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ORIGINAL RESEARCH

Rapid Response of Biologic Treatments of Moderate-to-Severe Plaque Psoriasis: A Comprehensive Investigation Using Bayesian and Frequentist Network Meta-analyses

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ABSTRACT

Introduction: Rapid improvement of psoriasis is valued by patients and should be considered to be an important factor in treatment selection. We investigated Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) response rates within the first 12 weeks of treatment to compare the rapid response of 11 biologic therapies for moderate-to-severe psoriasis using Bayesian and Frequentist network meta-analyses (NMA).

Methods: A systematic literature review was conducted to identify phase 3, double-blind, randomized, controlled trials for adult patients with moderate-to-severe psoriasis treated with interleukin (IL)-17 (brodalumab, ixekizumab, secukinumab), IL-12/-23 (ustekinumab), IL-23 (guselkumab, risankizumab, tildrakizumab), or tumor necrosis factor inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab). Outcome measures extracted from 32 publications were ≥ 75, ≥ 90, or 100% improvement in PASI score (PASI 75, PASI 90, or PASI 100, respectively) at weeks 2, 4, 8, and 12 and DLQI (0,1), where score (0,1) indicates no effect on patient's life, at week 12. Bayesian NMA (BNMA) used fixed-treatment effect and random-baseline effect, normal independent models. Frequentist NMA (fNMA) was conducted as sensitivity analyses to test the robustness of the findings.

Results: Based on BNMA and fNMA, brodalumab and ixekizumab showed the most rapid treatment effects on PASI 75 at weeks 2, 4, and 8 and on PASI 90 and PASI 100 at weeks 2, 4, 8, and 12; ixekizumab overlapped with risankizumab on PASI 75 at week 12. Brodalumab, ixekizumab, and secukinumab yielded higher DLQI (0,1) gains at week 12 compared to all of the other biologics studied. Additional measures of quality of life were not assessed in this report.

Conclusions: Ixekizumab and brodalumab provide the most rapid response and earliest

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clinical benefit at week 2 among all of the biologics studied, including other biologic treatments such as secukinumab, ustekinumab, guselkumab, adalimumab, and etanercept. BNMA and fNMA results showed similar relative effect estimates and treatment rankings.
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Keywords: Biologics; Meta-analysis; Psoriasis

Key Summary Points
Why carry out this study?
Multiple biologic drugs are approved for the treatment of moderate-to-severe plaque psoriasis based on efficacy and safety established in phase 3, double-blind, randomized, controlled trials, but direct comparisons of response rates in head-to-head trials are rare, and indirect comparisons using network meta-analyses are limited
What was learned from the study?
This comprehensive network meta-analysis (NMA) examined a large number of biologics for the treatment of moderate-to-severe psoriasis (adalimumab, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab, ustekinumab) and focused on higher clinical response rates than previously published NMA investigations
We focused specifically on rapid response rates within 12 weeks of treatment because rapid skin clearance and quality of life improvement are important patient preferences in biologic treatment

DIGITAL FEATURES

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INTRODUCTION

Plaque psoriasis is a chronic, inflammatory skin disease with an estimated prevalence of 1.5–5% in the general population [1, 2]. Psoriasis significantly impairs patients' quality of life [1, 2], underscoring the need for timely and effective treatments.

Biologic therapies have transformed the treatment of moderate-to-severe psoriasis and have markedly improved multiple patient outcomes [3, 4]. Several biologics are available, including inhibitors of interleukin (IL)-17 (brodalumab, ixekizumab, secukinumab), IL-12/-23 (ustekinumab), IL-23 (guselkumab, risankizumab, tildrakizumab), or tumor necrosis factor (adalimumab, certolizumab pegol, etanercept, infliximab) [5, 6]. These biologics are approved for patients with moderate-to-severe plaque psoriasis based on efficacy and safety established in phase 3, double-blind, randomized, controlled trials (RCTs).

Rapid efficacy is important to patients and clinicians [4, 7–10], but head-to-head comparisons of biologics are rare, and none conducted to date have had speed of onset as a primary objective. We present a comprehensive network meta-analysis (NMA) that indirectly compares rapid response rates at early time points ($\leq$ 12 weeks of treatment) for 11 approved biologics for moderate-to-severe psoriasis. Bayesian and Frequentist NMA (BNMA and fNMA, respectively) were used to investigate Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) response from phase 3 RCTs identified by systematic literature review.

METHODS

Inclusion criteria for the studies with available data to include in the NMA have previously been reported and are listed in Electronic Supplementary Material (ESM) Table 1. These studies included patients who were $\geq$ 18 years of age with moderate-to-severe psoriasis.

