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Choosing a biologic for psoriasis: is it a sprint or a marathon?

For patients with psoriasis, both rapid and enduring clearance are highly valued when making treatment choices.^{1–4} Rapidity of clearance has been the focus of two recent network meta-analyses (NMAs) and a systematic review, which conclude that ixekizumab and brodalumab, two agents that inhibit interleukin (IL)-17A, are the fastest-acting treatments when compared with other biologics and conventional systemic agents.^{5–7} Similarly, a study examining the time-effectiveness of simulated induction sequences revealed that initiating treatment with ixekizumab resulted in the shortest time to achieving a clinically significant reduction in dermatology life quality index (DLQI) for 25% of patients (1.4 weeks).⁸ However, to place these findings in context, a recent update of a Cochrane NMA of overall clinical effectiveness, rather than speed of action, in achieving $\geq 90\%$ reduction in their Psoriasis Area and Severity Index score (PASI 90) in the induction phase (8–24 weeks), established that infliximab, all the IL-17 inhibitors (ixekizumab, secukinumab, bimekizumab and brodalumab), and IL-23 inhibitors (risankizumab and guselkumab, but not tildrakizumab) were similar in efficacy.⁹

In this issue of the *BJD*, Blauvelt *et al.* report on the 12-week results of a novel head-to-head 24-week trial comparing ixekizumab with guselkumab (IXORA-R).¹⁰ This is only the second randomized controlled trial to compare an IL-17A inhibitor with an IL-23p19 inhibitor, and is the first to use PASI 100 at 12 weeks as a primary outcome measure. Secondary endpoints focused on speed of response. The final 24-week results for secondary outcomes, including adverse events, have not yet been reported. At 12 weeks there was a significantly higher PASI 100 response for ixekizumab than for guselkumab [215 of 520 patients (41%) vs. 126 of 507 patients (25%), odds ratio 2.14 (95% confidence interval 1.63–2.81, $P < 0.001$)], with a response difference of 16.5% (10.8–22.2). For the secondary endpoints, significantly more patients in the

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ixekizumab group attained PASI 50 at week 1, PASI 75 at week 2, PASI 90 at weeks 4 and 8, and PASI 100 at weeks 4 and 8. Patient-reported outcomes were also significantly different; however, the confidence intervals were very close by week 12, particularly for patient's global assessment of disease severity and DLQI. Of note, there was no significant difference between the two agents in median improvement in PASI at any timepoint. Exploratory analyses suggest that improvement in DLQI was related to early clearance of psoriasis, which was achieved by more patients in the ixekizumab group. Adverse events were similar for both agents, although injection-site reactions were more common in the ixekizumab group (13% vs. 3%).

The results support mounting evidence of earlier onset of action for IL-17 inhibitors compared with IL-23 inhibitors; however, it remains uncertain which class of biologic offers superior longer-term efficacy. An earlier head-to-head trial comparing the IL-23 and IL-17 inhibitors guselkumab and secukinumab revealed that although secukinumab performed better until week 12 (76% of patients achieving PASI 90 for secukinumab vs. 69% for guselkumab), the response declined after week 20. In contrast, the proportion of patients achieving PASI 90 in the guselkumab group peaked at week 28, surpassing secukinumab, and remained stable until week 48. The final results at week 48 for PASI 90 were 84% for guselkumab and 70% for secukinumab.¹¹

The differences in speed of action may in part be due to dosing frequency. Ixekizumab is administered every 2 weeks for the first 12 weeks, whereas guselkumab, after doses at 0 and 4 weeks, is administered every 8 weeks. In addition, the anti-IL-17 agents directly block the effector cytokine, resulting in a more immediate response, whereas the IL-23 inhibitors act proximal to this in the inflammatory cascade, decreasing IL-17 production, possibly explaining the lag in efficacy. However, it is speculated that the broader immunosuppressant effect of the anti-IL-23 agents contributes to a more enduring response. Furthermore, owing to the IL-23 dependence of tissue-resident memory T cells, IL-23 inhibition may be responsible for preventing relapse.¹¹

There is no doubt that early and complete clearance is of critical importance to patients; however, evidence of durable response is also essential to making treatment decisions. The 24-week results will be of great interest, as will emergent real-world data from biologics registries.

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