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REVIEW

Biologics for the Treatment of Moderate-to-Severe Plaque Psoriasis: A Systematic Review and Network Meta-analysis

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ABSTRACT

Introduction: Moderate-to-severe plaque psoriasis is a chronic disease impacting quality of life (QoL). This network meta-analysis (NMA) compared efficacy and safety of all biologics approved for the treatment of moderate-to-severe plaque psoriasis to better inform providers on mid-term outcomes, with a focus on the interleukin-23 p19 inhibitor tildrakizumab.

Methods: MEDLINE®, Embase, and CENTRAL were searched for randomized clinical trials (RCT) from inception through January 2024. RCTs comparing biologics against placebo or each other reporting Psoriasis Area and Severity Index (PASI), Physician Global Assessment (PGA) 0/1, or Dermatology Life Quality Index (DLQI) 0/1 responses and safety outcomes (adverse events [AEs] or serious AEs [SAEs]) were sought. Bayesian NMAs were performed at week 28 as the primary time point of interest. Analyses were also performed at weeks 12 and 16. Findings were expressed as risk ratios (RR; efficacy outcomes), risk differences (RD; safety outcomes), and numbers needed to treat (NNT) with 95% credible intervals.

Results: Of 7418 publications screened, 187 describing 124 RCTs of 12 biologics were included in the systematic literature review, and 103 RCTs were included for NMA. All treatments demonstrated improved efficacy and QoL vs. placebo at week 28. Tildrakizumab efficacy at

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week 28 was comparable to risankizumab and guselkumab, respectively, for PASI 75 (RR 8.74 vs. 8.92 and 8.91), PASI 90 (RR 14.09 vs. 14.81 and 14.77), and PGA 0/1 (RR 9.34 vs. 10.29 and 10.23). No biologics exhibited an increased risk of SAEs vs. placebo; tildrakizumab exhibited no increased risk vs. placebo for AEs.

Conclusions: The investigated biologics demonstrated improved efficacy and QoL relative to placebo at week 28, with no increased risk of SAEs vs. placebo through week 16. At week 28, efficacy of tildrakizumab, risankizumab, and guselkumab was comparable. Limitations include lack of placebo comparators after week 12 or 16, which could affect results.

Keywords: Biologics; Network meta-analysis; Psoriasis; Systematic review; Tildrakizumab

Key Summary Points
Why carry out this study?
Moderate-to-severe plaque psoriasis is a chronic, immune-mediated condition that can be treated with biologic therapies.
Comparisons of biologics in systematic literature reviews and network meta-analyses often focus on the induction (weeks 12–16) or long-term maintenance period (week 52).
Comparison of biologics during the mid-range of treatment (such as week 28) may help healthcare providers to make informed treatment decisions.
What was learned from the study?
In the week 28 meta-analysis, 12 investigated biologics remained superior to placebo across multiple efficacy measures and demonstrated improvements in quality of life.
Tildrakizumab 100 mg demonstrated continued improvement in efficacy from week 12 onward, with a comparable efficacy profile at week 28 and safety profile at week 16 relative to those of other biologics.

These efficacy findings through week 28 provide additional information for making informed treatment decisions when managing patients with moderate-to-severe psoriasis.

INTRODUCTION

Psoriasis (PsO) is a chronic inflammatory skin condition that affects an estimated 2%–3% of adults worldwide [1, 2]. Plaque PsO is an immune-mediated systemic disease and presents as red, scaly plaques [2]. In addition to the cutaneous manifestations, PsO affects numerous aspects of patients' quality of life [3]. Some patients are able to control their symptoms with topical treatments or phototherapy; however, these options may not be sufficient in patients with moderate-to-severe disease [2].

Patients with moderate-to-severe PsO have benefited greatly from the addition of biologics to the treatment landscape, as these patients experience improved symptom control with biologics compared with conventional systemic treatments, topical treatments, or phototherapy [4]. There are multiple classes of biologics used to treat moderate-to-severe plaque PsO, including tumor necrosis factor alpha (TNFα) inhibitors (adalimumab, certolizumab, etanercept, infliximab), interleukin (IL)-17 inhibitors (secukinumab, ixekizumab, brodalumab, bimekizumab), IL-12/23 inhibitors (ustekinumab), and IL-23 inhibitors (tildrakizumab, risankizumab, guselkumab) [2]. Although biologics overall are highly effective for the treatment of moderate-to-severe PsO [5], clinicians and patients may understandably wish to compare efficacy and safety among classes of biologics and individual agents. Direct head-to-head clinical trials are often not feasible given the number of comparisons required, and ongoing drug development means that some biologics lack head-to-head comparisons with newer competitor data.

Systematic literature reviews (SLRs) and network meta-analyses (NMAs) provide another route to compare the efficacy and safety of biologics for the treatment of plaque PsO. Recent

SLRs and NMAs have examined efficacy across the induction period after randomization (up to weeks 10–16), during which time placebo data are available and primary efficacy is often evaluated [6, 7]. Later time points were also included in the efficacy analyses, ranging from weeks 44 to 60 [6, 7].

Mid-range time points, such as week 28, are frequently omitted from NMAs because of the lack of placebo data for network comparisons and thus represent an important gap in the literature, particularly as some approved biologics do not reach full efficacy until well after week 16. For example, tildrakizumab, an anti-IL-23 p19 antibody used to treat moderate-to-severe plaque PsO in adults [8, 9], showed peak efficacy at week 22, although it met its co-primary endpoints of a ≥75% reduction in Psoriasis Area and Severity Index score (PASI 75) and a Physician Global Assessment score of 0 or 1 (PGA 0/1) with a ≥2-point reduction from baseline at week 12 in the phase 3 pivotal trials reSURFACE 1 and reSURFACE 2 [10]. Comparisons among biologics at time points shortly after the induction period will therefore be beneficial for healthcare providers (HCPs) to understand comparative efficacy over time among the different treatments for PsO and might be beneficial in understanding clinical relevance in daily practice.

