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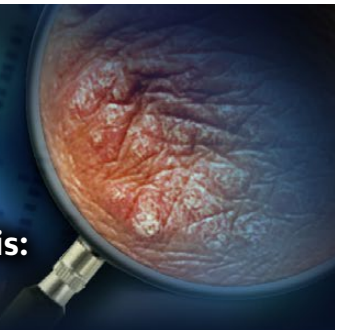
STUDY REVIEW

Ixekizumab vs guselkumab for moderate-to-severe plaque psoriasis: 24-week efficacy and safety results from the IXORA-R trial



Making Education Easy 2021

Independent commentary by Dr Diana Rubel

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Abbreviations used in this review:

AE = adverse event; **BSA** = body surface area; **CI** = confidence interval; **DLQI** = Dermatology Life Quality Index; **IBD** = inflammatory bowel disease; **IL** = interleukin; **sPGA** = static Physician's Global Assessment of Disease; **PASI** = Psoriasis Area and Severity Index.

This review summarises 24-week efficacy and safety data from the IXORA-R head-to-head randomised, double-blinded trial comparing ixekizumab, an IL-17A inhibitor, and guselkumab, an IL-23p19 inhibitor, in adult patients with moderate-to-severe plaque psoriasis.[1] The study was published in the British Journal of Dermatology and demonstrated that ixekizumab cleared skin and nail lesions more rapidly, with a greater cumulative benefit than guselkumab. There were no new safety findings with ixekizumab. Both ixekizumab and guselkumab are approved and funded for use in Australia for adult patients aged ≥18 years with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[2-5]

Introduction

Biologic therapies such as ixekizumab and guselkumab have fulfilled long unmet clinical needs in patients with moderate-to-severe plaque psoriasis.[6,7] Interim analysis of data from the IXORA-R head-to-head trial has shown that after 12 weeks of treatment, ixekizumab provides more rapid achievement of fully clear skin than guselkumab.[8] In addition, more rapid relief of itch and skin pain was also achieved by ixekizumab recipients.[8] In the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey, undertaken in North America and Europe and involving over 3000 patients, 43% reported itching as their most bothersome symptom.[9]

Coexisting nail psoriasis, with pitting, onycholysis, subungual hyperkeratosis, splinter haemorrhages and/or dystrophy, is observed in 25% of psoriasis patients.[10] This is of more than cosmetic concern, as nail psoriasis can be both painful and physically impairing.[10,11] Furthermore, approximately 80% of psoriatic arthritis patients exhibit nail psoriasis.[12] Unfortunately, nails are often more difficult to treat than skin, because of their structure and rate of growth, and they take longer to respond.[10,13] When total skin clearance is the goal, this should include all psoriasis types and conditions, as visible residual psoriasis may negatively impact quality of life.[14]

This analysis of data from IXORA-R includes both 24-week skin and nail clinical outcomes and patient-reported outcomes and safety results.[1] Additional efficacy and safety data from the 12-week report are also included, along with analyses examining full cumulative results.[1]

Methods

The 24-week, multicentre, randomised, double-blinded, parallel-group, phase IV IXORA-R study (NCT03573323) was conducted between 9 November 2018 and 8 January 2020 and had a primary endpoint at 12 weeks.[1] All patients gave informed consent. IXORA-R was conducted according to the International Conference on Harmonisation Good Clinical Practice guidelines and Declaration of Helsinki, and was approved by local ethical review boards.

Eligible chronic plaque psoriasis patients were ≥18 years old with an sPGA score of ≥3 (moderate), a PASI score of ≥12, and ≥10% BSA involvement; 20% of patients were from Canada and 80% were from the US.[1] Patients with prior use of IL-23p19 antagonists or any conditions or contraindications specified in local labelling for guselkumab were excluded. Prior biologics were permitted if the biologic was not administered within a specified period prior to baseline. Prior use of another IL-17 antagonist was permitted if there had been a response to therapy. For full inclusion and exclusion criteria see the initial 12-week publication.[8]

Patients were randomly assigned 1:1 to subcutaneous ixekizumab (n = 520) or guselkumab (n = 507).[1,8] Ixekizumab recipients received a 160 mg starting dose at week 0 (2 x 80-mg injections), then 80 mg every 2 weeks from weeks 2 to 12 and every 4 weeks from weeks 12 to 24. Guselkumab recipients received 100 mg injections at weeks 0, 4, 12 and 20; in order to maintain blinding, guselkumab recipients received one placebo injection at weeks 0, 2, 6, 8, 10 and 16. Study visits occurred at screening and weeks 0 (baseline), 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24.

