BJD
British Journal of Dermatology

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

DOI: 10.1111/bjd.19038

Linked Article: Blauvelt *et al. Br J Dermatol* 2020; **182**:1348–1358.

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 ≥ 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, bimekixumab 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 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.

Acknowledgments: Thanks to Associate Professor Peter Foley for critically reviewing this commentary.

E. Veysey

Dermatology, St Vincent's Hospital, Melbourne Pty Ltd, Fitzroy, Vic, Australia
Email: *ecveysey@gmail.com*

Conflicts of interest: The author declares no conflicts of interest.

References

1 Blome C, Gosau R, Radtke MA *et al.* Patient-relevant treatment goals in psoriasis. *Arch Dermatol Res* 2016; **308**:69–78.

2 Seston EM, Ashcroft DM, Griffiths CE. Balancing the benefits and risks of drug treatment: a stated-preference, discrete choice experiment with patients with psoriasis. *Arch Dermatol* 2007; **143**:1175–9.
3 Torbica A, Fattore G, Ayala F. Eliciting preferences to inform patient-centred policies: the case of psoriasis. *Pharmacoeconomics* 2014; **32**:209–23.
4 Carrascosa JM, de la Cueva P, Herranz P *et al.* Perception of psoriasis treatment in the outpatient setting: survey of patients and their prescribing physicians. *J Dermatolog Treat* 2017; **28**:188–99.
5 Warren RB, Gooderham M, Burge R *et al.* Comparison of cumulative clinical benefits of biologics for the treatment of psoriasis over 16 weeks: results from a network meta-analysis. *J Am Acad Dermatol* 2019. https://doi.org/10.1016/j.jaad.2019.12.038.
6 Warren RB, See K, Burge R *et al.* Rapid response of biologic treatments of moderate-to-severe plaque psoriasis: a comprehensive investigation using Bayesian and frequentist network meta-analyses. *Dermatol Ther (Heidelb)* 2020; **10**:73–86.
7 Egeberg A, Andersen YMF, Halling-Overgaard AS *et al.* Systematic review on rapidity of onset of action for interleukin-17 and interleukin-23 inhibitors for psoriasis. *J Eur Acad Dermatol Venereol* 2020; **34**:39–46.
8 Zidane M, Dressler C, Gaskins M, Nast A. Decision-analytic modeling for time-effectiveness of the sequence of induction treatments for moderate to severe plaque psoriasis. *JAMA Dermatol* 2019. https://doi.org/10.1001/jamadermatol.2019.2941.
9 Sbidian E, Chaimani A, Afach S *et al.* Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev* 2020; **1**:CD011535.
10 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* 2020; **182**:1348–58.
11 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**:831–9.

Hedgehog pathway inhibitors come of age

DOI: 10.1111/bjd.18737

Linked Article: Dummer *et al. Br J Dermatol* 2020; **182**:1369–1378.

The vast majority of basal cell carcinomas (BCCs) are cured at first treatment. However, sometimes, in spite of optimal treatment, the BCC recurs, most commonly those with high-risk pathological subtypes such as infiltrative or micronodular BCC. Rarely, BCCs are 'neglected' and present very late with underlying organ damage. Extensive surgery and/or radiotherapy may be required in cases of locally recurrent or neglected BCC. The surgery in some cases can cause life-changing severe facial disfigurement, such as orbital exenteration.

Hedgehog pathway inhibitors (HPIs) have transformed the management of these 'difficult-to-treat' BCCs. Significant efficacy is seen both in patients with locally advanced (la)BCC and metastatic BCC[1,2] and in those with Gorlin syndrome (basal cell naevus syndrome).[3]

Two HPIs are approved: vismodegib received Food and Drug Administration approval in 2012 (for locally advanced and metastatic BCC) and sonidegib in 2015 (for locally advanced BCC). The final results of the BOLT sonidegib trial are published in this issue of the *BJD*.[4] Both drugs are inhibitors of the smoothened component of the patched–smoothened transmembrane hedgehog receptor complex; pathway mutations are present in most BCCs.

There are important pharmacokinetic differences between vismodegib and sonidegib. Vismodegib has unusual pharmacokinetics; it is highly bound to plasma proteins, particularly alpha-1-acid glycoprotein, and biological activity does not increase with dose.[5] Sonidegib has a more conventional dose–response relationship. For this reason the two registration studies had different deigns. ERIVANCE was a phase II study of vismodegib in advanced BCC,[1] whereas BOLT was a phase II randomized comparison of 200 mg vs. 800 mg sonidegib (1 : 2 randomization).[2] Both studies have now reported long-term results: 39 months for ERIVANCE[6] and 42 months for BOLT[4] (in this issue of the *BJD*).

Both studies had the same primary end point of objective response rate (ORR) by central review. It is important to note that the details of the response assessments differed between the two studies, although colour photographs and multiple biopsies were used in both. Additionally, although the inclusion criteria were similar, the baseline patient characteristics differed between the two studies. Therefore the results cannot be directly compared between the trials. In the BOLT study, the comparison between the 200-mg and 800-mg doses showed similar response rates but higher rates of adverse events at 800 mg; the approved treatment dose is therefore 200 mg.[2]

The BOLT study reports an ORR by central review at primary analysis of 43% (5% complete response) for laBCC,[2] and at 42 months of 56% for laBCC (200-mg dose).[4] The median duration of response was 26 months. The ERIVANCE study reported a central-review ORR in the primary analysis[1] for laBCC of 43%, with 21% complete response. The final 39-month analysis reported investigator-assessed 60% ORR and a 26·2-month median duration of response.[6] The disease control rate (complete response + partial response + stable disease) was around 90% in both studies. In essence, both drugs appear to have similar efficacy and a median duration of response of over 2 years. This is despite the median treatment duration being 10–12 months. Treatment breaks are not associated with loss in efficacy.

The most common adverse effects of HPIs are muscle spasms, alopecia, dysgeusia and weight loss. These were somewhat more common for vismodegib (104 and 1215 patients evaluated)[1,7] than for sonidegib at 200 mg (79 patients evaluated),[2] although greater numbers of patients have been evaluated for vismodegib.

We now have consistent and promising long-term efficacy data on both HPIs. However, these are expensive drugs with unpleasant side-effects that preclude long-term use in the majority of patients. The challenge is to define the best way of using them in patients with advanced BCC. For patients with Gorlin syndrome or multiple ultraviolet-induced BCCs who require frequent and extensive surgery, intermittent therapy