

Efficacy and Safety of Interleukin-23 P19 Inhibitors in Moderate-to-Severe Plaque Psoriasis: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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Abstract

Background: Interleukin-23 (IL-23) drives the Th17 pathway that sustains psoriatic inflammation. Three monoclonal antibodies that block its p19 subunit, guselkumab, risankizumab and tildrakizumab, have been approved for moderate-to-severe plaque psoriasis, but their pooled short-term benefit and safety against placebo needed a combined estimate.

Aim: To estimate the efficacy and safety of IL-23 p19 inhibitors compared with placebo in adults with moderate-to-severe plaque psoriasis.

Materials and Methods: PubMed was searched from inception to 31 December 2020 for placebo-controlled randomised trials of guselkumab 100 mg, risankizumab 150 mg or tildrakizumab 100 mg. Co-primary outcomes were an Investigator or Physician Global Assessment score of 0 or 1 (IGA/PGA 0/1) and a 90% improvement in the Psoriasis Area and Severity Index (PASI 90) at the end of the placebo-controlled period. Secondary outcomes were PASI 75, any adverse event, serious adverse events and discontinuation due to adverse events. Risk ratios (RR) were pooled with a random-effects model. Risk of bias was assessed with RoB 2 and certainty with GRADE.

Results: Ten publications reporting 12 trials (4015 patients in eligible arms) were included. At week 12 to 16, IGA/PGA 0/1 was reached by 78.3% of patients on an IL-23 inhibitor and 7.0% on placebo (11 trials; RR 10.86, 95% CI 8.84 to 13.33; $I^2 = 0\%$). PASI 90 was reached by 64.4% and 2.3% (RR 24.26, 95% CI 16.92 to 34.79; $I^2 = 0\%$), and PASI 75 by 79.7% and 6.6% (RR 11.81, 95% CI 9.40 to 14.85). The three drugs did not differ significantly. Rates of any adverse event (RR 0.94, 95% CI 0.87 to 1.02) and serious adverse events (RR 0.74, 95% CI 0.39 to 1.39) were similar to placebo, and discontinuation due to adverse events was less frequent (RR 0.23, 95% CI 0.09 to 0.61). The certainty of evidence was high for efficacy.

Conclusion: IL-23 p19 inhibitors bring about clear or almost clear skin in most patients with moderate-to-severe plaque psoriasis within 16 weeks, with a short-term safety profile similar to placebo.

Keywords: Biological Therapy; Guselkumab; Interleukin-23; Meta-Analysis; Psoriasis; Risankizumab; Tildrakizumab.

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Introduction

Psoriasis is a chronic immune-mediated inflammatory disease of the skin and joints. A global modelling study estimated its prevalence in adults at between 0.14% in East Asia and 1.99% in Australasia, with higher rates in high-income regions [1]. In India, hospital-based studies report a prevalence of 0.44% to 2.8%, and plaque psoriasis is the most common form [2]. The disease is lifelong and is associated with psoriatic arthritis, metabolic syndrome and cardiovascular disease [3]. Its effect on physical and mental functioning is comparable to that of cancer, heart disease and diabetes [4]. Advances in immunology have

changed the treatment of psoriasis. Interleukin-23 (IL-23), produced by dendritic cells, maintains the Th17 cells that release IL-17 and IL-22 and drive keratinocyte proliferation [5]. IL-23 is a heterodimer of a p40 subunit, which it shares with IL-12, and a p19 subunit unique to IL-23. Ustekinumab blocks p40 and so inhibits both cytokines. The newer agents guselkumab, risankizumab and tildrakizumab bind p19 and block IL-23 alone, which leaves IL-12-mediated immunity intact [5,6]. Their long dosing intervals, every 8 to 12 weeks after induction, are a practical advantage.