The objective of the current SLR/NMA was to address this gap by comparing the clinical efficacy at 28 weeks of biologics approved for the treatment of moderate-to-severe plaque psoriasis, including inhibitors of TNFα, IL-17, IL-12/23, and IL-23.

METHODS

This SLR and NMA of therapies for moderate-to-severe plaque PsO was performed through adhering to a protocol developed a priori collaboratively by the research team. Findings from this review have been reported according to the PRISMA Extension Statement for NMA (checklist provided in Online Appendix 1 of the online supplement) [11]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Study Selection Criteria

Study selection criteria were established using the PICOS (Population, Intervention, Comparator, Outcomes, Study design) framework. Eligibility criteria are described next.

Population. Studies that enrolled adults with moderate-to-severe plaque PsO were sought, while studies that enrolled patients with mild disease and other conditions were excluded.

Interventions/comparators. Studies that compared groups receiving tildrakizumab (TIL 100 mg Q12W), secukinumab (SEC 150 mg Q4W and SEC 300 mg Q4W), risankizumab (RIS 150 mg Q12W), ustekinumab (UST 45mg Q12W and UST 90 mg Q12W), ixekizumab (IXE 80 mg Q4W), guselkumab (GUS 100 mg Q8W), brodalumab (BRO 210 mg Q2W), adalimumab (ADA 40 mg Q2W), certolizumab pegol (CER 400 mg Q2W), etanercept (ETN 50 mg BIW/QW), infliximab (INF 5mg/kg Q8W), bimekizumab (BIM 320 mg Q4W), and placebo were of interest; studies of investigational or non-approved therapies were excluded.

Outcomes. An inclusive and representative set of efficacy outcomes was of a priori interest to the study team. These included measures of PASI response (PASI 75, 90, and 100, respectively), PGA 0/1 response, and DLQI 0/1 response. The primary time point of interest for efficacy outcomes was mid-term follow-up at 28 weeks, while analyses of 12-week and 16-week data were also performed to explore changes in treatment efficacy over time. Safety outcomes of interest were measured at week 16 and included the occurrence of any adverse event (AE) as well as serious adverse events (SAE).

Study design and language of publication. Only randomized clinical trials (RCTs) (excluding single-arm trials, observational studies, review articles, commentaries/letters) published in English were of interest for this review.

Searching the Literature

The research team conducted systematic searches of MEDLINE®, Embase, and the

Cochrane Central Register of Controlled Trials (CENTRAL) through the Ovid interface. The searches were initially conducted in July 2023 and updated in January 2024. Search strategies consisted of a combination of keywords and free text terms. The full set of search strategies is provided in Appendix 2 of the online supplement. Gray literature searching was also performed and included searching of US and European clinical trial registries, as well as conference abstracts from the American Academy of Dermatology and the European Academy of Dermatology and Venerology (range of years 2020–2022). Additionally, the bibliographies of previously published literature reviews were screened for any relevant studies not captured via the main searches.

Study Selection Process

The study selection process was performed by two independent reviewers who were responsible for reviewing abstracts, conference proceedings, and gray literature sources according to the pre-defined selection criteria describe above. All eligible studies identified during title/abstract screening proceeded to the full-text screening phase, where they were assessed for eligibility by the same reviewers. Selection criteria related to the outcomes of interest were applied only during the full-text screening phase. During each of the title/abstract and full-text screening phases, reviewers reconciled differences between their inclusion decisions. When necessary, a third reviewer was consulted to reach a consensus decision. Studies that matched the PICOS criteria following the full-text screening were included for data extraction. The screening process was summarized in a flow diagram as per PRISMA guidance.

Data Collection and Risk of Bias Appraisal

Collection of data from the set of included studies was performed by two independent reviewers using Microsoft Excel (Microsoft Corporation, Seattle, USA). In cases where reviewer extractions were discordant and could not be resolved by discussion, a third party was consulted to achieve consensus. Detailed data were gathered regarding publication-related information (e.g., authors, journal and year of publication, publication DOI), study design (e.g., methods of treatment assignment, outcome measurement, patient follow-up, blinding and allocation concealment, methods of analysis), intervention characteristics/administration, population enrollment criteria, key patient demographic and disease traits, and clinical outcome information (including the numbers of randomized patients and those experiencing the dichotomous outcomes of interest). Risk of bias appraisals were also performed for all trials using the Cochrane Risk of Bias (RoB) tool, version 2 [12]. The findings from these assessments were used to characterize strengths and weaknesses of the included studies as well as to use as criteria for secondary analyses.

Statistical Methods

Prior to meta-analyses, a feasibility assessment was conducted to examine the set of included RCTs with regard to similarity of study populations, connectivity of networks for each outcome, and other information [13]. This process involved review of study characteristics by the study team, as well as the distributions of effect-modifying covariates between studies and treatment comparisons. This exercise provided the authors with a firm grasp of the nature of clinical and methodologic heterogeneity across RCTs as well as the potential to perform NMAs of strong internal validity. Based upon this process as well as consideration of approaches used within NMAs related to PsO in recent years, it was determined that NMAs involving adjustment for baseline risk represented the best modeling approach to account for differences between studies [14].

Regarding primary analyses at mid-term follow-up of 28 weeks, if data were not available at week 28 the nearest data within 4 weeks of week 28 (before or after) were used. Regarding timing of outcome measurement for efficacy analyses at 12 weeks and 16 weeks, if a study reported data at weeks 10 and 14 instead of 12 and 16, we used week 10 in place of week 12

and week 14 in place of week 16. The majority of psoriasis trials end placebo treatment after 12–16 weeks; if placebo data were not reported for a time point, then the latest available placebo data were used (i.e., last observation carried forward).

