ORIGINAL ARTICLE

Comparative safety and benefit-risk profile of biologics and oral treatment for moderate-to-severe plaque psoriasis: A network meta-analysis of clinical trial data

Neil H. Shear, MD,[a] Keith A. Betts, PhD,[b] Ahmed M. Soliman, MS, PhD,[c] Avani Joshi, PhD,[c] Yan Wang, ScD,[b] Jing Zhao, PhD,[d] Paolo Gisondi, MD,[e] Ranjeeta Sinvhal, MD,[c] and April W. Armstrong, MD, MPH[f]
Toronto, Canada; Los Angeles, California; North Chicago, Illinois; Denver, Colorado; and Verona, Italy

Background: The comparative safety and benefit-risk profiles of moderate-to-severe psoriasis treatment have not been well studied.

Objective: To compare the short-term (12-16 weeks) and long-term (48-56 weeks) safety and benefit-risk profiles of moderate-to-severe psoriasis treatments.

Methods: A systematic literature review of phase II-IV randomized controlled trials of moderate-to-severe psoriasis treatments was conducted (cutoff: July 1, 2020). Any adverse events (AEs), any serious AEs, and AEs leading to treatment discontinuation were compared using Bayesian network meta-analyses (NMAs).

Results: Fifty-two and 7, respectively, randomized controlled trials were included in the short- and long-term NMAs, respectively. In the short-term NMA, the rates of any AEs were the lowest for tildrakizumab (posterior median: 46.0%), certolizumab (46.2%), and etanercept (49.1%). The rates of any serious AE were the lowest for certolizumab (0.8%), risankizumab (1.2%), and etanercept (1.6%). The rates of AEs leading to treatment discontinuation were the lowest for risankizumab (0.5%), tildrakizumab (1.0%), and guselkumab (1.5%). In the long-term NMA, risankizumab had the lowest rates of all 3 outcomes (67.5%, 4.4%, and 1.0%, respectively) and the most favorable benefit-risk profile.

Limitations: The results may not be generalizable to real-world populations.

Conclusions: Anti−interleukin 23 agents were associated with low rates of safety events. Risankizumab had the most favorable benefit-risk profile in the long term. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2021.02.057.)

Key words: network meta-analysis; outcomes; psoriasis; safety; treatment.

INTRODUCTION

Biologic therapies are frequently used as first-line agents to treat moderate-to-severe plaque psoriasis.[1] A number of biologics have been approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of psoriasis, including tumor necrosis factor (TNF)-inhibitors (adalimumab, etanercept,

From the Sunnybrook Health Sciences Centre, University of Toronto[a]; Analysis Group, Inc, Los Angeles[b]; AbbVie, North Chicago[c]; Analysis Group, Inc, Denver[d]; Department of Medicine, University of Verona[e]; Keck School of Medicine, University of Southern California, Los Angeles.[f]

Funding sources: Supported by AbbVie.

Part of this study was presented at the 24th World Congress of Dermatology, June 10-15, 2019, Milan, Italy.

IRB approval status: This was a network meta-analysis of previously published data; therefore, no institutional board review was required.

Accepted for publication February 4, 2021.

Correspondence and reprint requests to: April W. Armstrong, MD, MPH, Department of Dermatology, Keck School of Medicine, University of Southern California, HC4 2000 1450 San Pablo, Health Sciences Campus, Los Angeles, CA 90033. E-mail: aprilarmstrong@post.harvard.edu.

Published online April 24, 2021.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2021.02.057

infliximab, and certolizumab), anti–interleukin (IL) 12/23 monoclonal antibodies (ustekinumab), anti–IL-17A agents (secukinumab, ixekizumab, and brodalumab), and anti–IL-23 agents (risankizumab, tildrakizumab, and guselkumab).[2-6]

Although biologic agents are generally safe and well tolerated, like any other medications, they are associated with adverse effects that may be related to their mechanism of action, dosing, or other factors. Several registries, including Psoriasis Longitudinal Assessment and Registry, British Association of Dermatologists Biologic Interventions Register, and PsoBest, have been collecting safety data for all biologic agents used for psoriasis treatment over extended periods of follow up.[7-10] Increased rates of infection have been reported in patients receiving TNF inhibitors, with upper respiratory tract infections, pharyngitis, sinusitis, and rhinitis as the most commonly reported infections.[11] Cases of tuberculosis have also been reported during clinical trials of TNF inhibitors.[11,12] Long-term safety studies of anti–IL-12/23 agents have reported upper respiratory tract infections, nasopharyngitis, headache, and arthralgia as the most common adverse events (AEs).[13-15] IL-17–deficient patients with psoriasis are also at an increased risk of *Candida* infection while undergoing treatment with anti–IL-17 agents,[16] and anti–IL-17 medications may exacerbate or even induce inflammatory bowel disease.[17]

Evidence of both the efficacy and safety of the existing psoriasis treatments is important for therapeutic decision making. The comparative efficacy of psoriasis treatments has been well studied.[18-22] However, few studies have evaluated the comparative safety or benefit-risk profiles of these treatments. In this study, network meta-analyses (NMA) were conducted to assess the comparative safety profiles of FDA- or EMA-approved biologic and oral treatments for patients with moderate-to-severe psoriasis who are eligible for systemic therapy or phototherapy. The comparative safety data were used in conjunction with published comparative efficacy data to characterize the benefit-risk profile of each treatment.

CAPSULE SUMMARY

- This network meta-analysis of moderate-to-severe psoriasis treatments found that anti–interleukin 23 agents were associated with low safety event rates and that risankizumab had the most favorable long-term benefit-risk profile.
- The comparative safety data for psoriasis treatments can enable informed treatment decision making in conjunction with established treatment guidelines.