Treatment goals have also become stricter. A 75% improvement in the Psoriasis Area and Severity Index (PASI 75) was the traditional benchmark, but PASI 90 is now regarded as the new standard for effective therapy [7]. Current guidelines recommend biologic agents for patients with moderate-to-severe disease [8]. Network meta-analyses have ranked IL-23 and IL-17 inhibitors among the most effective systemic treatments [9,10], but they combine many drug classes and do not report a direct pooled estimate for p19 inhibitors as a group against placebo. We therefore carried out a systematic review and meta-analysis of placebo-controlled randomised trials to estimate the efficacy and safety of IL-23 p19 inhibitors, at their approved doses, in moderate-to-severe plaque psoriasis.

Materials and Methods

Protocol and Reporting: This review followed the PRISMA statement [11]. It used only published data, so ethics committee approval was not required. The protocol was not registered.

Search Strategy: PubMed/MEDLINE was searched from inception to 31 December 2020 with the string: (guselkumab OR CNTO1959 OR risankizumab OR BI 655066 OR ABBV-066 OR tildrakizumab OR MK-3222 OR SCH 900222) AND psoriasis AND (randomised OR placebo). No language filter was applied. The reference lists of the included trials and of earlier network meta-analyses were checked by hand.

Eligibility Criteria: Trials were included if they (a) were randomised controlled trials; (b) enrolled adults with moderate-to-severe chronic plaque psoriasis; (c) compared guselkumab 100 mg, risankizumab 150 mg or tildrakizumab 100 mg, the approved doses, with placebo; and (d) reported IGA/PGA response, PASI response or adverse events at the end of the placebo-controlled period. Trials without a placebo arm, phase 1 single-dose studies, trials in psoriatic arthritis or palmoplantar pustulosis, and secondary, pooled or post hoc analyses were excluded. Only the arms at the approved dose and the placebo arm were used from multi-arm trials. To keep within the review period, a report whose final version was published after 2020 was excluded.

Outcomes: The co-primary outcomes were the proportion of patients with an Investigator or Physician Global Assessment score of 0 or 1 (clear or almost clear; IGA/PGA 0/1) and the proportion with PASI 90 at the primary end point of each trial (week 16 for guselkumab and risankizumab, and week 12 for the phase 3 tildrakizumab trials). Secondary outcomes were PASI 75, any adverse

event, serious adverse events and discontinuation due to adverse events during the placebo-controlled period.

Data Extraction and Risk of Bias: Data were extracted on a predesigned form and checked against the source on a second occasion. The items extracted were drug, dose, phase, setting, number randomised, time point and the number of events in each arm. Non-responder imputation results, as reported by the trials, were used. When only percentages were reported, event counts were back-calculated from the percentage and the number randomised. When safety tables were not in the abstract, they were taken from the open-access full text or from regulatory and published secondary sources that reproduced the trial tables. Risk of bias was assessed with the Cochrane RoB 2 tool across five domains: the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [12].

Statistical Analysis: Risk ratios (RR) with 95% confidence intervals (CI) were pooled with the DerSimonian and Laird random-effects model [13]. Heterogeneity was assessed with the χ^2 test (significant at $p < 0.10$) and quantified with the I^2 statistic [14]. For trials with no events in one arm, 0.5 was added to each cell [15]. Subgroups were defined by drug and compared with a test of interaction. Sensitivity analyses used the Mantel-Haenszel fixed-effect model, excluded the two phase 2 dose-ranging trials, excluded trials with zero events in an arm, and removed each trial in turn. Publication bias was assessed with funnel plot asymmetry and Egger's test when ten or more trials contributed [16]. The certainty of evidence was rated with GRADE [17]. Analyses were performed in Python 3 with the NumPy and SciPy libraries, using the same formulas as Review Manager. A p value below 0.05 was regarded as statistically significant.

Results

Study Selection: The search identified 132 records (Figure 1). After title and abstract screening, 110 were excluded, mostly reviews, meta-analyses, secondary or pooled analyses of the same trials, trials in psoriatic arthritis or palmoplantar pustulosis, and pharmacokinetic studies. Twenty-two full-text articles were assessed. Twelve were excluded: seven had no placebo arm (head-to-head or switching trials) [18-20], four were phase 1 single-dose studies, and one Korean trial was excluded because its final version was published in 2022. Ten publications reporting 12 randomised trials were included [21-30].