All outcomes were dichotomous and were modeled using an established and commonly used generalized linear model framework with a logit link [15]. As recommended by the National Institute for Health and Care Excellence (NICE), a fixed effects (FE) model was planned for use if there was only one trial per treatment comparison; in all other cases, both the FE model and the random effects (RE) model were fit and the model with better fit was used to draw interpretations. Model fit was assessed using the deviance information criterion (DIC), a measure of model goodness-of-fit which is penalized for model complexity since a more complex model will result in better fit at the expense of parsimony [16]. Models associated with smaller DIC values generally are viewed to have a better model fit; however, Spiegelhalter et al. (2002) [17] suggest that models with DIC values within 1–2 of each other deserve consideration. In the current review, we used the FE model if its DIC was lower than that for the RE model by at least three points, and otherwise we used the RE model. To hasten the convergence of the RE binomial model, we used informative heterogeneity priors (log-normal with mean − 2.34 and standard deviation 1.62). All models included baseline risk as a covariate, unless including it prevented simulation convergence, in which case the adjustment of baseline risk was to be removed. The importance of the regression adjustment was confirmed using NICE recommended criteria based upon significance of the regression coefficient, a reduction in DIC, and a reduction in the between-study variance parameter [18]. The consistency assumption for NMA was assessed by fitting the unrelated means model; a comparison of DIC between this model and the consistency model was performed using a three-point threshold as a sign of an important difference between models, and deviance residuals from both models were also compared using scatterplots [19].

Findings from NMAs are reported in terms of risk ratios (RR) and the number needed to treat (NNT) along with 95% CrIs for clinical efficacy and quality of life outcomes, while findings pertaining to the safety endpoints of interest are reported in terms of risk differences (RD) and NNT along with 95% CrI. Both tables and forest plots are presented to summarize the effects of biologics versus placebo. Based upon the objectives of the review, interpretations are focused in part on the performance of tildrakizumab relative to other biologics.

RESULTS

Findings from Literature Search

The process of study selection is summarized in a flow diagram in Fig. 1. A total of 10,683 unique citations were identified by the multi-database search, and a total of 7418 unique citations remained for screening following removal of duplicates. A total of 751 citations (including articles identified from other sources) were retained for full-text screening; following dual independent review, a total of 124 RCTs [10, 20–133] described in 187 publications [10, 20–203] were retained, including three trials of TIL 100 mg. A total of 103 RCTs [10, 21–31, 33–50, 52–109, 116, 117, 122, 129, 130, 132, 143, 144] were included in the NMA. A complete list of all included studies is provided in Online Appendix 3 of the online supplement. Study characteristics are presented in Online Appendix 4 of the online supplement.

Study Characteristics and Risk of Bias

The publication year of included studies ranged from 2001 to 2022 (median 2017). Median study size was 250 (range 12 to 1881). The setting for the majority of trials ($n = 58$; 56.3%) was intercontinental; additionally, 12 (11.7%) were conducted in North American countries, 10 (9.7%) were conducted in the USA, 6 (5.8%) were conducted in Japan, 5 (4.9%) were conducted in European countries, 3 (2.9%) were performed in Asian countries, 3 in China (2.9%), and others

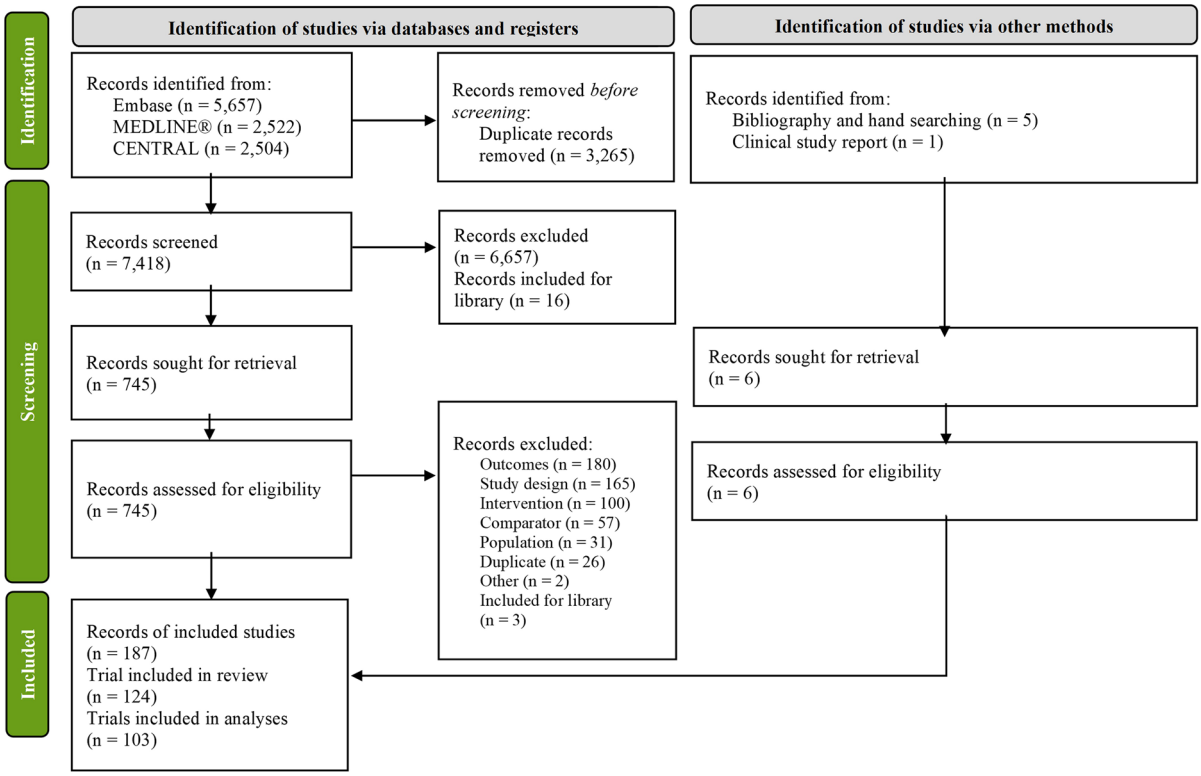

Fig. 1 Study selection process

were performed in Germany ($n=1$), Korea ($n=1$), Kuwait ($n=1$), and Russia ($n=1$). Almost all trials were double-blinded and conducted as multicenter trials.