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

PASI 75, PASI 90, and PASI 100 endpoints (≥ 75, ≥ 90, and 100% improvement in PASI score, respectively) were analyzed at weeks 2, 4, 8, and 12, and missing values were handled using nonresponder imputation (NRI) in all studies, with the exception of four studies (CIMPACT [11], CIMPASI-1 [12], CIMPASI-2 [12], CLARITY [13]) that reported endpoints based on multiple imputation (MI). DLQI (0,1) status, where (0,1) indicates no effect/no impact on patient's life, was assessed at week 12, and missing values were handled using NRI in all studies, except for five studies (CIMPASI-1 [12], CIMPASI-2 [12], CLARITY [13], CLEAR [14], ERASURE [15]) that used last observation carried forward and one study (FIXTURE [15]) that did not mention how missing values were treated. When required data were imputed differently (e.g., MI vs. NRI) or analyzed (mixed model for repeated measures vs. analysis of covariance) differently, they were included in the data analysis based on the assumption that the impact of the chosen imputation/analytical method was negligible for treatment effects.

Systematic Literature Review

Efficacy data on PASI response rates (PASI 75/90/100) at weeks 2, 4, 8, and 12 and DLQI (0,1) response rates at week 12 were obtained from a systematic literature review of the OvidSP platform for literature published since 1 January 1990. The last update search was performed on 12 December 2018. The search parameters were designed to identify publications that reported data from phase 3 RCTs of biologics approved for the treatment of moderate-to-severe psoriasis. Studies included in the NMA are listed in ESM Table 1 [11–42]. The Cochrane Handbook for Systematic Reviews of Interventions guidance was followed [43].

Outcome Measures Extracted

We report the relative effects versus placebo for all biologics included in this study, except where data were unavailable. PASI 75/90/100 response data were unavailable at week 2 for risankizumab and tildrakizumab; PASI 100 response data were unavailable at weeks 2, 4, 8, and 12 for certolizumab pegol and infliximab; and DLQI (0,1) response data were unavailable at week 12 for guselkumab, infliximab, and risankizumab.

BNMA used fixed-treatment effect and random-baseline effect, normal independent models [44, 45]. Convergence for all models was assessed using trace plots as modified by Brooks and Gelman [46]. Model fit was assessed using the deviance information criterion, and residual deviance (technical model details are given in the ESM). fNMA were conducted as sensitivity analyses to test the robustness of the findings. BNMA were performed in JAGS via R using the R2JAGS package, and fNMA analysis was run using R version 3.4.2 R package with netmeta [47]. BNMA and fNMA included data from all biologic doses obtained during the systematic literature review (see ESM).

RESULTS

Based on the BNMA analysis, IL-17 antagonists showed the most rapid treatment effects, with ixekizumab and brodalumab being similar for rapid skin and quality of life responses (Figs. 1, 2, 3; Tables 1, 2).

Ixekizumab and brodalumab showed more rapid treatment effects on PASI 75 response rates at weeks 2, 4, and 8 compared with all other biologics included in the analysis (Figs. 1, 2; Table 1). At week 12, ixekizumab and risankizumab had the most rapid treatment effects; the distribution for ixekizumab overlapped with risankizumab, and the distribution for risankizumab overlapped with brodalumab, secukinumab, infliximab, and guselkumab (Figs. 1, 2; Table 1).

Similarly, ixekizumab and brodalumab showed more rapid treatment effects on PASI 90 response rates at weeks 2, 4, 8, and 12 than did all of the other biologics included in the analysis (Figs. 1, 2; Table 1). Ixekizumab and brodalumab had the most rapid treatment effects at week 2, brodalumab had the most rapid treatment effects at week 4, and ixekizumab and brodalumab had the most rapid treatment effects at weeks 8 and 12 where distributions overlapped (Figs. 1, 2; Table 1). Ixekizumab and brodalumab had no overlap but were followed at week 4 by infliximab and secukinumab and at