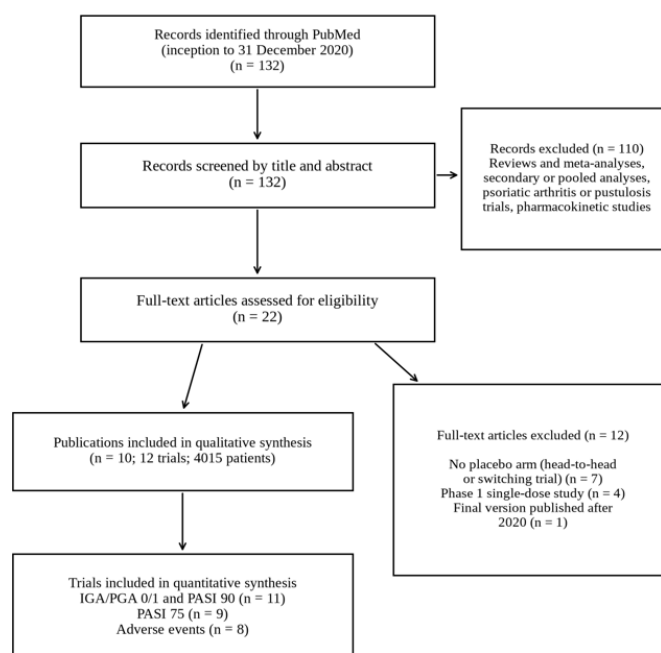


Figure 1: Flow diagram of study identification, screening and inclusion

The diagram follows the PRISMA statement. IGA/PGA: Investigator or Physician Global Assessment; PASI: Psoriasis Area and Severity Index.

Characteristics of Included Trials: The 12 trials randomised 4015 patients to an approved dose of an IL-23 p19 inhibitor (2757 patients) or to placebo (1258 patients) (Table 1). Five trials tested guselkumab [21-25], four tested risankizumab [26-28] and three tested tildrakizumab [29,30]. Nine were phase 3 trials, one was a combined phase 2/3 trial [28] and two were phase 2 dose-ranging trials [21,30].

Two trials were done in Japan [24,28], and the rest were multinational or North American. Six trials also included an active comparator arm (adalimumab, ustekinumab or etanercept), which was not used in this review [21-23,26,29].

All trials were double-blind and enrolled adults with a PASI of at least 12 and a body surface area involvement of at least 10%.

Table 1: Characteristics of the included randomised controlled trials

Trial	Drug and dose	Setting	Phase	IL-23i / placebo (n)	Week	Outcomes used
X-PLORE 2015 [21]	Guselkumab 100 mg, weeks 0, 8, then every 8 weeks	North America, Europe	2	42 / 42	16	PGA, PASI 75, PASI 90
VOYAGE 1 2017 [22]	Guselkumab 100 mg, weeks 0, 4, then every 8 weeks	Multinational	3	329 / 174	16	IGA, PASI 75, PASI 90, AE
VOYAGE 2 2017 [23]	Guselkumab 100 mg, weeks 0, 4, then every 8 weeks	Multinational	3	496 / 248	16	IGA, PASI 75, PASI 90
Ohtsuki 2018 [24]	Guselkumab 100 mg, weeks 0, 4, then every 8 weeks	Japan	3	63 / 64	16	IGA, PASI 75, PASI 90, AE
ORION 2020 [25]	Guselkumab 100 mg by One-Press injector	Multicentre	3	62 / 16	16	IGA, PASI 90
UltiMMa-1 2018 [26]	Risankizumab 150 mg, weeks 0, 4, then every 12 weeks	Multinational	3	304 / 102	16	sPGA, PASI 90, AE
UltiMMa-2	Risankizumab 150 mg,	Multinational	3	294 / 98	16	sPGA, PASI