Study enrollment criteria were generally similar across RCTs. In studies reporting related population data, the median patient age across RCTs was 45.2 years (range 39.3–53.9 years), the median proportion of female patients was 31.3% (range 14.9%–62.5%), and the median measure of average body weight was 89.2 kg (range 67.9–111.1 kg). The median PASI score was 20.2 (range 6.8–32.3), the median % BSA was 27.3% (range 7.7%–47.4%), and the median proportion with psoriatic arthritis was 22.8% (range 3.6%–40.4%). The median measure of average DLQI at baseline was 12.6 (range 10.0–19.7), and the median proportion with PGA of severe or very severe grade was 29.2% (range 6.9%–53.0%). In addition to variation in patient characteristics, we also observed variability in placebo group response rates for most efficacy outcomes. Investigation of box plots and bar plots during the feasibility assessment process confirmed the appropriateness of utilizing NMAs that included adjustment for placebo group response to address the potential for residual confounding in evidence syntheses.

Results from study-level risk of bias appraisals are provided in Online Appendix 5 of the online supplement. Overall, study weaknesses generally related to concerns of not reporting details regarding the randomization, missing outcome data, deviations from intended interventions, and selective reporting bias. More than half of all studies appraised were judged to be at moderate or high risk of bias.

The overall evidence network of all included RCTs is presented in Fig. 2. The number of RCTs per NMA varied according to outcome reporting across trials; Online Appendix 6 of the online supplement details the numbers of RCTs included for each efficacy analysis.

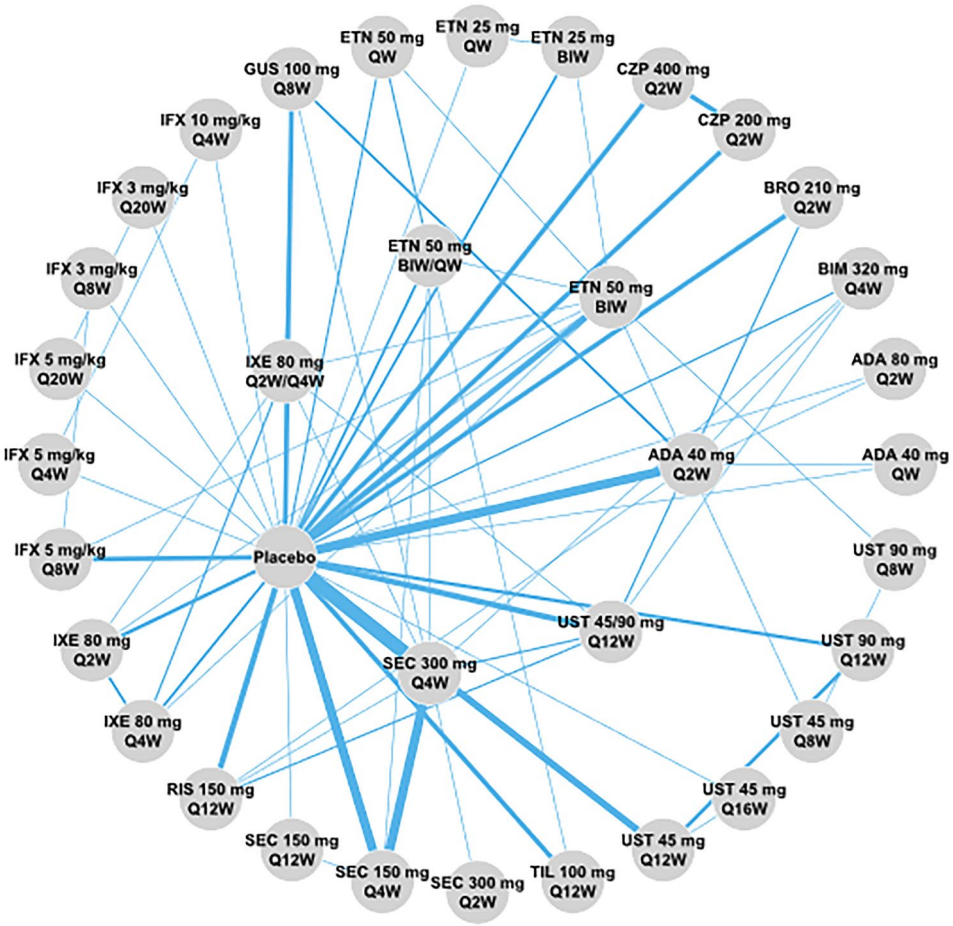

Fig. 2 Network diagram of included trials and comparisons. A network diagram depicting the totality of RCTs included in the review ($N = 103$ studies) is shown above. Edges are proportionately sized to reflect the relative numbers of studies informing each treatment comparison. The structure of the network and the number of included RCTs per NMA varied according to the availability of data per study. *ADA* adalimumab, *BIM* bimekizumab, *BIW* twice weekly, *BRO* brodalumab, *CZP* certolizumab pegol, *ETN* etanercept, *GUS* guselkumab, *IFX* infliximab, *IXE* ixekizumab, *Q#W* every # weeks, *QW* once weekly, *RIS* risankizumab, *SEC* secukinumab, *TIL* tildrakizumab, *UST* ustekinumab

Findings, Clinical Efficacy (PASI Responses and PGA 0/1)

PASI 75 Response

A placebo-adjusted RE NMA of PASI 75 response at week 28 mid-term follow-up was performed ($n = 58$ RCTs). RRs comparing each biologic with placebo are presented in Table 1 while corresponding NNTs are reported in Fig. 3. All treatments demonstrated improved levels of PASI 75 response compared to placebo. Tildrakizumab 100 mg was associated with an RR of 8.74 (95% CrI 7.98, 9.42) and an NNT of 1.36 (95% CrI 1.32, 1.46), both of which demonstrated comparable magnitudes of clinical benefit relative to other biologics. NMAs performed at week 12 and week 16 consisted of 87 and 59 RCTs, respectively. Results from NMAs (see Online Appendix 7 of online supplement for details) suggested that at week 12 (RR 8.29, 95% CrI 7.27, 9.34; NNT 1.75, 95% CrI 1.56, 1.99) and week 16 (RR 8.93, 95% CrI 7.92, 9.80;