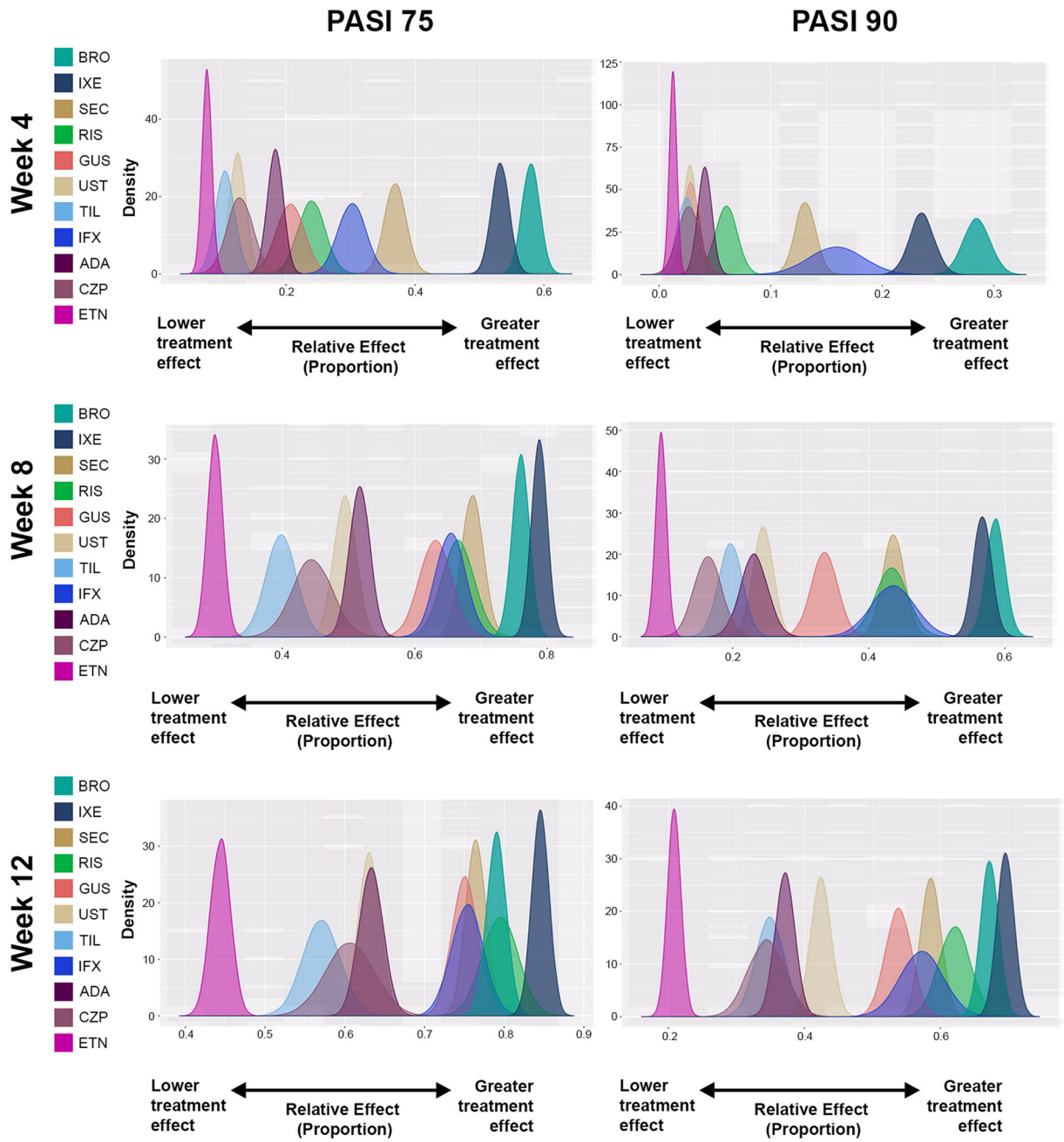

Fig. 1 Treatment effects on Psoriasis Area and Severity Index (*PASI*) 75 and PASI 90 response rates (≥ 75 and ≥ 90% improvement in PASI, respectively) at weeks 4, 8, and 12 based on Bayesian Network Meta-Analysis (BNMA). Data are presented as the posterior mean density relative to placebo. On-label doses are represented. *ADA* Adalimumab, *BRO* brodalumab, *CZP* certolizumab pegol, *ETN* etanercept, *GUS* guselkumab, *IFX* infliximab, *IXE* ixekizumab, *RIS* risankizumab, *SEC* secukinumab, *TIL* tildrakizumab, *UST* ustekinumab

week 8 by secukinumab, infliximab, and risankizumab, and distributions did overlap for those treatments. At week 12, distributions for ixekizumab and brodalumab overlapped, and the distribution for brodalumab overlapped with risankizumab, which in turn overlapped