2018 [26]	weeks 0, 4, then every 12 weeks					90, AE
IMMhance 2020 [27]	Risankizumab 150 mg, weeks 0, 4, then every 12 weeks	Multinational	3	407 / 100	16	sPGA, PASI 75, PASI 90, AE
SustaIMM 2019 [28]	Risankizumab 150 mg, weeks 0, 4, then every 12 weeks	Japan	2/3	55 / 58	16	sPGA, PASI 75, PASI 90, AE
reSURFACE 1 2017 [29]	Tildrakizumab 100 mg, weeks 0, 4, then every 12 weeks	Multinational	3	309 / 155	12	PGA, PASI 75, PASI 90, AE
reSURFACE 2 2017 [29]	Tildrakizumab 100 mg, weeks 0, 4, then every 12 weeks	Multinational	3	307 / 156	12	PGA, PASI 75, PASI 90, AE
Papp 2015 [30]	Tildrakizumab 100 mg, weeks 0, 4, then every 12 weeks	Multinational	2b	89 / 45	16	PASI 75

Only the approved-dose and placebo arms are shown. AE: adverse events; IGA: Investigator Global Assessment; IL-23i: interleukin-23 p19 inhibitor; PASI 75/90: 75% or 90% improvement in Psoriasis Area and Severity Index; PGA: Physician Global Assessment; sPGA: static PGA.

Risk of Bias: All trials were double-blind and analysed patients by intention to treat with non-responder imputation. Ten trials were judged at low overall risk of bias (Table 2). The two phase 2 dose-ranging trials were judged to have some

concerns about selection of the reported result, because only some outcomes were reported as event counts for the approved-dose arm [21,30]. All trials were funded by the manufacturer.

Table 2: Risk of bias in the included trials (Cochrane RoB 2 tool)

Trial	Randomisation	Deviations	Missing data	Measurement	Reporting	Overall
X-PLORE 2015	Low	Low	Low	Low	Some concerns	Some concerns
VOYAGE 1 2017	Low	Low	Low	Low	Low	Low
VOYAGE 2 2017	Low	Low	Low	Low	Low	Low
Ohtsuki 2018	Low	Low	Low	Low	Low	Low
ORION 2020	Low	Low	Low	Low	Low	Low
UltIMMa-1 2018	Low	Low	Low	Low	Low	Low
UltIMMa-2 2018	Low	Low	Low	Low	Low	Low
IMMhance 2020	Low	Low	Low	Low	Low	Low
SustaIMM 2019	Low	Low	Low	Low	Low	Low
reSURFACE 1 2017	Low	Low	Low	Low	Low	Low
reSURFACE 2 2017	Low	Low	Low	Low	Low	Low
Papp 2015	Low	Low	Low	Low	Some concerns	Some concerns

Deviations: deviations from intended interventions; Measurement: measurement of the outcome; Reporting: selection of the reported result.

IGA/PGA score of 0 or 1: Eleven trials with 3880 patients reported the proportion of patients who were clear or almost clear. This was achieved by 2090 of 2668 patients (78.3%) on an IL-23 p19 inhibitor and 85 of 1212 (7.0%) on placebo (RR

10.86, 95% CI 8.84 to 13.33; $p < 0.001$) (Figure 2). There was no heterogeneity ($I^2 = 0\%$; $p = 0.98$). Each trial individually favoured the IL-23 inhibitor. The RR was 11.02 (95% CI 8.21 to 14.77) for guselkumab, 11.61 (8.02 to 16.81) for

risankizumab and 9.49 (6.03 to 14.92) for tildrakizumab, with no significant difference

between drugs ($p = 0.79$).