METHODS

Data source

Trial identification. A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines on December 4, 2017, and updated on September 17, 2018, December 4, 2019, and July 1, 2020, to identify the clinical trials of treatments for moderate-to-severe plaque psoriasis. The EMBASE, MEDLINE, and Cochrane libraries were searched, and additional searches were conducted for reference lists of included studies, conference proceedings, previous health technology assessment submissions, and clinical trial registries. The systematic literature review was registered with the International Prospective Register of Systematic Reviews (PROSPERO #146674).

Inclusion criteria. Trials eligible for inclusion in the NMAs were required to meet the following criteria: a phase II, III, or IV randomized controlled clinical trial of adults with moderate-to-severe psoriasis who were eligible for systemic therapies and phototherapy; included FDA or EMA-approved treatments and dosages for moderate-to-severe psoriasis (a full list of the treatments and dosing schedules is provided in Supplemental Methods, available via Mendeley at https://doi.org/10.17632/hp35wm5kft.1); and reported at least one safety outcome of interest (any AE, any serious AE [SAE], or AEs leading to treatment discontinuation) in the primary response period (12-16 weeks from baseline [short term]) and/or at the end of the maintenance period (48-56 weeks from baseline [long term]).

Exclusion criteria. For the long-term NMA, the trials were excluded if any of the following criteria was met: patients were crossed over from 1 treatment to another before weeks 48-56; patients received a different dosage from the originally randomized dose during the postinduction period; or patients were rerandomized based on certain efficacy criteria, such as the Psoriasis Area and Severity Index (PASI) 75, during the postinduction period.

Outcomes

The outcomes of interest in this study included the proportions of patients with any AE, any SAE, and AEs leading to treatment discontinuation in the primary response period (weeks 12-16) and at the end of the maintenance period (weeks 48-56). Additionally, the benefit-risk profiles were assessed using the comparative safety data in

Abbreviations used:

AE:	adverse event
CrI:	credible interval
FDA:	Food and Drug Administration
EMA:	European Medicines Agency
IL:	interleukin
NMA:	network meta-analysis
PASI:	Psoriasis Area and Severity Index
SAE:	serious adverse event
SUCRA:	surface under the cumulative ranking curve
TNF:	tumor necrosis factor
Q2W:	every 2 weeks
Q12W:	every 12 weeks

conjunction with comparative PASI 90 data reported previously.[18]

Statistical methods

For each safety outcome, NMA was conducted using a Bayesian logistic regression model. Random-effects models were used for short-term safety outcomes to account for potential cross-trial heterogeneities in treatment effects. Fixed-effects models were used for long-term safety outcomes because of the sparsity of networks. Markov Chain Monte Carlo was used to estimate the posterior probability distribution, with 5000 adaptive iterations, 50,000 burn-in iterations, a thinning factor of 10, and 50,000 posterior iterations, using 3 parallel chains.[23-25] Vague priors were used such that the posterior distribution was driven primarily by the observed likelihood. Posterior medians and the associated 95% credible intervals (CrIs) of the rates of each safety outcome were estimated for each treatment. Additionally, pairwise comparisons between treatments were summarized using posterior median odds ratios and associated 95% CrIs; comparisons were considered statistically significant if 95% CrI for the pairwise odds ratio did not include 1. Because the estimated rates were correlated, a comparison of the event rates for 2 treatments could still be statistically significant even when 95% CrIs of the estimated rates overlapped. The ranking probabilities of each safety outcome were obtained using the surface under the cumulative ranking curve (SUCRA) score.[26] A higher SUCRA score indicated a higher probability of a treatment being in the top ranks (ie, a lower probability of having safety events).

A benefit-risk assessment was conducted by graphically cross-tabulating the estimated safety rates obtained from the current NMA with the estimated PASI 90 rates obtained from a published psoriasis meta-analysis for both short-term and long-term efficacy.[18] Treatments plotted in the lower right hand have the combination of high efficacy and safety.

All the analyses were performed using statistical software R (R Development Core Team) and Just Another Gibbs Sampler (JAGS) (Martyn Plummer).

RESULTS

The systematic literature review helped identify 52 trials that met the inclusion/exclusion criteria for NMAs (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram is shown in Supplemental Fig 1). The evidence networks for the short-term safety outcomes (n = 52 trials; 16 treatments) and long-term safety outcomes (n = 7 trials; 6 treatments) are presented in Fig 1, *A* and *B*, respectively.[27-73] A list of the clinical trials included and details of the data extraction performed are summarized in Supplemental Table I.

Short-term NMA of any AE

A total of 47 trials that reported the rates of any AE were included in the network. The treatments associated with the lowest rates were tildrakizumab (46.0% [95% CrI: 39.2%, 52.9%] for 200 mg every 12 weeks (Q12W) and 46.3% [39.5%, 53.2%] for 100 mg Q12W); certolizumab (46.2% [37.0%, 55.5%] for 200 mg every 2 weeks (Q2W) and 52.2% [43.3%, 61.1%] for 400 mg Q2W); etanercept (49.1% [35.5%, 62.9%]); risankizumab (52.4% [47.3%, 57.4%]); and guselkumab (55.8% [50.9%, 60.3%]) (Table I).

Tildrakizumab (100 mg Q12W and 200 mg Q12W), certolizumab (200 mg Q2W), and risankizumab were all associated with statistically significantly lower odds of experiencing any AE compared to dimethyl fumarate, infliximab, apremilast, ixekizumab, secukinumab, and brodalumab. Etanercept was associated with statistically significantly lower odds of experiencing any AEs compared with dimethyl fumarate, infliximab, and apremilast (Supplemental Table II).

Short-term NMA of any SAE

A total of 51 trials that reported the percentages of patients experiencing any SAE were included in the network. The treatments associated with the lowest rates were certolizumab (200 mg Q2W; 0.8% [95% CrI: 0.2%, 3.0%]), risankizumab (1.2% [0.6%, 2.4%]), etanercept (1.6% [0.3%, 7.5%]), and dimethyl fumarate (1.8% [0.5%, 7.0%]) (Table I).