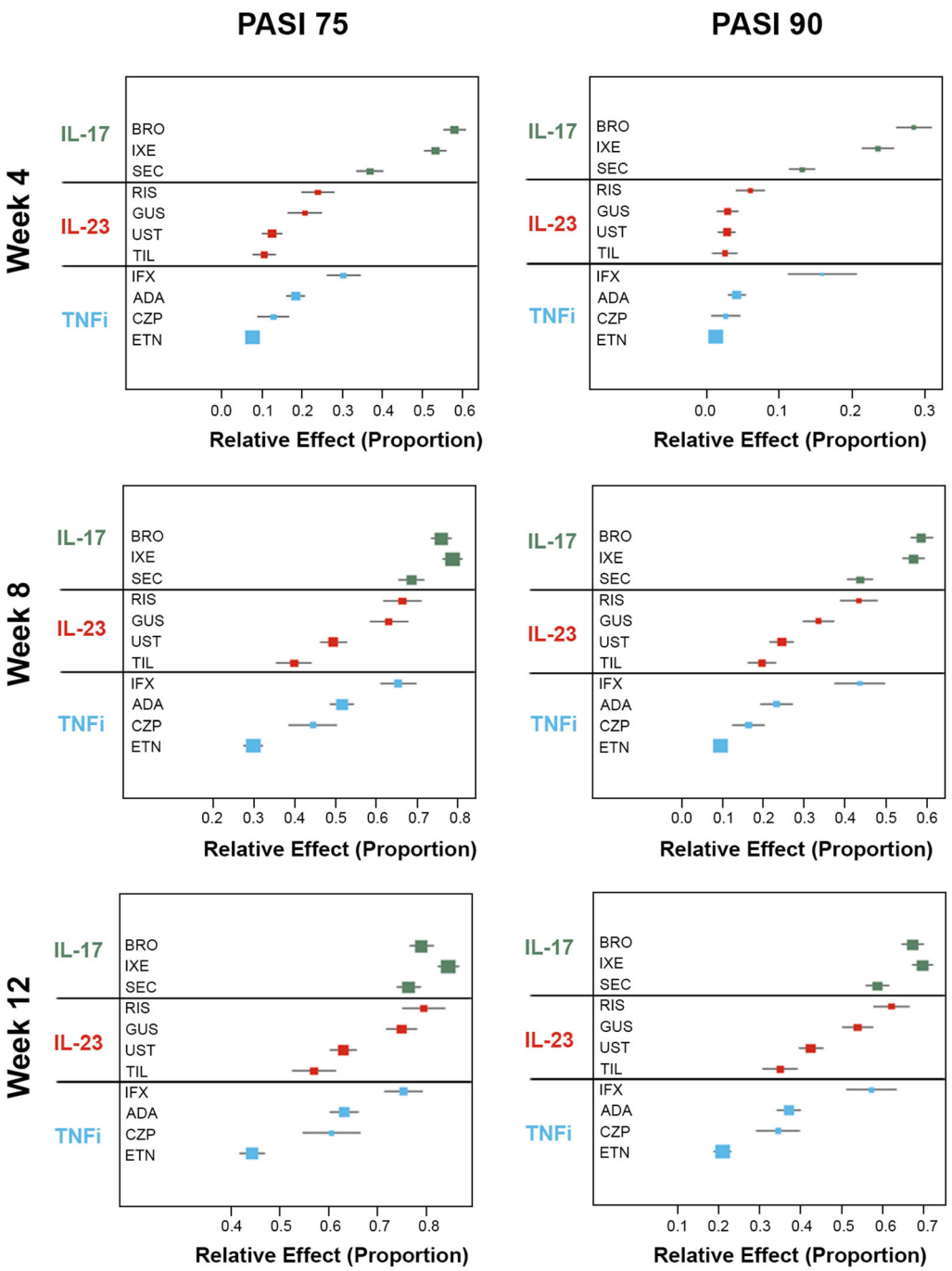

Fig. 2 Treatment effects on PASI 75 and PASI 90 response rates at weeks 4, 8, and 12 based on BNMA. Data are presented as the posterior mean and 95% credible interval relative to placebo. Boxes indicate sample size. Ustekinumab is an interleukin (*IL*)-12/-23 inhibitor. On-label doses are represented. *TNFi* Tumor necrosis factor inhibitor

with secukinumab and infliximab (Figs. 1, 2; Table 1).