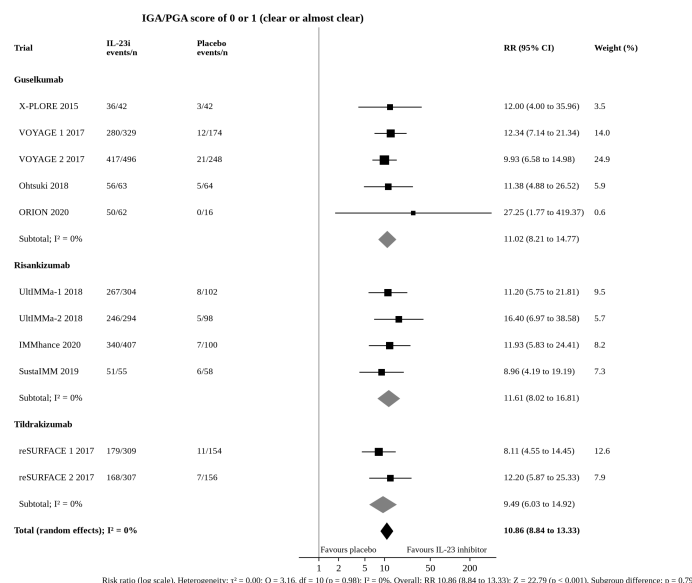


Figure 2: Forest plot of the proportion of patients with an IGA or PGA score of 0 or 1 with IL-23 p19 inhibitors compared with placebo, by drug

Squares show trial estimates, sized by random-effects weight; horizontal lines show 95% confidence intervals; grey diamonds show subgroup estimates and the black diamond the overall estimate. A continuity correction of 0.5 was used for ORION 2020. IGA/PGA: Investigator or Physician Global Assessment; IL-23i: interleukin-23 p19 inhibitor; RR: risk ratio.

PASI 90 and PASI 75: PASI 90 was reported by the same 11 trials. It was achieved by 1719 of 2668 patients (64.4%) on an IL-23 inhibitor and 28 of

1212 (2.3%) on placebo (RR 24.26, 95% CI 16.92 to 34.79; $p < 0.001$; $I^2 = 0\%$) (Figure 3).

The RR was 28.39 for guselkumab, 23.97 for risankizumab and 17.52 for tildrakizumab (p for subgroup difference = 0.62). In crude terms, PASI 90 was reached by 71.1% of patients on guselkumab and 74.3% on risankizumab at week 16, and by 36.7% on tildrakizumab at week 12. PASI 75, reported by nine trials with 3138 patients, was achieved by 79.7% of patients on an IL-23 inhibitor and 6.6% on placebo (RR 11.81, 95% CI 9.40 to 14.85; $I^2 = 0\%$).

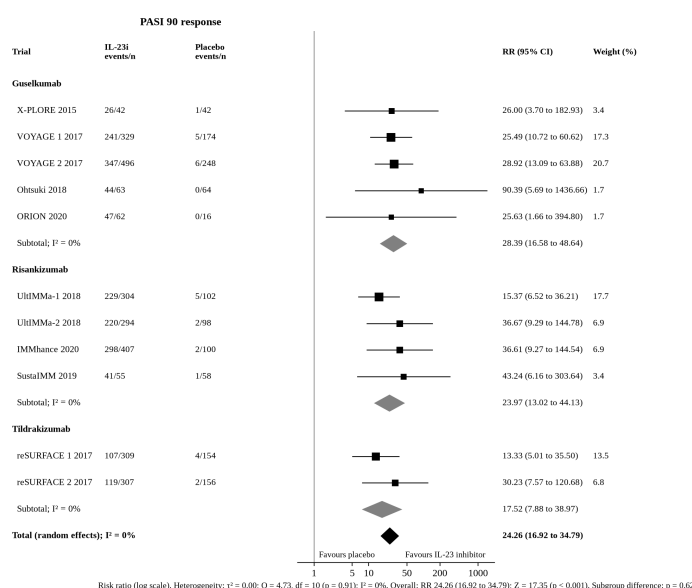


Figure 3: Forest plot of PASI 90 response with IL-23 p19 inhibitors compared with placebo, by drug

A continuity correction of 0.5 was used for trials with no placebo responders (Ohtsuki 2018 and ORION 2020). IL-23i: interleukin-23 p19 inhibitor; PASI 90: 90% improvement in Psoriasis Area and Severity Index; RR: risk ratio.