The primary efficacy endpoint (PASI 100 at week 12) and seven of eight major secondary endpoints were met.[8] The eighth major secondary endpoint, PASI 100 superiority of ixekizumab at week 24, is reported in this paper. Sample size was estimated to have 98% power for superiority of ixekizumab over guselkumab for PASI 100 at week 12 using a two-sided 5% type I error rate.[8] Efficacy analyses included all randomised patients according to the treatment assigned (intent-to-treat population).[1] Safety data used the safety population (all patients who received at least one dose).

Statistical comparisons used the Cochran-Mantel-Haenszel test stratified by pooled site.[1] Missing binary data were imputed as non-responders, while missing continuous measures were imputed using the modified baseline-observation-carried-forward method. To control the overall family-wise type I error rate at a two-sided alpha level of 0.05, a multiple-testing strategy was implemented for primary and major secondary endpoints. A prespecified noninferiority test of ixekizumab versus guselkumab for PASI 100 at week 24 was calculated using a prespecified noninferiority margin of -11.4%. There was no adjustment for multiple comparisons with exploratory and *post hoc* analyses. Cerebrocardiovascular AEs and suspected IBD were adjudicated by an external clinical event committee.[8]

Expert comment

In previously published results, a head-to-head study between ixekizumab and guselkumab confirmed the efficacy of both biologic agents in adults with moderate-to-severe chronic plaque psoriasis, over the initial 12-week induction phase of therapy.[8] Ixekizumab achieved clearance more rapidly than guselkumab, with rapid reduction of itch and pain – symptoms which we often forget to ask our patients about, but are an issue for almost half of psoriatic patients. The corollary to this study, analysis of the 12-24 week data comparing ixekizumab to guselkumab in the same cohort of patients, investigated the frequency of PASI 100 achievement in both groups at week 24, response of nail changes and psoriatic arthritis symptoms to therapy, and the safety and tolerability profile of both therapies.

Results

Overall, 1027 patients were randomised, of whom 465 of 520 (89%) ixekizumab recipients and 459 of 507 (91%) guselkumab recipients completed the 24-week trial (**Figure 1**).[1] Baseline characteristics were described in the initial 12-week report.[8]

Clinical outcomes

Ixekizumab was superior to guselkumab in the primary outcome, PASI 100 at week 12, and the 7 other major secondary outcomes as reported in the interim 12-week study report.[8] Full results are presented in **Figure 2**.[1] Significantly more ixekizumab than guselkumab recipients achieved a PASI 100 and an sPGA score of 0 during weeks 2 to 16 ($p < 0.01$; **Figure 2a,b**) and more patients receiving ixekizumab achieved PASI 90 at week 2 (5.2% vs 0.6%; $p < 0.001$) and PASI 75 at week 1 (4.8% vs 1.0%; $p < 0.001$). This difference remained statistically significant to week 12 for PASI 90 ($p < 0.001$; **Figure 2c**) and week 10 for PASI 75 ($p < 0.01$; **Figure 2d**). More patients achieved PASI 50 with ixekizumab than with guselkumab at weeks 1 to 6 **(Figure 2e; p** < 0.01).

The eighth major secondary outcome for IXORA-R, superiority of ixekizumab versus guselkumab for patients achieving PASI 100 at week 24, was not achieved (50% vs 52%; $p = 0.41$ (**Figure 2a**).[1] However, ixekizumab was noninferior to guselkumab at week 24 (difference -2.3%; 95% CI -8.4 to 3.8) within the prespecified noninferiority margin of -11.4%.

Fingernail psoriasis was evaluated using the PGA of Fingernail psoriasis (PGA-F) at baseline and week 24 to allow for nail regrowth in most patients.[13] At baseline, 83 (16%) ixekizumab and 59 (12%) guselkumab recipients had moderate-to-severe nail psoriasis (PGA-F ≥3).[1] At week 24, more ixekizumab than guselkumab recipients achieved clear or minimal (PGA-F 0/1 with ≥2-point improvement) nail psoriasis (75% vs 54%; $p = 0.020$; **Figure 3**) or complete clearance (PGA-F 0; 52% vs 31%; $p = 0.007$; **Figure 3**). As the number of patients who had PGA-F scores ≥3 at baseline was imbalanced, an additional *post hoc* analysis was conducted including any patient who had nail psoriasis at baseline (PGA-F >0; ixekizumab n = 264; guselkumab n = 239). In this analysis, more ixekizumab than guselkumab recipients achieved complete clearance (63% vs 44%; $p < 0.001$ (**Figure 3**).