Certolizumab (200 mg Q2W) was associated with statistically significantly lower odds of SAEs compared with certolizumab (400 mg Q2W). No other statistically significant differences were found (Supplemental Table III).

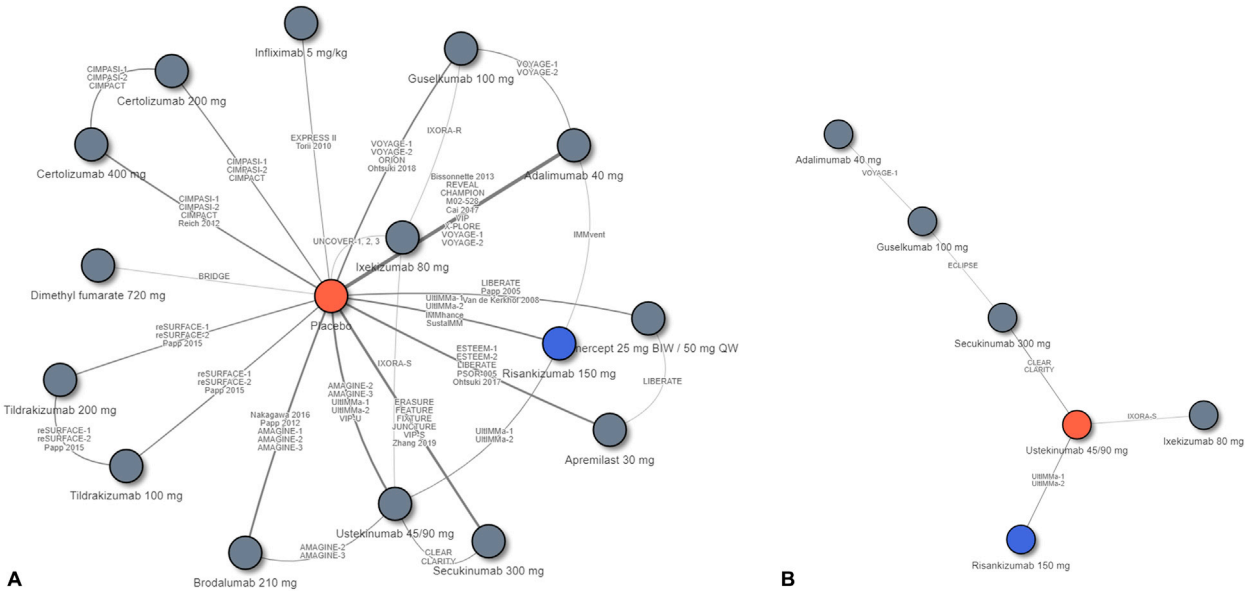

Fig 1. Evidence network for NMA of short- and long-term safety outcomes. **A**, Short-term NMAs. The reference citations for this NMA are as follows: Bissonnette 2013,[27] REVEAL,[28] CHAMPION,[29] M02-528,[12] Cai 2017,[30] VIP,[31] ESTEEM-1,[32] ESTEEM-2,[33] LIBERATE,[34] PSOR-005,[35] Ohtsuki 2017,[36] Nakagawa 2016,[37] Papp 2012,[38] AMAGINE-1,[39] AMAGINE-2,[40] AMAGINE-3,[40] CIMPASI-1,[41] CIMPACT,[42] Reich 2012,[43] BRIDGE,[44] Papp 2005,[45] Van de Kerkhof 2008,[46] X-PLORE,[47] VOYAGE-1,[48] VOYAGE-2,[49] ORION,[50] Ohtsuki 2018,[51] EXPRESS II,[11] Torii 2010,[52] UNCOVER-1, -2, -3,[53] IXORA-R,[54] IXORA-S,[55] UltIMMa-1,[56] UltIMMa-2,[56] IMMvent,[57] IMMhance,[58] SustalMM,[59] ERASURE,[60] FEATURE,[61] FIXTURE,[60] JUNCTURE,[62] CLEAR,[63] CLARITY,[64] VIP-S,[65] Zhang 2019,[66] reSURFACE-1,[67] reSURFACE-2,[67] Papp 2015,[68] and VIP-U.[69] **B**, Long-term NMAs. The reference citations for this NMA are as follows: VOYAGE-1,[48] ECLIPSE,[70] IXORA-S,[71] CLEAR,[72] CLARITY,[73] UltIMMa-1,* and UltIMMa-2.* *NMA*, network meta-analysis. * Data on file (AbbVie, 2018).

Short-term NMA of AEs leading to treatment discontinuation

A total of 45 trials that reported the rates of AEs leading to treatment discontinuation were included in the network. The estimated rates were the lowest for risankizumab (0.5% [95% CrI: 0.2%, 1.3%]), tildrakizumab at 100 mg Q12W (1.0% [0.2%, 4.4%]), guselkumab (1.5% [0.7%, 3.1%]), ustekinumab (1.6% [0.7%, 3.4%]), etanercept (1.7% [0.6%, 4.8%]), and adalimumab (1.7% [0.8%, 3.6%]) (Table I).

Risankizumab was associated with statistically significantly lower odds of AEs, leading to treatment discontinuation, compared with ustekinumab, adalimumab, secukinumab, placebo, brodalumab, apremilast, ixekizumab, certolizumab, and dimethyl fumarate (Supplemental Table IV).

The SUCRA scores for all 3 short-term safety outcomes showed a ranking consistent with that of the estimated rates (Supplemental Table V).