Table 1 Summary of risk ratios from NMAs of clinical efficacy outcomes at week 28

Intervention vs. placebo	Risk ratio (RR; 95% CrI)				
	PASI 75	PASI 90	PASI 100	PGA 0/1	DLQI 0/1
RIS 150 mg Q12W	8.92 (8.37, 9.49)	14.81 (13.68, 15.73)	20.65 (17.95, 22.64)	10.29 (9.53, 11.02)	NA
GUS 100 mg Q8W	8.91 (8.36, 9.49)	14.77 (13.64, 15.70)	17.99 (15.69, 20.11)	10.23 (9.43, 11.00)	12.37 (9.22, 15.41)
BIM 320 mg Q4W	8.88 (8.32, 9.48)	14.76 (13.57, 15.71)	21.31 (19.19, 22.80)	10.24 (9.45, 11.00)	11.38 (8.44, 14.70)
UST 90 mg Q12W	8.88 (8.29, 9.47)	14.58 (13.01, 15.61)	13.53 (11.33, 15.84)	10.01 (8.92, 10.88)	13.65 (11.11, 16.24)
IFX 5 mg/kg Q8W	8.86 (8.27, 9.47)	14.36 (12.32, 15.59)	NA	10.11 (9.06, 10.93)	13.40 (9.81, 16.07)
SEC 300 mg Q4W	8.81 (8.21, 9.43)	13.58 (12.31, 14.77)	16.01 (14.05, 17.85)	9.59 (8.80, 10.49)	11.89 (9.10, 14.74)
IXE 80 mg Q2W/Q4W	8.76 (8.15, 9.38)	14.14 (12.63, 15.36)	17.53 (15.06, 19.96)	9.66 (8.67, 10.68)	12.52 (8.28, 15.67)
TIL 100 mg Q12W	8.74 (7.98, 9.42)	14.09 (11.77, 15.50)	10.05 (7.74, 12.26)	9.34 (7.79, 10.68)	10.19 (7.58, 13.49)
CZP 400 mg Q2W	8.70 (7.70, 9.40)	14.07 (11.12, 15.52)	11.61 (3.85, 19.68)	9.94 (8.47, 10.92)	11.14 (7.90, 14.54)
BRO 210 mg Q2W	8.66 (7.51, 9.35)	13.98 (10.52, 15.49)	18.53 (8.65, 22.3)	9.88 (8.18, 10.82)	NA
UST 45 mg Q12W	8.58 (7.89, 9.28)	13.53 (11.82, 15.13)	9.74 (8.04, 11.66)	9.20 (7.99, 10.40)	12.26 (9.83, 14.93)
SEC 150 mg Q4W	8.38 (7.72, 9.09)	11.55 (9.80, 13.31)	10.58 (8.52, 12.83)	8.58 (7.60, 9.64)	10.62 (6.83, 14.36)
ADA 40 mg Q2W	7.26 (6.61, 7.93)	10.18 (8.69, 11.68)	9.99 (8.39, 11.50)	7.62 (6.63, 8.56)	8.23 (5.61, 11.09)
ETN 50 mg BIW/QW	7.23 (6.48, 8.01)	8.60 (6.87, 10.60)	5.15 (3.73, 6.96)	7.76 (5.91, 9.58)	7.37 (4.63, 11.19)

Estimates of risk ratios (RR) derived from random effects NMAs adjusted for placebo group response are presented for all interventions at week 28. Values of RR above 1 are indicative of preferred interventions. Treatments are sorted in order of decreasing magnitude of RR for PASI 75 response

ADA adalimumab, *BIM* bimekizumab, *BIW* twice weekly, *BRO* brodalumab, *CrI* credible interval, *CZP* certolizumab pegol, *ETN* etanercept, *GUS* guselkumab, *IFX* infliximab, *IXE* ixekizumab, *NA* not applicable, *PASI* Psoriasis Area and Severity Index, *Q#W* every # weeks, *QW* once weekly, *RIS* risankizumab, *SEC* secukinumab, *TIL* tildrakizumab, *UST* ustekinumab