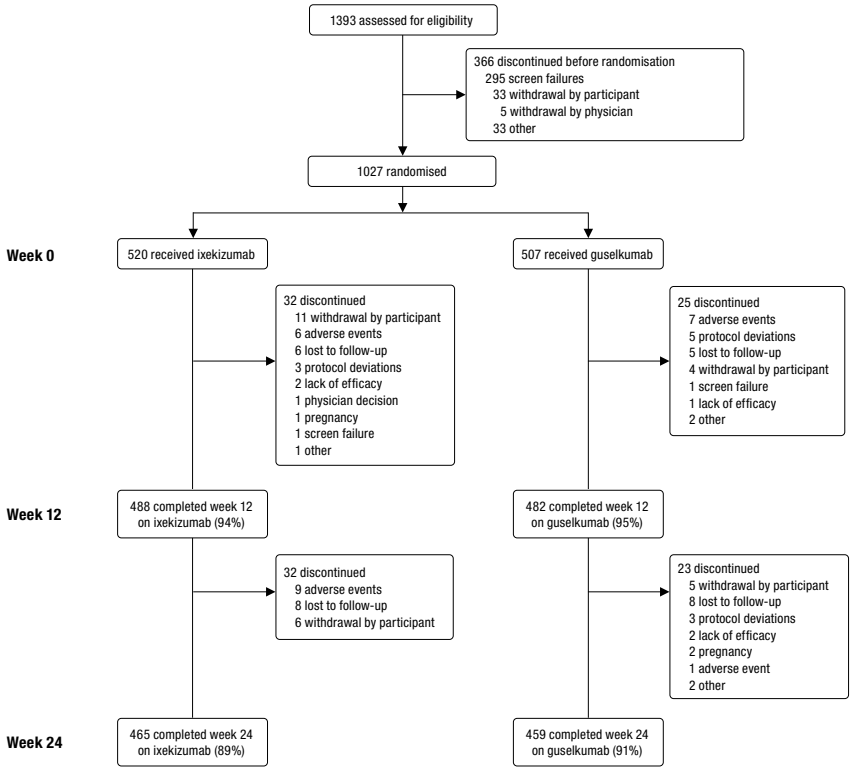

Figure 1: Disposition of patients according to CONSORT statement for reporting randomised controlled trials.[1]

