Imsidolimab: an emerging biological therapy for generalized pustular psoriasis

Linked Article: Warren *et al. Br J Dermatol* 2023; **189**:161–169.

https://doi.org/10.1093/bjd/ljad128

Generalized pustular psoriasis (GPP) is a rare, debilitating autoinflammatory disorder that presents with flares of widespread sterile pustules and erythema, and is accompanied by systemic inflammation. GPP follows a relapsing or persisting course, and is often recalcitrant to treatment.[1,2] Dysregulated interleukin (IL)-36 signalling has been implicated as a key pathogenic driver of disease.[3] A randomized placebo-controlled trial of spesolimab indicated that therapeutic IL-36 receptor (IL-36R) blockade results in rapid, clinically meaningful benefit.[4] In the spesolimab trial, the primary endpoint was measured at 1 week, so further research is required on the role of IL-36 blockade for ongoing disease control.

In this issue of the *BJD*, Warren *et al.* report on their open-label, single-arm, phase II study of imsidolimab, a monoclonal antibody that inhibits IL-36R.[5] Eight participants were recruited, with six completing the trial. Fifty per cent were female, with a mean (SD) age of 51.3 (14.9) years and a mean (SD) time since GPP diagnosis of 4.0 (6.5) years. Baseline severity was mild ($n = 1$), moderate ($n = 5$) or severe ($n = 2$). Five had concomitant plaque psoriasis. All participants had homozygous wild-type IL36RN, CARD14 and AP1S3 alleles.

The primary efficacy endpoint was the proportion of participants who achieved a response (minimal, much improved, very much improved) according to the Clinical Global Impression scale at weeks 4 and 16. This was observed in six (75%) participants, with three 'very much improved'. Improvements were also seen in the secondary endpoints. The mean body surface area (BSA) covered by erythema with pustules (24% at baseline) was reduced by 60% at day 8 and by 94% at day 29. Reductions were seen in mean BSA with erythema (30% reduction at day 29) and oedema (77% reduction at day 29). Mean Dermatology Life Quality Index improved from 15.8 (baseline) to 11.7 at day 29 and to 9.7 at day 141. These findings highlight a fast onset and sustained improvement with treatment.

Treatment-emergent adverse events occurred in six (75%) participants; two were of 'moderate' severity (moderate flare of plaque psoriasis and moderate sore throat). Two serious adverse events occurred, including the development of *Staphylococcus aureus* bacteraemia-related sepsis in one patient who fully recovered following antibiotic therapy but later discontinued the trial.

A key point of interest is the mixed treatment delivery method; participants received an initial intravenous infusion followed by monthly subcutaneous dosing. This is an attractive treatment approach for GPP, potentially facilitating rapid control of flares and convenient disease maintenance. It represents an advance from previous intravenous-only trials of IL-36 inhibitors.[4]

While promising, the study was open label, lacked a comparator, and had a small sample size and relatively high dropout rate ($n = 2$; 25%). GPP is estimated to be five times more common in Asia than Europe, so a further limitation is that seven of the participants were of white ethnicity.[6,7] The Generalised Pustular Psoriasis Physician's Global Assessment (GPPPGA) score was introduced partway through the trial, so baseline data were only available for five participants, rendering it difficult to draw conclusions from this metric.

This small open-label trial indicates that imsidolimab may be an efficacious treatment in GPP. It builds on the promising outcomes of trials of spesolimab (recently approved by the US Food and Drugs Administration and European Medicines Agency), reinforcing the pathogenic role of IL-36 in GPP. Phase III placebo-controlled trial data of imsidolimab in larger cohorts are awaited.

David Gleeson and Satveer K. Mahil

St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK

Corresponding author: Satveer Mahil. Email: satveer.mahil@kcl.ac.uk

Funding sources: D.G. is a National Institute for Health and Care Research (NIHR) Academic Clinical Fellow. S.K.M. is supported by an NIHR Advanced Fellowship (NIHR302258).

Conflicts of interest: D.G. has received educational support from Lilly. S.K.M. reports departmental income from AbbVie, Almirall, Eli Lilly, Janssen-Cilag, Novartis, Sanofi and UCB, outside the submitted work.

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