Long-term NMAs of any AE, any SAE, and AEs leading to treatment discontinuation

A total of 7 trials were included in the networks for any AE, any SAE, and AEs leading to treatment discontinuation in the long term. Risankizumab was associated with the lowest rates of any AE (67.5% [95% CrI: 57.8%, 75.6%]), any SAE (4.4% [2.4%, 8.1%]), and AEs leading to treatment discontinuation (1.0% [0.2%, 4.1%]) (Table I). Guselkumab was associated with the second lowest rates of any AE (72.2% [95% CrI: 63.7%, 79.5%]) and the third lowest rates of AEs leading to treatment discontinuation (2.5% [0.8%, 7.2%]).

Risankizumab was associated with significantly lower odds of any AE compared with ustekinumab and secukinumab. No other significant differences were found in the pairwise comparisons (Supplemental Tables VI to VIII).

The SUCRA scores showed a ranking consistent with the rates (Supplemental Table IX).

Benefit-risk assessment

The cross-tabulation of the estimated safety event rates and estimated PASI 90 rates obtained from a published efficacy meta-analysis for both the short and long terms are presented in Fig 2.[18]

In a comparison of any AE versus PASI 90 in the short term, risankizumab and guselkumab

Table I. Short- and long-term rates of any AE, any SAE, and AE leading to treatment discontinuation

	Short-term			Long-term		
Treatment	Any AE, posterior median (95% CrI)	Any SAE, posterior median (95% CrI)	AEs leading to treatment discontinuation, posterior median (95% CrI)	Any AE, posterior median (95% CrI)	Any SAE, posterior median (95% CrI)	AEs leading to treatment discontinuation, posterior median (95% CrI)
Certolizumab at 400 mg at weeks 0, 2, and 4, then 200 mg Q2W	46.2% (37.0%, 55.5%)	0.8% (0.2%, 3.0%)	4.1% (0.7%, 24.9%)	-	-	-
Risankizumab at 150 mg at weeks 0 and 4, then Q12W	52.4% (47.3%, 57.4%)	1.2% (0.6%, 2.4%)	0.5% (0.2%, 1.3%)	67.5% (57.8%, 75.6%)	4.4% (2.4%, 8.1%)	1.0% (0.2%, 4.1%)
Etanercept at 25 mg BIW or 50 mg QW	49.1% (35.5%, 62.9%)	1.6% (0.3%, 7.5%)	1.7% (0.6%, 4.8%)	-	-	-
Dimethyl fumarate uptitrated to a maximum daily dose of 720 mg	79.2% (69.7%, 86.1%)	1.8% (0.5%, 7.0%)	12.1% (4.8%, 30.2%)	-	-	-
Placebo	52.0% (50.7%, 53.3%)	1.9% (1.6%, 2.3%)	2.0% (1.6%, 2.4%)	-	-	-
Brodalumab at 210 mg at weeks 0, 1, and 2, then Q2W	59.9% (55.5%, 64.2%)	1.9% (0.9%, 4.1%)	2.2% (1.0%, 5.1%)	-	-	-
Apremilast at 30 mg BID after initial titration schedule	65.3% (60.2%, 70.2%)	2.0% (0.9%, 4.5%)	2.8% (1.5%, 5.2%)	-	-	-
Adalimumab at 80 mg at week 0, then 40 mg Q2W	55.8% (51.8%, 59.7%)	2.0% (1.1%, 3.7%)	1.7% (0.8%, 3.6%)	72.9% (61.4%, 82.0%)	5.4% (2.1%, 13.5%)	3.4% (0.8%, 12.7%)
Tildrakizumab at 100 mg at weeks 0, and 4, then Q12W	46.3% (39.5%, 53.2%)	2.1% (0.7%, 7.4%)	1.0% (0.2%, 4.4%)	-	-	-
Ustekinumab at 45 mg for ≤100 kg, 90 mg for >100 kg at weeks 0, and 4, then Q12W	57.8% (53.7%, 61.9%)	2.1% (1.1%, 3.9%)	1.6% (0.7%, 3.4%)	76.9% (74.5%, 79.2%)	5.7% (4.5%, 7.1%)	2.2% (1.5%, 3.2%)
Infliximab at 5 mg/kg at weeks 0, 2, and 6, then Q8W	68.3% (59.6%, 76.0%)	2.1% (0.6%, 7.1%)	3.7% (1.3%, 10.8%)	-	-	-
Guselkumab at 100 mg at weeks 0 and 4, then Q8W	55.8% (50.9%, 60.3%)	2.2% (1.1%, 4.6%)	1.5% (0.7%, 3.1%)	72.2% (63.7%, 79.5%)	5.9% (3.1%, 10.9%)	2.5% (0.8%, 7.2%)
Certolizumab at 400 mg Q2W	52.2% (43.3%, 61.1%)	2.6% (1.0%, 7.3%)	3.2% (0.7%, 15.0%)	-	-	-
Ixekizumab at 160 mg at week 0, then 80 mg Q2W	61.1% (56.1%, 65.6%)	2.7% (1.3%, 6.3%)	3.0% (1.4%, 6.5%)	80.9% (68.7%, 89.3%)	10.4% (3.8%, 27.0%)	4.4% (0.7%, 29.0%)
Secukinumab at 300 mg at weeks 0, 1, 2, 3, and 4, then Q4W	60.9% (56.8%, 65.0%)	2.7% (1.4%, 5.2%)	1.9% (0.9%, 4.0%)	76.6% (71.8%, 80.9%)	6.9% (4.4%, 10.6%)	3.2% (1.7%, 6.1%)
Tildrakizumab at 200 mg at weeks 0 and 4, then Q12W	46.0% (39.2%, 52.9%)	3.4% (1.2%, 11.0%)	2.3% (0.7%, 8.8%)	-	-	-

AE, Adverse event; *BID*, twice a day; *BIW*, twice a week; *CrI*, credible interval; *QW*, once every week; *Q2W*, once every 2 weeks; *Q4W*, once every 4 weeks; *Q8W*, once every 8 weeks; *Q12W*, once every 12 weeks; *SAE*, serious adverse event.

