design.

Conclusion

This NMA is methodologically sound and is the first NMA of all approved PsA therapies to date that accounts for early placebo switching and permits for pairwise comparisons between all agents. This analysis found that secukinumab 150 and 300 mg were superior to apremilast and demonstrated good efficacy across all outcomes; furthermore, in the mixed population, both doses of secukinumab were superior to ustekinumab 45 mg in terms of ACR outcomes, and superior to adalimumab, certolizumab and etanercept in terms of PASI outcomes. Of the

other treatments examined, the anti-TNF agents infliximab and golimumab also demonstrated superiority to the small-molecule inhibitor apremilast across ACR and PASI outcomes and PsARC responses.

As well as providing comparative evidence, indirect treatment comparisons can generate hypotheses that can be tested in future RCTs. Head-to-head superiority trials in PsA, such as the ongoing trial EXCEED 1 [12], which has been initiated to compare adalimumab and secukinumab, and SPIRIT-H2H [13], comparing adalimumab and secukinumab, will be needed to provide directly comparative results.

Summary points

- Biologics and targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs) are recommended for the treatment of active psoriatic arthritis (PsA) if conventional DMARDs employed as first-line therapies are not successful.
- Given the limited number of head-to-head randomized, controlled trials comparing biologics and targeted synthetic DMARDs for PsA, adjusted indirect comparisons, such as network meta-analysis, provide valuable evidence differentiating between treatments.
- We conducted a systematic review to identify relevant trials for adalimumab, apremilast, certolizumab, etanercept, golimumab, infliximab, secukinumab and ustekinumab.
- Separate networks were developed for full (mixed) study populations, for biologic-naïve patients and for biologic-experienced patients.
- In the mixed populations, secukinumab, adalimumab, golimumab and infliximab were associated with the highest response rates according to American College of Rheumatology criteria at 16 weeks.
- Secukinumab and infliximab demonstrated the highest Psoriasis Area Severity Index response rates at 12–16 weeks in the mixed populations.
- Infliximab and etanercept demonstrated the highest Psoriatic Arthritis Response Criteria response rates at 12–16 weeks in the mixed populations.
- In this comprehensive network meta-analysis of licensed treatments for active PsA, secukinumab demonstrated good efficacy across all outcomes examined in the mixed study populations.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/cer-2018-0075

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Ethical conduct of research

This study was of non-interventional nature and did not include primary data collection (i.e., was based on published secondary data only). Therefore, ethic committee or institutional review board approval was not required. Data used were taken from published

randomized controlled trials, which were conducted according to the principles of the Declaration of Helsinki and with informed consent from participants.

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