Ixekizumab and brodalumab showed the most rapid treatment effects for PASI 100 at

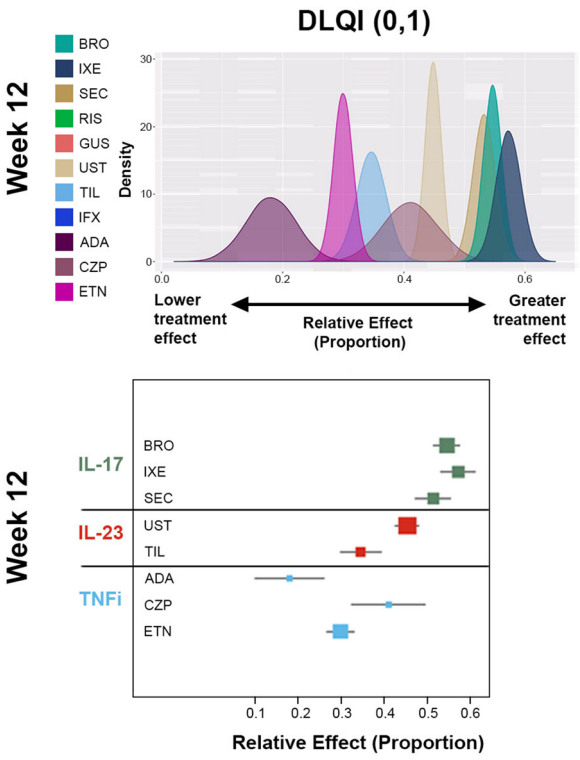

Fig. 3 Treatment effects on the Dermatology Life Quality Index (DLQI) (0,1) response rates at week 12 based on BNMA. Score (0,1) indicates no effect on patient. Data are presented as the posterior mean density relative to placebo. Guselkumab and infliximab data were not available at week 12. Ustekinumab is an IL-12/-23 inhibitor. On-label doses are represented

weeks 4 and 12, and brodalumab showed the most rapid treatment effects at week 8 (Table 1; ESM Figs. 1, 2).

Average (i.e., posterior mean) relative treatment effect was greatest for ixekizumab, brodalumab, and secukinumab on the DLQI (0,1) response rates at week 12, where distributions overlapped for these three treatments (Fig. 3; Table 2).

Results from fNMA were consistent with those from BNMA, with similar treatment rankings for PASI 75/90/100 at weeks 2, 4, 8, and 12 and for DLQI (0,1) at week 12. PASI 90 at week 12 rankings are presented (Table 3). Ixekizumab and brodalumab were ranked highest compared with the other biologics included in the fNMA analysis. Network diagrams are presented for PASI 90 at week 12 (Fig. 4). In Fig. 4, lines represent direct comparisons using RCTs, and numbers represent the number of RCTs included in each comparison.

DISCUSSION

In this comprehensive NMA of phase 3 RCTs, ixekizumab and brodalumab provided the most rapid and highest clinical response of PASI 75, PASI 90, or PASI 100 as early as week 2 compared to other biologic treatments (secukinumab, ustekinumab, guselkumab, adalimumab, and etanercept). DLQI (0,1) response rate distributions at week 12 overlapped for ixekizumab, brodalumab, and secukinumab. BNMA and fNMA results showed similar relative effect estimates with comparable treatment rankings. These findings align with previously published reports of rapid clinical improvement for patients with moderate-to-severe psoriasis treated with ixekizumab or brodalumab [48–50].

Rapid improvements in skin and the ability to feel better quickly are important treatment attributes of a psoriasis therapy. These are important patient preferences for treatments and are ranked among the highest desired priorities in multiple reports [2, 4, 9, 10, 51, 52]. However, rapid effect is also tied to longer-term outcomes, including skin improvement, quality of life, and reduction in itch [50, 53–55], though it must be noted that an association between rapid effect and long-term outcomes was not assessed in this analysis. It is also important to note that each patient has different treatment expectations [51, 56] and that the alignment of individual patient needs with physician goals may improve adherence and satisfaction with therapy [56].

Several limitations to this study should be considered. NMA differs from a traditional meta-analysis in that it is not an analysis of only head-to-head studies of the same intervention with the same comparator. NMA relies on a network of evidence from RCTs where relevant treatments are connected by trials, and this provides a combination of direct and indirect comparisons for analysis of the comparative effects of many interventions [57]. RCTs are

Table 1 Bayesian network meta-analysis relative treatment effect summary by highest to lowest average rank for Psoriasis Area and Severity Index 75/90/100 response at weeks 2, 4, 8, and 12