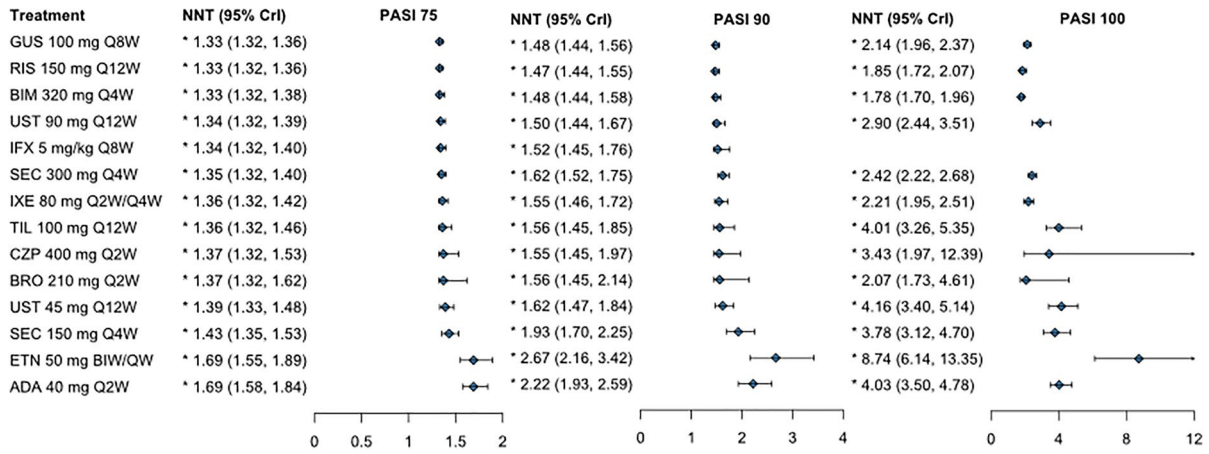

Fig. 3 Forest plot of NNTs vs. placebo for PASI 75/90/100 at week 28. Estimates of the NNT derived from random effects NMAs adjusted for placebo group response are presented for all interventions at week 28 for PASI 75, 90, and 100 response. Values of NNT closer to 1 are indicative of preferred interventions. Interventions are sorted in terms of increasing magnitude of NNT for PASI 75 response. *Statistically significant vs. placebo. *ADA* adalimumab, *BIM* bimekizumab, *BIW* twice weekly, *BRO* brodalumab, *CrI* credible interval, *CZP* certolizumab pegol, *ETN* etanercept, *GUS* guselkumab, *IFX* infliximab, *IXE* ixekizumab, *NNT* number needed to treat, *PASI* Psoriasis Area and Severity Index, *Q#W* every # weeks, *QW* once weekly, *RIS* risankizumab, *SEC* secukinumab, *TIL* tildrakizumab, *UST* ustekinumab

NNT 1.42, 95% CrI 1.34, 1.56), tildrakizumab 100 mg was associated with smaller estimates of benefit, demonstrating that the effects of tildrakizumab increased over time from week 12 to week 28.

PASI 90 and PASI 100 Response

Corresponding baseline risk adjusted NMAs of PASI 90 and PASI 100 response were performed at both week 28 mid-term follow-up and after completion of induction therapy (weeks 12/16). Corresponding numbers of included trials were 55 (week 28), 85 (week 12), and 57 (week 16) for PASI 90 response, and 40, 57, and 40 for PASI 100 response, respectively. Findings presented in Fig. 3 show that tildrakizumab 100 mg again demonstrated comparable risk ratios and NNTs versus placebo relative to other biologics at mid-term follow-up at week 28 for PASI 90 response (RR 14.09, 95% CrI 11.77, 15.50 and NNT 1.56, 95% CrI 1.45, 1.85); findings for PASI 100 response were associated with fewer benefits compared to placebo than other certain biologics (RR 10.05, 95% CrI 7.74, 12.26 and NNT 4.01, 95% CrI 3.26, 5.35). Findings from NMAs using data from the end of induction (weeks 12, 16) presented in Online Appendix 7 of the online supplement showed that tildrakizumab 100 mg was associated with smaller estimated RRs and NNTs at week 12 (PASI 90: RR 11.69, 95% CrI 9.01, 14.45 and NNT 2.51, 95% CrI 2.02, 3.31; PASI 100: RR 4.90, 95% CrI 3.35, 6.70 and NNT 10.13, 95% CrI 6.88, 16.77) and week 16 (PASI 90: RR 12.70, 95% CrI 9.96, 15.41 and NNT 1.94, 95% CrI 1.60, 2.44; PASI 100: RR 7.35, 95% CrI 5.21, 9.33 and NNT 6.08, 95% CrI 4.60, 9.00), again demonstrating its improved clinical efficacy over time from week 12 to 28.

PGA 0/1 Response

The baseline risk adjusted NMA of PGA 0/1 response at week 28 mid-term follow-up consisted of data from 49 RCTs, while totals of 78 RCTs and 55 RCTs contributed to corresponding analyses at week 12 and 16, respectively. RRs summarizing comparisons between biologics and placebo at week 28 are summarized in Table 1 while associated NNTs are provided in Fig. 4. All biologics again demonstrated significantly greater likelihood of PGA 0/1 response