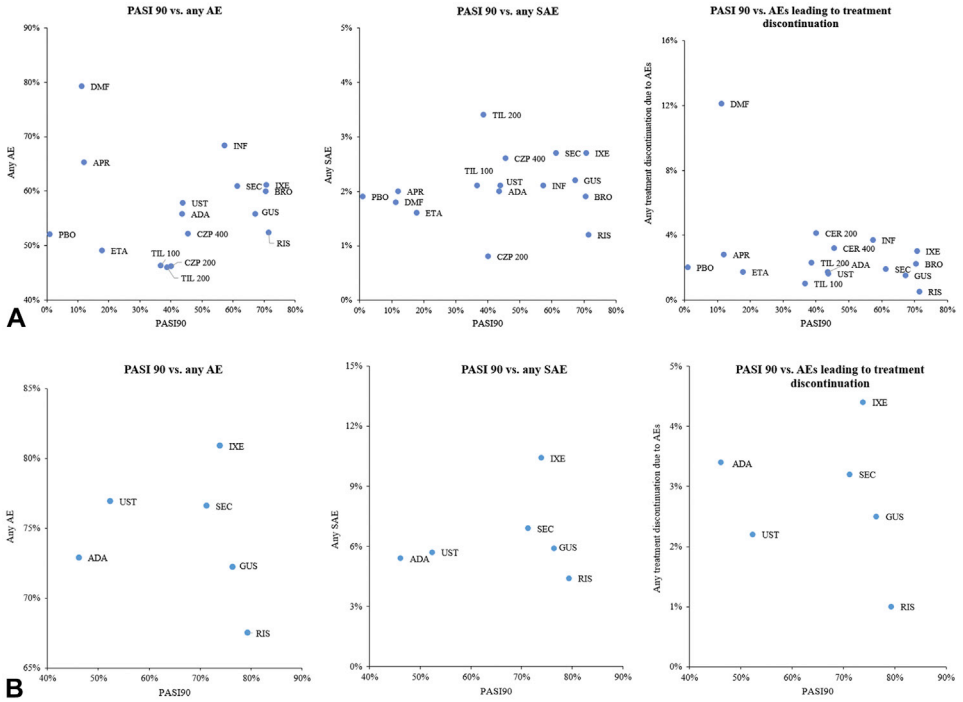

Fig 2. Benefit-risk assessment of safety rates and short- and long-term PASI 90 rates. **A**, Short-term PASI 90 versus safety outcomes. **B**, Long-term PASI 90 versus safety outcomes. Note that the scale of the Y-axes differs across safety outcomes. *ADA*, Adalimumab; *APR*, apremilast; *BRO*, brodalumab; *CZP*, certolizumab; *DMF*, dimethyl fumarate; *ETA*, etanercept; *GUS*, guselkumab; *INF*, infliximab; *IXE*, ixekizumab; *PASI 90*, Psoriasis Area and Severity Index 90; *PBO*, placebo; *RIS*, risankizumab; *SEC*, secukinumab; *TIL*, tildrakizumab; *UST*, ustekinumab.

(anti—IL-23 agents) had similarly low rates of any AE and similarly high rates of PASI 90. In comparison, certolizumab at 200 mg (anti-TNF agent), tildrakizumab at 100 mg (anti—IL-23 agent), and etanercept (anti-TNF agent) had higher safety but lower efficacy. Anti—IL-17 agents (brodalumab, secukinumab, and ixekizumab) had higher efficacy but lower safety relative to risankizumab and guselkumab.

In a comparison of any SAE versus PASI 90 in the short term, risankizumab had high efficacy and safety profiles. In comparison, certolizumab at 200 mg an (anti-TNF agent) had higher safety but lower efficacy. Brodalumab, secukinumab, and ixekizumab (anti—IL-17 agents) had higher efficacy but lower safety relative to risankizumab.

In a comparison of AEs leading to treatment discontinuation versus PASI 90 in the short term, risankizumab and guselkumab were associated with the most favorable benefit-risk profiles. In comparison, tildrakizumab at 100 mg (anti—IL-23 agent) had higher safety but lower efficacy. Brodalumab, secukinumab, and ixekizumab (anti—IL-17 agents) had higher efficacy but lower safety relative to risankizumab.

For the long-term outcomes, risankizumab consistently had the highest efficacy and safety across all the safety outcomes, followed by guselkumab. In comparison, secukinumab and ixekizumab (anti—IL-17 agents) had lower safety and higher efficacy, whereas adalimumab (anti-TNF agent) and ustekinumab (anti—IL-12/23 agent) had lower efficacy and safety than the anti—IL-23 agents.

DISCUSSION

The advent of immunomodulatory agents has brought about a paradigm shift in the treatment of psoriasis.[74,75] Long-term observational data have indicated a consistent and reassuring safety profile.[76] However, the management of AEs remains an important consideration for treatment-related decision making. A physician and patient preference study reported that "overall safety" and "low potential for AEs" in real-world use were the highest rated attributes for treatments of moderate and severe psoriasis.[77]

This study suggested that the anti—IL-23 agents (eg, guselkumab, risankizumab, and tildrakizumab) were associated with low rates of safety events in the short term, among which risankizumab and guselkumab also had favorable efficacy profiles. In the long term, risankizumab was associated with the most favorable benefit-risk profile compared with

the anti—IL-17 agents (ixekizumab and secukinumab), adalimumab, and ustekinumab.