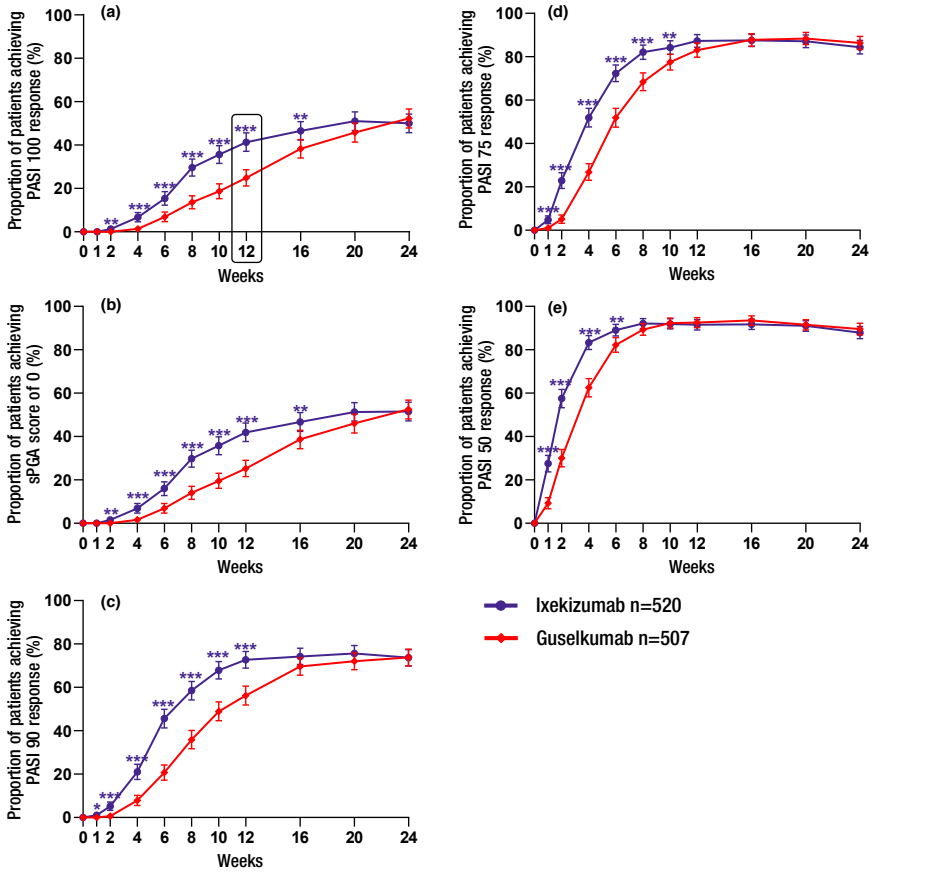

Figure 2: Clinical endpoints (percentages + 95% CIs) through week 24 in ixekizumab and guselkumab recipients.[1]

Proportions of patients achieving (**a**) 100% improvement in Psoriasis Area and Severity Index (PASI 100), (**b**) static Physician's Global Assessment (sPGA) score of 0, (**c**) PASI 90, (**d**) PASI 75 and (**e**) PASI 50. In panel (**a**) the box denotes the primary endpoint (PASI 100 at week 12). Missing data were corrected using non-responder imputation. 95% CIs constructed using the asymptotic method did not use continuity correction (i.e., normal approximation to the binomial distribution). ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

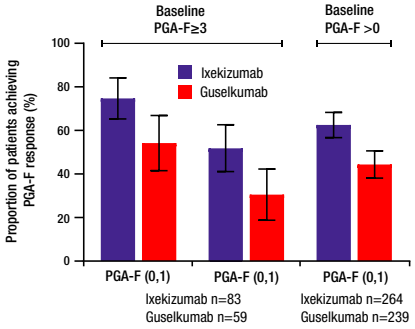

Figure 3: Physician's Global Assessment of Fingernail Psoriasis (PGA-F) response at week 24 in ixekizumab and guselkumab recipients.[1] Data are percentages with 95% CI. Missing data was corrected using non-responder imputation. 95% CIs constructed using the asymptotic method did not use continuity correction (i.e., normal approximation to the binomial distribution). n = number of patients with PGA-F ≥3 (left and centre columns) or number of patients with PGA-F >0 (right column).

Patients with a prior diagnosis of psoriatic arthritis, 122 (24%) ixekizumab and 103 (20%) guselkumab recipients, had a significant improvement in psoriatic arthritis (PGA Disease Activity) at 12 and 24 weeks.[1] However, differences between the treatment groups were not significant.

Patient-reported outcomes

Among patients with itch numerical rating scale (NRS) score >0 at baseline, significantly more ixekizumab than guselkumab recipients reported complete resolution of itch at week 4 and through week 16 (41% vs 33%; $p < 0.05$).[1] In those achieving an sPGA score 0/1, Patient's Global Assessment score 0/1 and a DLQI of 0/1, there were no significant differences between ixekizumab and guselkumab from week 16 to week 24.

Efficacy onset speed

To compare the speed of efficacy onset, the median percentage of PASI improvement was compared over 24 weeks (**Figure 4a**); imputation for missing data used a modified baseline observation carried forward method.[1] Ixekizumab recipients achieved PASI 50, PASI 75, PASI 90 and PASI 100 more rapidly than those receiving guselkumab (**Figure 4a**), and median times to PASI levels were significantly shorter with ixekizumab; for PASI 50 and 75 a median of 2.0 weeks earlier than with guselkumab ($p < 0.001$; **Figure 4b**). Median PASI 90 achievement was 2.1 weeks sooner with ixekizumab ($p < 0.001$; **Figure 4b**) and 7.5 weeks earlier for PASI 100 (12.6 vs 20.1 weeks; $p < 0.001$; **Figure 4b**). Median time to first achievement of DLQI of 0/1 was 5.8 weeks earlier with ixekizumab versus guselkumab (6.3 vs 12.1 weeks; $p = 0.002$; **Figure 4b**) and the median time to first achievement of itch NRS of 0 was 4.2 weeks shorter with ixekizumab (16.1 vs 20.3 weeks; $p = 0.001$; **Figure 4b**).