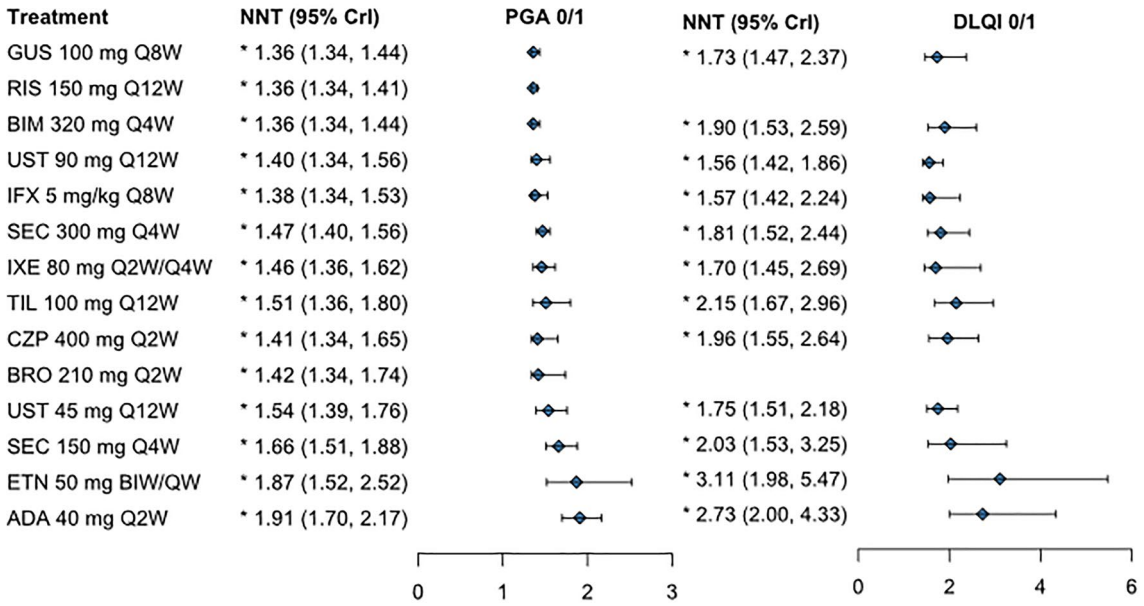

Fig. 4 Forest plot of NNTs vs. placebo for PGA 0/1 and DLQI 0/1 at week 28. Estimates of the NNT derived from random effects NMAs adjusted for placebo group response are presented for all interventions at week 28 for PGA 0/1 and DLQI 0/1 response. Values of NNT closer to 1 are indicative of preferred interventions. Interventions are sorted in terms of increasing magnitude of NNT for PASI 75 response as per Fig. 3 for consistency. *Statistically significant vs. placebo. *ADA* adalimumab, *BIM* bimekizumab, *BIW* twice weekly, *BRO* brodalumab, *CrI* credible interval, *CZP* certolizumab pegol, *DLQI* Dermatology Life Quality Index, *ETN* etanercept, *GUS* guselkumab, *IFX* infliximab, *IXE* ixekizumab, *NNT* number needed to treat, *PGA* Physician Global Assessment, *Q#W* every # weeks, *QW* once weekly, *RIS* risankizumab, *SEC* secukinumab, *TIL* tildrakizumab, *UST* ustekinumab

compared to placebo; tildrakizumab 100 mg was associated with an RR of 9.34 (95% CrI 7.79, 10.68) and an NNT of 1.51 (95% CrI 1.36, 1.80), both of which were of comparable magnitude of effect relative to other biologics. Results from NMAs at week 12 (RR 7.76, 95% CrI 6.47, 9.29; NNT 2.18, 95% CrI 1.82, 2.67) and week 16 (RR 9.65, 95% CrI 8.12, 11.39; NNT 1.63, 95% CrI 1.43, 1.89) again demonstrated smaller estimates of clinical benefit, suggesting the presence of improving benefits over time with tildrakizumab from week 12 to week 28.

Findings, Quality of Life (DLQI 0/1 Response)

Baseline risk adjusted NMAs for impact of treatment on quality of life as measured by DLQI 0/1 response consisted of totals of 18, 26, and 25 RCTs at week 28, 12, and 16, respectively. RRs summarizing comparisons between biologics and placebo at week 28 are presented in Table 1 while associated NNTs are summarized in Fig. 4. All biologics again demonstrated significantly greater likelihood of DLQI 0/1 response compared to placebo. Tildrakizumab 100 mg was associated with an RR of 10.19 (95% CrI 7.58, 13.49) and an NNT of 2.15 (95% CrI 1.67, 2.96), both of which were of comparable magnitude of effect relative to other biologics. Results from NMAs at the earlier follow-up times of week 12 (RR 7.76, 95% CrI 6.47, 9.29; NNT 2.18, 95% CrI 1.82, 2.67) and week 16 (RR 9.65, 95% CrI 8.12, 11.39; NNT 1.63, 95% CrI 1.43, 1.89) again demonstrated smaller estimates of clinical benefit, suggesting the presence of improving benefits over time with tildrakizumab from week 12 to week 28.

Findings, Tolerability (Adverse Events and Serious Adverse Events)

Detailed findings from NMAs for any AE and for any SAE at week 16 are reported within Appendix 8 of the online supplement. For any AE, there were no differences in risk compared to placebo with the exception of higher risk for infliximab 5 mg/kg (RD 16.951%, 95% CrI 6.504 to 27.814; NNT 5.899, 95% CrI 3.595, 15.375); tildrakizumab was associated with an RD of − 2.871 (95% CrI − 28.691, 16.205) compared to placebo and an NNT of − 34.835 (95% CrI undefined, − 3.485).

For the occurrence of any SAE, there were no observed significant risk differences compared to placebo. Tildrakizumab was associated with an RD of − 2.376 (95% CrI − 3.789, 3.939) versus placebo, and an NNT of − 42.080 (95% CrI undefined, − 26.394). Both of these findings suggested tildrakizumab was not associated with any significantly increased safety risk and was of comparable tolerability relative to other biologics.

Model Fit and Checks of Evidence Consistency

Details regarding model fit and evaluation of the consistency assumption for NMA are presented in Appendix 9 of the online supplement.

DISCUSSION

The present analyses compared the efficacy of biologics for the treatment of moderate-to-severe plaque PsO through 28-week treatment, a duration that is underreported in the literature and that may be beneficial for HCPs to understand comparative efficacy and clinical relevance in daily practice. Efficacy and quality of life responses were comparable among the agents included by week 28. Furthermore, no biologics exhibited a risk difference for SAEs relative to placebo, and only infliximab exhibited a higher risk for AEs relative to placebo. These findings indicate that the analyzed biologics are similarly effective for the treatment of moderate-to-severe PsO by week 28.

The methodology of the present study is validated by previously published SLRs/NMAs. For example, the current analysis shows similar differences among biologics at week 12 and week 16 as in previous reports. However, these analyses relied mainly on data during the induction period and did not account for the potential further improvement following this timeframe.

Further validating the focus on week 28, the peak efficacy of tildrakizumab was not reached until approximately week 22 in the pivotal trials reSURFACE 1 and reSURFACE 2. Despite the later peak, tildrakizumab had met its co-primary endpoints at week 12 [10]. As an example of tildrakizumab's increasing efficacy over time, in patients randomized to tildrakizumab 100 mg, PASI 75 response rates increased from 64% at week 12 to to 80% at week 28 in reSURFACE 1 and increased from 61% to 73% during the same time period in reSURFACE 2 [10]. Quality of life on tildrakizumab, as measured by achievement of DLQI 0/1, also improved between week 12 and week 28, from 42% to 52% of patients in reSURFACE 1 and from 40% to 54% of patients in reSURFACE 2 [10]. Comparison at a mid-range time point such as week 28 as well as at earlier time points is thus valuable to clinicians to determine whether a patient's response trajectory is typical for the chosen biologic or whether a switch may be warranted.