Week	PASI 75[a]			PASI 90[a]			PASI 100[a]		
	Biologic	Treatment effect relative to PBO (95% CrI)	Average rank	Biologic	Treatment effect relative to PBO (95% CrI)	Average rank	Biologic	Treatment effect relative to PBO (95% CrI)	Average rank
2	BRO	0.22 (0.198–0.242)	1.165	BRO	0.05 (0.038–0.060)	1.130	BRO	0.01 (0.004–0.014)	1.224
	IXE	0.20 (0.182–0.226)	1.835	IXE	0.04 (0.030–0.051)	1.871	IXE	0.01 (0.001–0.009)	2.551
	IFX	0.05 (0.031–0.070)	3.314	ADA	0.01 (− 0.001–0.012)	3.846	ADA	0.01 (− 0.001–0.010)	2.821
	ADA	0.03 (0.011–0.055)	4.590	IFX	0.01 (− 0.014–0.023)	5.247	GUS	0 (− 0.003–0.008)	4.198
	CZP	0.03 (0.007–0.061)	4.608	UST	0 (− 0.002–0.009)	4.830	UST	0 (0–0)	5.731
	UST	0.02 (0.003–0.029)	6.429	GUS	0 (− 0.001–0.001)	6.864	ETN	0 (0–0)	5.736
	GUS	0.02 (− 0.003–0.037)	6.480	ETN	0 (0–0)	7.066	SEC	0 (0–0)	5.738
	ETN	0.01 (0.002–0.014)	7.646	SEC	0 (0–0)	7.072	–		
	SEC	0 (0–0)	8.934	CZP	0 (0–0)	7.074	–		
4	BRO	0.58 (0.553–0.606)	1.007	BRO	0.29 (0.261–0.308)	1.001	BRO	0.09 (0.071–0.100)	1.100
	IXE	0.53 (0.506–0.559)	1.993	IXE	0.24 (0.214–0.257)	2.001	IXE	0.07 (0.060–0.086)	1.900
	SEC	0.37 (0.337–0.402)	3.007	IFX	0.16 (0.112–0.206)	3.136	TIL	0.01 (0–0.016)	3.465
	IFX	0.30 (0.261–0.344)	4.010	SEC	0.13 (0.113–0.149)	3.862	RIS	0.01 (0–0.012)	3.792
	RIS	0.24 (0.199–0.280)	5.130	RIS	0.06 (0.041–0.079)	5.065	UST	0 (0–0)	6.941
	GUS	0.21 (0.164–0.249)	6.006	ADA	0.04 (0.029–0.053)	6.261	ADA	0 (0–0)	6.946
	ADA	0.18 (0.160–0.207)	6.861	GUS	0.03 (0.014–0.043)	8.205	GUS	0 (0–0)	6.952
	CZP	0.13 (0.090–0.168)	8.604	UST	0.03 (0.016–0.040)	8.334	ETN	0 (0–0)	6.949
	UST	0.13 (0.100–0.149)	8.715	CZP	0.03 (0.007–0.046)	8.543	SEC	0 (0–0)	6.955
	TIL	0.11 (0.076–0.134)	9.716	TIL	0.03 (0.008–0.042)	8.799	–		
	ETN	0.08 (0.063–0.092)	10.952	ETN	0.01 (0.006–0.019)	10.794	–		