Cumulative benefit

The cumulative benefit of ixekizumab and guselkumab treatment over 24 weeks was assessed by calculating the area under the curve from the time-course data.[1] Ixekizumab recipients had significantly more days of PASI 100 (55.6 vs 42.2 days; $p < 0.001$) and PASI 90 (95.2 vs 78.6 days; $p < 0.001$) than guselkumab recipients. Ixekizumab recipients also had more days without psoriasis, impacting their quality of life (DLQI 0/1; 84.9 vs 77.4 days; $p = 0.026$) and days without itch (itch NRS score 0; 51.2 vs 41.5 days; $p = 0.002$).

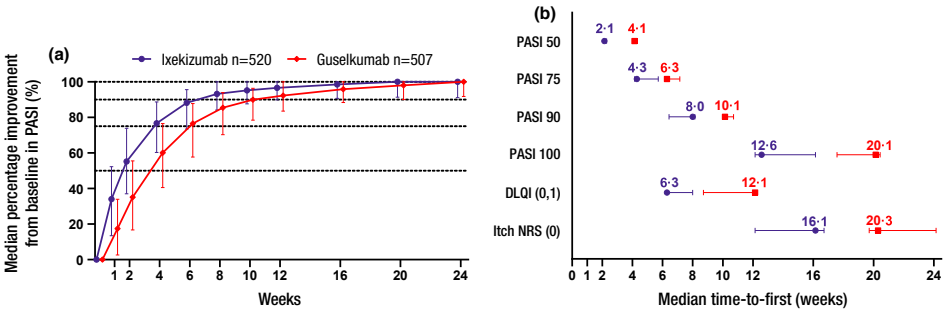

Figure 4: Comparison of speed of improvement in outcomes in ixekizumab and guselkumab recipients.[1] (**a**) Median percentage improvement from baseline in Psoriasis Area and Severity Index (PASI) – median percentage with interquartile range. Dashed lines mark 50%, 75%, 90% and 100% thresholds for PASI improvement. (**b**) Median time to PASI 50/75/90/100, Dermatology Life Quality Index (DLQI) 0/1 and itch numerical rating scale (NRS) score of 0. Data shown as median (95% CI) determined using Kaplan-Meier analyses. Intention-to-treat population was used for all analyses apart from itch NRS score 0 – for that analysis, the intention-to-treat population with a baseline Itch NRS score of >0 was used. In panel b, the p value for each pair of medians was ≤ 0.001 and was based on adjusted log-rank test stratified by treatment.

Expert comment

Although the eighth prespecified primary end point (superiority of ixekizumab vs guselkumab at week 24 with respect to PASI 100) was not demonstrated, a number of interesting findings emerged from this analysis. Rapidity of onset of skin clearance of ixekizumab was demonstrated as early as week 1, across a number of endpoints including PASI 75 and sPGA score 0. Secondly, at week 24, more ixekizumab than guselkumab recipients achieved clear or minimal (PGA-F 0/1 with ≥2-point improvement) nail psoriasis (75% vs 54%; $p = 0.020$), and in a *post hoc* analysis conducted due to imbalance of psoriatic patients with nail disease in the intention-to-treat population, more ixekizumab than guselkumab recipients achieved complete clearance (63% vs 44%; $p < 0.001$).

Approximately 20% of our patients with moderate-to-severe psoriasis will also have significant joint involvement; in this study 122 (24%) of ixekizumab and 103 (20%) guselkumab recipients had a prior history of psoriatic arthritis, and had a significant improvement in psoriatic arthritis (PGA Disease Activity) at 12 and 24 weeks. However, differences between the treatment groups were not significant.

Patient-reported outcomes (itch, pain, DLQI) showed significant improvement over the 24-week period, with the median time to first achievement of DLQI of 0/1 being 5.8 weeks earlier with ixekizumab versus guselkumab. Finally, the cumulative benefit analysis (assessed by calculating the area under the curve of time-course data) demonstrated that patients receiving ixekizumab experienced significantly more days of PASI 100, DLQI 0/1, and itch-free days.

Safety

Treatment-emergent adverse events (TEAEs) were reported in similar proportions between treatment groups, with 62% of ixekizumab and 57% of guselkumab recipients reporting at least one TEAE. Serious AEs were reported by 3% of each group. Discontinuations due to an AE were also similar between the ixekizumab and guselkumab recipients (3% and 2%). No deaths occurred during the study. The most common TEAE was upper respiratory tract infection (8% in each group). Infections included mucocutaneous candidiasis (3 with ixekizumab) and herpes zoster (2 with ixekizumab and 1 with guselkumab), with no deep organ or systemic opportunistic infections. More ixekizumab than guselkumab recipients experienced injection-site reactions (13% vs 4%), but most were mild.