A few prior studies have assessed the comparative safety profiles of treatments for psoriasis using NMA. An NMA by Lv et al[78] showed that anti—IL-17 agents caused significantly more all-cause AEs relative to a placebo. This was consistent with the findings of our NMA that showed that secukinumab, brodalumab, and ixekizumab had relatively high rates of any AE among the assessed treatments. In the short term, anti—IL-23 agents (guselkumab, risankizumab, and tildrakizumab) generally had lower rates of any AE compared with anti—IL-17 agents (brodalumab, secukinumab, and ixekizumab). This finding may be explained by the different mechanisms of action of anti—IL-17 versus anti—IL-23. IL-17 plays a role in host defense against bacterial, fungal, viral, and parasitic infections. In comparison, IL-23 is mainly involved in host protection against bacterial and parasitic infections.[79] A Cochrane library review suggested that no significant differences existed between any of the interventions (conventional agents, small molecules, and biologics) and placebo for any SAE, which is similar to the results of the present study.[22] An NMA conducted by the British Association of Dermatologists suggested that risankizumab had the best safety profile (measured based on drug withdrawal because of AEs) and the most favorable benefit-risk profile compared with other biologics in the short term, which aligns with the conclusion of the present study.[21] There is, however, little evidence for the comparisons of long-term safety outcomes in the literature.

The present study conducted a comprehensive assessment of the short- and long-term safety profiles among all therapies approved by FDA or EMA to date. NMA provides valuable evidence regarding the comparative safety profiles of competing treatments (that were not directly compared in randomized controlled trials) to enable informed decision making in conjunction with the established treatment guidelines. This study also integrated comparative safety with Armstrong et al.'s evaluation of comparative effectiveness using PASI 90[18] to assess the benefit-risk profile of licensed therapies for moderate-to-severe psoriasis.

The results of this study are subject to several limitations. First, because of the use of randomized controlled trial data, the results of NMAs may not be generalizable to the real-world patient population. Second, heterogeneity in the patient populations and in how the studies were conducted might have influenced the magnitude of the results. Third, the safety outcomes were evaluated in the primary response period according to the trial design, which varied across treatments and ranged from 12 to 16 weeks, and at the end of the maintenance period, which varied between 48 and 56 weeks. The majority of the trials reassigned the patients from placebo arms to active treatment arms after the primary response period, which led to a relative dearth of long-term safety data among patients using a treatment continuously. Fourth, comparisons of specific AEs, such as infections and malignancies, were not feasible using NMA and were, therefore, not included in the present study. Fifth, because of the limited data reported, the AE rates were used without further adjustment for the duration of treatment exposure. Sixth, different trials might have applied different methodologies for the collection, assessment, and analysis of AE, SAE, and AEs leading to treatment continuation,[80] which might have limited the comparability of the safety event rates across the studies. This limitation may have contributed to the differences in the safety event rates within the same drug class. Lastly, the NMAs were not adjusted for psoriasis-related comorbidities, such as psoriatic arthritis and metabolic syndromes.

CONCLUSIONS

This study provides an evidence-based and clinically relevant synthesis of the comparative safety and benefit-risk profiles of FDA- or EMA-approved therapies for moderate-to-severe psoriasis in the short and long terms. In the short term, anti—IL-23 agents (eg, guselkumab, risankizumab, and tildrakizumab) generally had the lowest rates of safety events, whereas risankizumab demonstrated the lowest rates of safety events in the long term. Risankizumab was also associated with the most favorable benefit-risk profile in the long term.

We would like to acknowledge Sophie Gao, MS, Zhaocheng Yi, BA, Xiaoran Yang, MPH, and Eugene Chen, BA, employees of Analysis Group, Inc, for their analytical support. Editorial assistance was provided by Shelley Batts, PhD, an employee of Analysis Group, Inc. Funding for this assistance was provided by AbbVie Inc. Those acknowledged here have nothing to declare other than employment. AbbVie participated in the interpretation of data, review, and approval of the manuscript.

Conflicts of interest

Dr Shear is a paid consultant for AbbVie, Amgen, Lilly, Leo, Bausch Health, Sun Pharma, Janssen, Galderma, Otsuka, UCB, Celgene, Sanofi Genzyme, Novartis, and Pfizer. Drs Joshi, Soliman, and Sinvhal are employees of AbbVie and may own AbbVie stock or stock options. Drs Betts, Wang, and Zhao are employees of Analysis Group, Inc, which received payment from AbbVie Inc for participation in this research. Dr Gisondi has served as a speaker or an advisory board member for AbbVie, Almirall, Amgen,

BMS, Celgene, Eli-Lilly, Janssen, Leo-pharma, Merck, MSD, Novartis, Pfizer, Sanofi, Sandoz, and UCB Pharma. Dr Armstrong has served as a research investigator or consultant to Leo, AbbVie, UCB, Janssen, Lilly, Novartis, Ortho Dermatologics, Sun, Dermavant, BMS, Sanofi, Regeneron, Dermira, and Modmed.