Table 1 continued

Week	PASI 75[a]			PASI 90[a]			PASI 100[a]		
	Biologic	Treatment effect relative to PBO (95% CrI)	Average rank	Biologic	Treatment effect relative to PBO (95% CrI)	Average rank	Biologic	Treatment effect relative to PBO (95% CrI)	Average rank
8	IXE	0.79 (0.766–0.811)	1.048	BRO	0.59 (0.560–0.613)	1.152	BRO	0.30 (0.274–0.321)	1.001
	BRO	0.76 (0.735–0.784)	1.953	IXE	0.57 (0.542–0.593)	1.848	IXE	0.25 (0.225–0.270)	1.999
	SEC	0.69 (0.655–0.719)	3.365	SEC	0.44 (0.406–0.467)	3.947	SEC	0.17 (0.142–0.193)	3.105
	RIS	0.67 (0.618–0.712)	4.300	IFX	0.44 (0.374–0.497)	3.991	RIS	0.14 (0.114–0.173)	3.900
	IFX	0.65 (0.612–0.697)	4.756	RIS	0.43 (0.387–0.479)	4.066	GUS	0.09 (0.066–0.118)	5.292
	GUS	0.63 (0.584–0.677)	5.578	GUS	0.34 (0.297–0.372)	5.996	UST	0.08 (0.062–0.099)	5.975
	ADA	0.52 (0.487–0.547)	7.178	UST	0.25 (0.216–0.274)	7.310	ADA	0.07 (0.051–0.081)	7.226
	UST	0.50 (0.463–0.527)	7.910	ADA	0.23 (0.193–0.270)	7.806	TIL	0.06 (0.041–0.082)	7.502
	CZP	0.45 (0.386–0.504)	9.015	TIL	0.20 (0.163–0.230)	8.995	ETN	0.02 (0.010–0.029)	9.000
	TIL	0.40 (0.354–0.442)	9.897	CZP	0.16 (0.125–0.203)	9.889	–		
	ETN	0.30 (0.276–0.321)	11.000	ETN	0.10 (0.079–0.111)	10.999	–		
12	IXE	0.85 (0.825–0.866)	1.019	IXE	0.70 (0.671–0.720)	1.099	BRO	0.40 (0.375–0.426)	1.182
	RIS	0.80 (0.752–0.839)	2.650	BRO	0.67 (0.647–0.698)	1.929	IXE	0.38 (0.359–0.408)	1.819
	BRO	0.79 (0.767–0.814)	2.710	RIS	0.62 (0.577–0.665)	3.173	RIS	0.31 (0.267–0.344)	3.248
	SEC	0.76 (0.740–0.789)	4.334	SEC	0.59 (0.558–0.615)	4.262	SEC	0.29 (0.262–0.316)	3.752
	IFX	0.75 (0.715–0.793)	4.981	IFX	0.57 (0.511–0.634)	4.730	GUS	0.21 (0.177–0.248)	5.003
	GUS	0.75 (0.719–0.782)	5.307	GUS	0.54 (0.501–0.576)	5.806	UST	0.16 (0.143–0.173)	6.038
	ADA	0.63 (0.604–0.662)	7.682	UST	0.42 (0.395–0.453)	7.011	ADA	0.13 (0.114–0.152)	7.285
	UST	0.63 (0.604–0.658)	7.790	ADA	0.37 (0.343–0.399)	8.374	TIL	0.12 (0.096–0.152)	7.674
	CZP	0.61 (0.548–0.665)	8.722	TIL	0.35 (0.308–0.390)	9.253	ETN	0.05 (0.040–0.064)	9.000
	TIL	0.57 (0.526–0.616)	9.806	CZP	0.34 (0.293–0.396)	9.363	–		
	ETN	0.44 (0.420–0.468)	11.000	ETN	0.21 (0.189–0.228)	11.000	–		

On-label doses are represented

Dashes indicate that data were unavailable

ADA adalimumab, *BRO* brodalumab, *CrI* credible interval, *CZP* certolizumab pegol, *ETN* etanercept, *GUS* guselkumab, *IFX* infliximab, *IXE* ixekizumab, *PBO* placebo, *RIS* risankizumab, *SEC* secukinumab, *TIL* tildrakizumab, *UST* ustekinumab

[a] Psoriasis Area and Severity Index (PASI). PASI 75, 90, and 100 endpoints represent ≥ 75, ≥ 90, and 100% improvement in PASI score, respectively, from baseline

Table 2 Bayesian network meta-analysis relative treatment effect summary by highest to lowest average rank for the Dermatology Life Quality Index (0,1) response at week 12

DLQI (0,1) response at week 12		
Biologic	**Treatment effect relative to PBO (95% CrI)**	**Average rank**
IXE	0.57 (0.533–0.612)	1.207
BRO	0.55 (0.517–0.576)	2.120
SEC	0.53 (0.497–0.567)	2.680
UST	0.45 (0.423–0.474)	4.209
CZP	0.41 (0.324–0.497)	4.892
TIL	0.35 (0.300–0.393)	5.942
ETN	0.30 (0.269–0.330)	6.953
ADA	0.18 (0.101–0.260)	7.997

On-label doses are represented
DLQI (0,1) Dermatology Life Quality Index (0,1)

Table 3 Frequentist network meta-analysis treatment rankings for Psoriasis Area and Severity Index 90 response rates at week 12

Biologic	Treatment effect relative to PBO (95% CI)	Rank (*P* score)
IXE	0.70 (0.671–0.720)	0.995
BRO	0.67 (0.647–0.698)	0.951
RIS	0.62 (0.577–0.665)	0.865
SEC	0.59 (0.557–0.614)	0.780
IFX	0.57 (0.511–0.633)	0.756
GUS	0.54 (0.502–0.577)	0.695
UST	0.42 (0.395–0.453)	0.526
ADA	0.37 (0.344–0.400)	0.359
TIL	0.35 (0.308–0.390)	0.287
CZP	0.34 (0.284–0.391)	0.257
ETN	0.21 (0.188–0.227)	0.105