The current NMA demonstrates that further improvement after weeks 12 to 16 results in the majority of included biologics achieving comparable efficacy for the treatment of moderate-to-severe plaque PsO by week 28. The positive trend is highlighted by the achievement by many patients of complete or near-complete resolution of symptoms at this later time point. Data from head-to-head trials support these findings. For example, ixekizumab was statistically superior to guselkumab at week 12 based on PASI 90, PASI 100, and sPGA 0 response rates in the head-to-head trial IXORA-R [43, 142]; however, these differences disappeared by week 24. These data highlight that recent NMAs comparing biologics for the treatment of PsO only through the

induction period may not capture the full efficacy profile of all treatments [6, 7].

The current analysis adds to the results of the 2023 update to the Cochrane Database NMA. The Cochrane database reported that risankizumab and guselkumab, but not tildrakizumab, were superior to ustekinumab, adalimumab, certolizumab pegol, and deucravacitinib for the achievement of PASI 90 during the induction period, defined as weeks 8 to 24. However, only data up to week 16 were included for tildrakizumab [204]. The findings of the present analysis show that the efficacy of tildrakizumab was comparable to other IL-23 p19 inhibitors by week 28, 4 weeks past the end of the induction period studied by Cochrane.

Several properties of biologics may account for differences in timing of peak efficacy between and within classes. Biologics that are approved for the treatment of moderate-to-severe plaque PsO have a variety of targets (including TNFα, IL-17, IL-12/23 p40, and IL-23 p19) [2], so some interclass differences in rapidity of response may be due to specific mechanisms of action. Furthermore, even biologics within the same class may have slightly different mechanisms of action due to binding different epitopes of the target molecule [205, 206]. Different dosing regimens or pharmacokinetic profiles may also contribute; IL-17 inhibitors such as ixekizumab are in general dosed more frequently than IL-23 inhibitors [207]. Although risankizumab, guselkumab, and tildrakizumab all target the p19 subunit of IL-23, they are dosed differently. Guselkumab is dosed at week 0, week 4, and every 8 weeks thereafter, whereas risankizumab and tildrakizumab are both dosed at week 0, week 4, and every 12 weeks thereafter [8, 208, 209]. Lastly, these agents also have distinct pharmacokinetic profiles, with differences in absorption, distribution, and elimination [8, 208, 209]. All of these factors may contribute to differences in the timing of full efficacy observed with the different biologics for the treatment of PsO.

Although the efficacy of tildrakizumab was comparable to that of guselkumab and risankizumab for PASI 75 and PASI 90 response at week 28, this was not the case for PASI 100. The PASI 100 response to tildrakizumab may be related to the variables discussed above.

NMAs are also valuable for comparing safety and quality of life. In the present study, infliximab was the only biologic that demonstrated a higher risk for any AE relative to placebo; no biologics demonstrated a difference in risk for any SAE relative to placebo. At the class level in both the 2022 and 2023 Cochrane Database NMAs, placebo ranked first in SUCRA for AEs, followed by anti-IL-23 therapies. For quality of life, anti-IL-23 and anti-IL-17 therapies alternated between first and second in SUCRA in both Cochrane NMAs [204, 210]. In both NMAs, at the drug level, tildrakizumab was ranked first in SUCRA for AEs and was ranked fifth for SUCRA in quality of life among the other examined medications (17 to 20 total) [204, 210]. In reSURFACE 1 and reSURFACE 2, no significant differences were noted between treatment groups for adverse events of special interest, such as severe infections, malignancies, confirmed major adverse cardiac events, and drug-related hypersensitivity [10]. These factors may influence improved drug adherence, as patients are less likely to experience side effects and experience improved quality of life.

Strengths of the current review include the use of restricted approaches to combining data across time points (maximum of a 2-week difference), which are more indicative of between-study differences than NMAs that use more liberal approaches for data combination. Additionally, network meta-regression was used to account for baseline risk to address between-study heterogeneity.

We also acknowledge limitations of this study. First, the placebo group was maintained only until week 12. To impute placebo group outcomes at the 28-week mid-term follow-up, the method of last observation carried forward (LOCF) was used. While LOCF is associated with certain limitations, this approach was necessary to facilitate analysis of comparative efficacy among biologics at mid-term follow-up. Second, this NMA was limited to English language publications. Third, as with all NMAs, the heterogeneity of study parameters, including study populations, placebo-controlled intervals, concomitant medications permitted, and rescue strategies for non-responders, can limit the generalizability of the outcomes.

To our knowledge, this review represents the most up-to-date SLR/NMA of biologic therapies to treat moderate-to-severe plaque PsO. The review was conducted using recommended practices including a feasibility assessment and quantitative methods to account for between-study heterogeneity from models that adjust for cross-trial differences in baseline risk. The selection of mid-term follow-up as the primary time point of interest is a pivotal aspect of the current review, to support HCP decision-making in the management of PsO.

CONCLUSIONS

This SLR and NMA used recommended methods to compare the efficacy and safety of IL-23, IL-17, IL-12/23, and TNFα inhibitors for the treatment of moderate-to-severe plaque PsO at a previously underreported mid-range time point. The biologics studied for the treatment of moderate-to-severe plaque psoriasis demonstrated improved efficacy relative to placebo at week 28 and also the efficacy of tildrakizumab, risankizumab, and guselkumab were comparable. Further, the included biologics exhibited similar benefits in quality of life improvement by week 28, and none were significantly different relative to placebo for the occurrence of SAEs through week 16. The dual findings regarding tildrakizumab—the comparable mid-term efficacy and safety data found in the current work, combined with well-established long-term effectiveness [211]—indicate that tildrakizumab offers a valuable treatment option for the management of moderate-to-severe plaque PsO.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Mark Lebwohl is an Editorial Board member of *Dermatology and Therapy* who was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. He is an employee of Mount Sinai; receives research funds from AbbVie, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Clexio, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen, Pfizer, Sanofi-Regeneron, and UCB; and is a consultant for Almirall, AltruBio Inc., Apogee, Arcutis, AstraZeneca, Atomwise, Avotres Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Dermsquared, Evommune, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Sanofi-Regeneron, Seanergy, Strata, Takeda, Trevi, and Verrica. André Carvalho acted as a consultant and/or speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers

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

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