Sensitivity Analyses and Publication Bias: The results were robust. With the Mantel-Haenszel fixed-effect model, the RR was 11.24 (95% CI 9.12 to 13.85) for IGA/PGA 0/1 and 26.80 (18.57 to 38.67) for PASI 90. Excluding the two phase 2 trials gave RRs of 10.82 and 24.21, and excluding trials with zero events in an arm gave 10.80 and 23.69. Removing each trial in turn gave RRs from 10.59 to 11.32 for IGA/PGA 0/1 and from 23.18 to 26.76 for PASI 90. Egger's test did not show significant small-study effects for IGA/PGA 0/1 ($p = 0.08$) or PASI 90 ($p = 0.10$), although the number of trials was too small for a firm conclusion.

Safety: Eight trials with 2974 patients reported adverse events in both arms (Figure 4). Any adverse event occurred in 983 of 2068 patients (47.5%) on an IL-23 inhibitor and 461 of 906 (50.9%) on placebo (RR 0.94, 95% CI 0.87 to 1.02; $p = 0.16$; $I^2 = 0\%$). Serious adverse events occurred in 41 patients (2.0%) and 23 patients (2.5%), respectively (RR 0.74, 95% CI 0.39 to 1.39; $p = 0.35$; $I^2 = 23\%$).

In five trials, treatment was stopped because of an adverse event by 6 of 1141 patients (0.5%) on an IL-23 inhibitor and 17 of 532 (3.2%) on placebo (RR 0.23, 95% CI 0.09 to 0.61; $p = 0.003$). The most common adverse events were nasopharyngitis, upper respiratory tract infection and headache [22,26,29]. Serious infections were rare, and no new safety signals emerged in the placebo-controlled period [24,26,27].

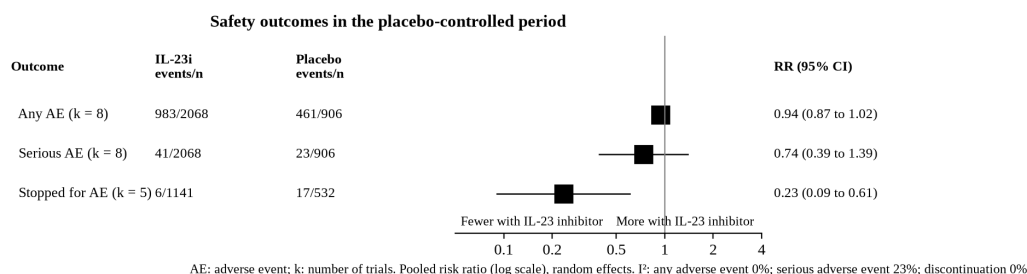


Figure 4: Pooled risk ratios for adverse events during the placebo-controlled period with IL-23 p19 inhibitors compared with placebo

Diamonds show pooled random-effects estimates; horizontal lines show 95% confidence intervals. AE: adverse event; IL-23i: interleukin-23 p19 inhibitor; k: number of trials; RR: risk ratio.

Certainty of Evidence: The certainty of evidence was rated high for IGA/PGA 0/1, PASI 90 and PASI 75, because the trials were large, at low risk

of bias and consistent, and the effects were very large (Table 3).

It was moderate for any adverse event, because four trials did not provide arm-level safety data, and low for serious adverse events and discontinuation, because of few events and wide confidence intervals.