Expert comment

It is vital to collect safety data at every opportunity to further support understanding of benefits versus risks of targeted therapies. In this study there were no notable deviations from our current understanding of the safety profile of ixekizumab and guselkumab. Mucocutaneous fungal infections are a known side effect of IL-17 inhibition but this did not lead to withdrawal from the current study.

Study interpretation

In the IXORA-R trial, 58% of ixekizumab and 30% of guselkumab recipients achieved a PASI 50 at week 2 with ixekizumab demonstrating a faster onset of action. More than 20% of ixekizumab recipients experienced even greater improvement after 2 weeks, achieving PASI 75 at week 2. Ixekizumab recipients achieved PASI 50 and 75 a median of 2 weeks earlier than guselkumab recipients.

A completely clear skin was achieved by more ixekizumab than guselkumab recipients at 4, 8, 12 and 16 weeks with 50% of ixekizumab recipients reaching PASI 100 by 12.6 weeks, which was 7.5 weeks sooner than with guselkumab. Patients with a clear skin within the first 6 weeks had significantly more days without psoriasis and this had a greater impact on their quality of life than reaching PASI 100 after 12 weeks.

Regardless of the baseline level of nail psoriasis more ixekizumab than guselkumab recipients achieved complete clearance of nail psoriasis, and the proportion of patients with complete nail clearance was similar to that observed in phase III ixekizumab registration studies, with greater proportions observed here than previously with guselkumab.[15,16]

Ixekizumab was noninferior to guselkumab in skin clearance at week 24; however, more ixekizumab recipients achieved skin clearance early in the study. This resulted in greater cumulative benefits with ixekizumab over the 24-week study period, with 13.4 more 'clear skin' days, 9.7 more 'itch-free' days, and 7.6 more days without an impact of psoriasis on quality of life over the 24-week study.

Safety data in this trial are consistent with previously published studies of ixekizumab and guselkumab for psoriasis.[7,17,18] TEAE frequency and severity, and serious AE rates were similar to previous clinical trials and consistent with the known safety profile of ixekizumab.

In conclusion, psoriasis patients receiving ixekizumab demonstrated more rapid resolution of skin and nail lesions over a 24-week period than guselkumab recipients and quality of life improved more rapidly with ixekizumab.

Take-home messages

- One-quarter of psoriasis patients experience nail involvement
- Significantly more ixekizumab than guselkumab recipients achieved a PASI 100 and an sPGA score of 0 during weeks 2 to 16
- Significantly more ixekizumab than guselkumab recipients achieved PASI 90 during weeks 2-12 and PASI 75 during weeks 1-10
- Superiority of ixekizumab versus guselkumab for patients achieving PASI 100 at week 24 (secondary outcome) was not achieved
- Ixekizumab was noninferior to guselkumab at week 24
- In a *post hoc* analysis more ixekizumab than guselkumab recipients achieved complete nail clearance
- Patient-reported outcomes (itch, pain, DLQI) showed significant improvement over the 24-week period, with the median time to first achievement of DLQI of 0/1 being 5.8 weeks earlier with ixekizumab versus guselkumab
- TEAEs were reported in similar proportions between treatment groups
- There were no new safety signals with ixekizumab.

Expert's concluding remarks

IXORA-R was a head-to-head study of ixekizumab versus guselkumab in patients with moderate-to-severe chronic plaque psoriasis. Its chief findings, faster onset of both objective and subjective improvement of psoriasis in the ixekizumab-treated patients, mirrored that seen in the pivotal phase III trials of this agent. However, a significant primary outcome at week 24 – superiority of ixekizumab achieving PASI 100 – was not met, but noninferiority conditions were met for this time course, and the advantage of significantly greater numbers of patients achieving rapid response in the first few weeks of the study positively impacted the cumulative benefits over the 24-week period. Additional advantages in nail clearance and improvement of psoriatic arthritis (PGA disease activity) in ixekizuamb-treated patients are encouraging, but the findings in joint disease will need to be assessed via more rigorous psoriatic arthritis-specific controlled trials in the future. We are fortunate to be able to offer chronic plaque psoriasis patients targeted therapies that continue to demonstrate a favourable safety and tolerability profile.

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