REFERENCES

1. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072.
2. Amin M, No DJ, Egeberg A, Wu JJ. Choosing first-line biologic treatment for moderate-to-severe psoriasis: what does the evidence say? *Am J Clin Dermatol*. 2018;19(1):1-13.
3. Haugh IM, Preston AK, Kivelevitch DN, Menter AM. Risankizumab: an anti-IL-23 antibody for the treatment of psoriasis. *Drug Des Devel Ther*. 2018;12:3879-3883.
4. AbbVie. European Commission approves SKYRIZI™ (risankizumab) for the treatment of moderate to severe plaque psoriasis 2019. Accessed April 1, 2020. Available at: https://news.abbvie.com/news/press-releases/european-commission-approves-skyrizi-risankizumab-for-treatment-moderate-to-severe-plaque-psoriasis.htm
5. Javor S, Drago F, Rebora A, Cozzani E, Parodi A. The prevalence of herpes zoster and pityriasis rosea in patients with psoriasis: a preliminary study. *J Eur Acad Dermatol Venereol*. 2016;30(2):382-383.
6. United States Food and Drug Administration. Highlights of prescribing information: SKYRIZI (risankizumab-rzaa) 2019. Accessed April 1, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761105s000lbl.pdf
7. Augustin M, Spehr C, Radtke MA, et al. German psoriasis registry PsoBest: objectives, methodology and baseline data. *J Dtsch Dermatol Ges*. 2014;12(1):48-57.
8. Papp KA, Strober B, Augustin M, et al. PSOLAR: design, utility, and preliminary results of a prospective, international, disease-based registry of patients with psoriasis who are receiving, or are candidates for, conventional systemic treatments or biologic agents. *J Drugs Dermatol*. 2012;11(10):1210-1217.
9. Iskandar IYK, Ashcroft DM, Warren RB, et al. Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *Br J Dermatol*. 2017;176(5):1297-1307.
10. Reich K, Mrowietz U, Radtke MA, et al. Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. *Arch Dermatol Res*. 2015;307(10):875-883.
11. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol*. 2007;56(1):31.e1-31.e15.
12. Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol*. 2006;55(4):598-606.
13. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371(9625):1675-1684.
14. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371(9625):1665-1674.
15. Lebwohl M, Leonardi C, Griffiths CE, et al. Long-term safety experience of ustekinumab in patients with moderate-to-severe psoriasis (part I of II): results from analyses of general safety parameters from pooled phase 2 and 3 clinical trials. *J Am Acad Dermatol*. 2012;66(5):731-741.
16. Blauvelt A, Lebwohl MG, Bissonnette R. IL-23/IL-17A dysfunction phenotypes inform possible clinical effects from anti-IL-17A therapies. *J Invest Dermatol*. 2015;135(8):1946-1953.
17. Hohenberger M, Cardwell LA, Oussedik E, Feldman SR. Interleukin-17 inhibition: role in psoriasis and inflammatory bowel disease. *J Dermatol Treat*. 2018;29(1):13-18.
18. Armstrong AW, Puig L, Joshi A, et al. Comparative efficacy of biologics and oral treatments for plaque psoriasis: a meta-analyses. *JAMA Dermatol*. 2020;156(3):258-269.
19. Signorovitch JE, Betts KA, Yan YS, et al. Comparative efficacy of biological treatments for moderate-to-severe psoriasis: a network meta-analysis adjusting for cross-trial differences in reference arm response. *Br J Dermatol*. 2015;172(2):504-512.
20. Armstrong AW, Betts KA, Signorovitch JE, et al. Number needed to treat and costs per responder among biologic treatments for moderate-to-severe psoriasis: a network meta-analysis. *Curr Med Res Opin*. 2018;34(7):1325-1333.
21. Smith CH, Yiu ZZ, Bale T, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update. *Br J Dermatol*. 2020;183(4):628-637.
22. Sbidian E, Chaimani A, Afach S, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev*. 2017;12(12):CD011535.
23. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 1: introduction to evidence synthesis for decision making. 2011. Accessed April 1, 2020. Available at: http://www.nicedsu.org.uk/TSD1%20Introduction.final.08.05.12.pdf
24. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials; 2014. Accessed April 21, 2021. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/A-general-linear-modelling-framework-for-pair-wise-and-network-meta-analysis-of-randomised-controlled-trials.pdf
25. Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU technical support document 3: heterogeneity: subgroups, meta-regression, bias, and bias-adjustment; 2011. Accessed April 21, 2021. Available at: https://www.ncbi.nlm.nih.gov/books/NBK395886/pdf/Bookshelf_NBK395886.pdf
26. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol*. 2011;64(2):163-171.
27. Bissonnette R, Tardif JC, Harel F, Pressacco J, Bolduc C, Guertin MC. Effects of the tumor necrosis factor-alpha antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. *Circ Cardiovasc Imaging*. 2013;6(1):83-90.
28. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58(1):106-115.
29. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol*. 2008;158(3):558-566.

30. Cai L, Gu J, Zheng J, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. *J Eur Acad Dermatol Venereol*. 2017;31(1):89-95.
31. Vascular inflammation in psoriasis trial. ClinicalTrials.gov identifier: NCT01553058. Accessed April 1, 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT01553058
32. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (efficacy and safety trial evaluating the effects of apremilast in psoriasis [ESTEEM] 1). *J Am Acad Dermatol*. 2015;73(1):37-49.
33. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *Br J Dermatol*. 2015;173(6):1387-1399.
34. Reich K, Gooderham M, Green L, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). *J Eur Acad Dermatol Venereol*. 2017;31(3):507-517.
35. Papp K, Cather JC, Rosoph L, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *Lancet*. 2012;380(9843):738-746.
36. Ohtsuki M, Okubo Y, Komine M, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: efficacy, safety and tolerability results from a phase 2b randomized controlled trial. *J Dermatol*. 2017;44(8):873-884.
37. Nakagawa H, Niiro H, Ootaki K, Japanese Brodalumab Study Group. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: efficacy and safety results from a phase II randomized controlled study. *J Dermatol Sci*. 2016;81(1):44-52.
38. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med*. 2012;366(13):1181-1189.
39. Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol*. 2016;175(2):273-286.
40. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med*. 2015;373(14):1318-1328.
41. Gottlieb AB, Blauvelt A, Thaci D, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: results through 48 weeks from 2 phase 3, multicenter, randomized, double-blinded, placebo-controlled studies (CIMPASI-1 and CIMPASI-2). *J Am Acad Dermatol*. 2018;79(2):302-314 e6.
42. Lebwohl M, Blauvelt A, Paul C, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: results through 48 weeks of a phase 3, multicenter, randomized, double-blind, etanercept- and placebo-controlled study (CIMPACT). *J Am Acad Dermatol*. 2018;79(2):266-276 e5.
43. Reich K, Ortonne JP, Gottlieb AB, et al. Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab' certolizumab pegol: results of a phase II randomized, placebo-controlled trial with a re-treatment extension. *Br J Dermatol*. 2012;167(1):180-190.
44. Mrowietz U, Szepietowski JC, Loewe R, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm((R)) - and placebo-controlled trial (BRIDGE). *Br J Dermatol*. 2017;176(3):615-623.
45. Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol*. 2005;152(6):1304-1312.
46. van de Kerkhof PC, Segaert S, Lahfa M, et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. *Br J Dermatol*. 2008;159(5):1177-1185.
47. Gordon KB, Duffin KC, Bissonnette R, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *N Engl J Med*. 2015;373(2):136-144.
48. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol*. 2017;76(3):405-417.
49. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017;76(3):418-431.
50. Ferris LK, Ott E, Jiang J, et al. Efficacy and safety of guselkumab, administered with a novel patient-controlled injector (One-Press), for moderate-to-severe psoriasis: results from the phase 3 ORION study. *J Dermatolog Treat*. 2020;31(2):152-159.
51. Ohtsuki M, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. *J Dermatol*. 2018;45(9):1053-1062.
52. Torii H, Nakagawa H, Japanese Infliximab Study Investigators. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. *J Dermatol Sci*. 2010;59(1):40-49.
53. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375(4):345-356.
54. Blauvelt A, Papp K, Gottlieb A, et al. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 12-week efficacy, safety and speed of response from a randomized, double-blinded trial. *Br J Dermatol*. 2019;182(6):1348-1358.
55. A study of ixekizumab (LY2439821) in participants with moderate-to-severe plaque psoriasis (OXPRA-S). ClinicalTrials.gov. NCT02561806. Accessed April 1, 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT02561806
56. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650-661.
57. Reich K, Gooderham M, Thaci D, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque

psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. *Lancet*. 2019;394(10198):576-586.
58. Blauvelt A, Leonardi C, Gooderham M, Papp K. Efficacy and safety of continuous q12w risankizumab versus treatment withdrawal: 2-year double-blinded results from the phase 3 IMMhance trial. Paper presented at: 24th World Congress of Dermatology; June 10-15, 2019; Milan, Italy.
59. Ohtsuki M, Fujita H, Watanabe M, et al. Efficacy and safety of risankizumab in Japanese patients with moderate to severe plaque psoriasis: results from the SustaIMM phase 2/3 trial. *J Dermatol*. 2019;46(8):686-694.
60. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med*. 2014;371(4):326-338.
61. Blauvelt A, Prinz JC, Gottlieb AB, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). *Br J Dermatol*. 2015;172(2):484-493.
62. Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). *J Eur Acad Dermatol Venereol*. 2015;29(6):1082-1090.
63. Thaci D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol*. 2015;73(3):400-409.
64. Bagel J, Nia J, Hashim PW, et al. Secukinumab is superior to ustekinumab in clearing skin in patients with moderate to severe plaque psoriasis (16-Week CLARITY results). *Dermatol Ther (Heidelb)*. 2018;8(4):571-579.
65. Gelfand JM, Shin DB, Duffin KC, et al. A randomized placebo controlled trial of secukinumab on aortic vascular inflammation in moderate to severe plaque psoriasis (VIP-S). *J Invest Dermatol*. 2020;140(9):1784-1793.
66. Zhang J, Gu H, Gu J, et al. Secukinumab 300 mg showed fast and high efficacy in Chinese moderate to severe plaque psoriasis patients. Paper presented at: American Academy of Dermatology (AAD) Meeting. Washington, District of Columbia; March 1, 2019.
67. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet*. 2017;390(10091):276-288.
68. Papp K, Thaci D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol*. 2015;173(4):930-939.
69. Gelfand JM, Shin DB, Alavi A, et al. A phase IV, randomized, double-blind, placebo-controlled crossover study of the effects of ustekinumab on vascular inflammation in psoriasis (the VIP-U Trial). *J Invest Dermatol*. 2020;140(1):85-93.e2.
70. Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet*. 2019;394(10201):831-839.
71. Paul C, Griffiths CEM, van de Kerkhof PCM, et al. Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: results from IXORA-S, a phase 3 study. *J Am Acad Dermatol*. 2019;80(1):70-79.e3.
72. Blauvelt A, Reich K, Tsai T-F, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1-year: results from the CLEAR study. *J Am Acad Dermatol*. 2017;76(1):60-69.e9.
73. Bagel J, Blauvelt A, Nia J, et al. Secukinumab maintains superiority over ustekinumab in clearing skin and improving quality of life in patients with moderate to severe plaque psoriasis: 52-week results from a double-blind phase 3b trial (CLARITY). *J Eur Acad Dermatol Venereol*. 2021;35(1):135-142.
74. Young M, Roebuck HL. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor: a novel treatment option for nurse practitioners treating patients with psoriatic disease. *J Am Assoc Nurse Pract*. 2016;28(12):683-695.
75. Kerdel F, Zaiac M. An evolution in switching therapy for psoriasis patients who fail to meet treatment goals. *Dermatol Ther*. 2015;28(6):390-403.
76. Carrascosa JM, Del-Alcazar E. New therapies versus first-generation biologic drugs in psoriasis: a review of adverse events and their management. *Expert Rev Clin Immunol*. 2018;14(4):259-273.
77. Alcusky M, Lee S, Lau G, et al. Dermatologist and patient preferences in choosing treatments for moderate to severe psoriasis. *Dermatol Ther (Heidelb)*. 2017;7(4):463-483.
78. Lv J, Zhou D, Wang Y, et al. Quantitative evaluation to efficacy and safety of therapies for psoriasis: a network meta-analysis. *Mol Pain*. 2018;14:1744806918762205.
79. Frieder J, Kivelevitch D, Haugh I, Watson I, Menter A. Anti-IL-23 and anti-IL-17 biologic agents for the treatment of immune-mediated inflammatory conditions. *Clin Pharmacol Ther*. 2018;103(1):88-101.
80. Phillips R, Hazell L, Sauzet O, Cornelius V. Analysis and reporting of adverse events in randomised controlled trials: a review. *BMJ Open*. 2019;9(2):e024537.