Table 3: Summary of findings and certainty of evidence (GRADE)

Outcome	Trials (patients)	Placebo vs IL-23i	RR (95% CI)	Certainty	Comment
IGA/PGA 0/1, week 12 to 16	11 (3880)	7.0% vs 78.3%	10.86 (8.84 to 13.33)	High	Consistent, $I^2 = 0\%$
PASI 90, week 12 to 16	11 (3880)	2.3% vs 64.4%	24.26 (16.92 to 34.79)	High	Consistent, $I^2 = 0\%$
PASI 75, week 12 to 16	9 (3138)	6.6% vs 79.7%	11.81 (9.40 to 14.85)	High	Consistent, $I^2 = 0\%$
Any adverse event	8 (2974)	50.9% vs 47.5%	0.94 (0.87 to 1.02)	Moderate	Data missing from four trials
Serious adverse event	8 (2974)	2.5% vs 2.0%	0.74 (0.39 to 1.39)	Low	Imprecision; few events
Discontinuation due to adverse event	5 (1673)	3.2% vs 0.5%	0.23 (0.09 to 0.61)	Low	Imprecision; few events

CI: confidence interval; IGA/PGA: Investigator or Physician Global Assessment; IL-23i: interleukin-23 p19 inhibitor; PASI: Psoriasis Area and Severity Index; RR: risk ratio.

Discussion

This meta-analysis of 12 placebo-controlled randomised trials found that IL-23 p19 inhibitors, at their approved doses, are highly effective in moderate-to-severe plaque psoriasis. About four in five patients were clear or almost clear at week 12 to 16, compared with fewer than one in ten on placebo.

Almost two in three patients reached PASI 90, a level of response that was rare with placebo. The effect was consistent across trials, drugs and populations, with no detectable heterogeneity. Short-term safety was similar to placebo, and fewer patients stopped treatment because of adverse events.

Our findings agree with network meta-analyses that ranked risankizumab and guselkumab among the most effective systemic agents for achieving PASI 90 [9,10]. Pooling only placebo-controlled data, by drug class and at approved doses, gives an estimate that is easy to apply in clinical practice and in discussions with patients. The very low placebo response, with PASI 90 in only 2.3% of patients, also shows how unlikely moderate-to-severe psoriasis is to clear without effective systemic therapy.

The relative effects of the three drugs did not differ, but the absolute response rates did. Crude PASI 90 rates were about 71% to 74% with guselkumab and risankizumab and about 37% with tildrakizumab. Part of this gap reflects the earlier primary end point of week 12 in the tildrakizumab phase 3 trials, because responses to tildrakizumab continued to rise up to week 28 [29].

Head-to-head trials, which were outside the scope of this review, have shown that risankizumab was more effective than ustekinumab and adalimumab [18,19,26], and that guselkumab was more effective than adalimumab in the short term and then secukinumab at week 48 [20,22,23]. Direct comparisons between p19 inhibitors were not available up to 2020.

The safety profile is relevant for Indian practice, where tuberculosis is common. By blocking IL-23 alone and sparing IL-12, p19 inhibitors may carry a lower risk of serious infection than older biologics [5,6]. In the included trials, serious infections were rare and no excess of serious adverse events was seen. The lower rate of discontinuation with IL-23 inhibitors probably reflects psoriasis flares and lack of efficacy in the placebo arms. The dosing schedule, every 8 weeks for guselkumab and every 12 weeks for risankizumab and tildrakizumab, may improve adherence and reduce clinic visits, although cost remains a major barrier for many Indian patients [2,8].

Strengths and Limitations: This review included only double-blind, placebo-controlled randomised trials, used only approved doses, assessed bias with RoB 2 and rated certainty with GRADE. It has limitations. Only PubMed was searched, and the review was limited to reports published up to 2020. All trials were funded by the manufacturers. The placebo-controlled period lasted only 12 to 16 weeks, so long-term efficacy and rare harms such as malignancy or major cardiovascular events could not be assessed. Some event counts were back-calculated from reported percentages, and safety data could not be obtained for four trials. Very few patients from South Asia were enrolled, so the results may not fully apply to Indian patients.

Conclusion

IL-23 p19 inhibitors (guselkumab, risankizumab and tildrakizumab) make clear or almost clear skin about eleven times more likely and PASI 90 about twenty-four times more likely than placebo within 16 weeks in moderate-to-severe plaque psoriasis, with short-term safety similar to placebo. The certainty of evidence for efficacy is high. Long-term comparative trials and studies in Indian patients, including those with latent tuberculosis, are needed.

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