On-label doses are represented

considered to be the gold standard for treatment comparisons and provide valuable clinical data, and the studies included in the analyses are assumed to be generally similar and consistent; however, heterogeneity still may exist. There may be clinical differences (participants, populations [naïve versus experienced], duration of follow-up, and mode of administration) and methodological differences (study design, approaches to analysis, and imputation methods) that may not be aligned due to the availability of or clarity in the published data. For example, an insufficient number of RCTs included in this analysis had DLQI (0,1) response rates available at time points earlier than week 12; the threshold for NMA inclusion was not met and, thus, earlier quality of life response was not evaluated. This may contribute to selection and reporting bias. The way endpoints were imputed was clear in the majority of studies included in the analysis; however, the imputation method used for DLQI (0,1) missing values was not mentioned in one study (FIXTURE [15]). Another important caveat is that quality of life was limited in this report by what the DLQI tool could capture in the narrow RCT population. Our focus was limited to the first 12 weeks of treatment, and as such, long-term quality of life impacts of psoriasis and costs associated with disease management were not examined. Safety and patient-reported outcomes data, including those related to quality of life, were not examined in this report. The NMA results presented here are not direct comparisons and should be interpreted with caution if used to inform future treatment choices. Finally, results cannot be generalized by class because not all members of the IL-17 superfamily of cytokines were shown to be rapid in this analysis and there was some overlap between these and members of different classes, such as IL-23.

CONCLUSIONS

Overall, this NMA demonstrates that ixekizumab and brodalumab provide the most rapid skin clearance and quality of life improvement within 12 weeks compared with other leading biologic treatments for patients with moderate-

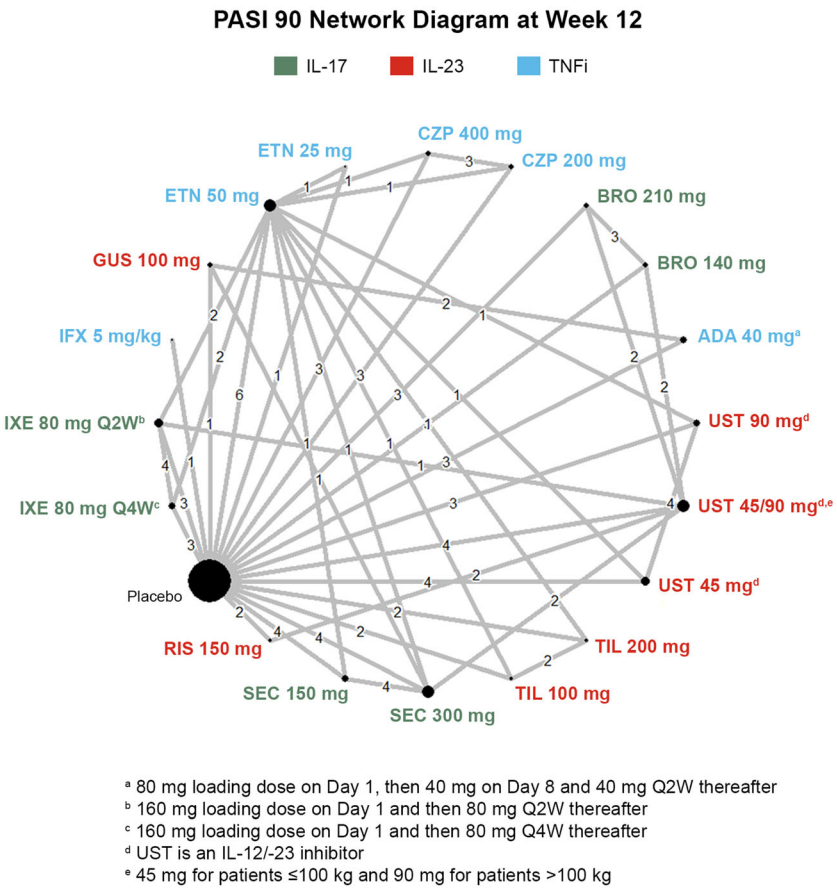

Fig. 4 PASI 90 network diagram at week 12. A total of 33 studies and 20 treatments are included. On- and off-label doses are represented. Lines represent direct comparisons using randomized, controlled trials (RCTs); numbers represent the number of RCTs included in each comparison; network diagrams are the same for both BNMA and frequentist network meta-analysis. *Q2W* Every 2 weeks, *Q4W* every 4 weeks

to-severe psoriasis, including secukinumab, an IL-17 antagonist, and biologics that inhibit the IL-12/-23, IL-23, or TNF pathways.

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

Data Availability. Portions of this work were presented at the American Academy of Dermatology Annual Meeting in Washington, DC; 1–5 March 2019. The datasets generated during and/or analyzed during the current study are not publicly available due to the systematic literature review/network meta-analysis (SLR/NMA) being completed before registration with a database such as The International Prospective Register of Systematic Reviews (PROSPERO) was a requirement. Any future updates to this SLR/NMA will be registered in PROSPERO. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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