*Br J Dermatol* 2025; **192**:i1–i2
https://doi.org/10.1093/bjd/ljae455



## Hidradenitis suppurativa*: BJD* state-of-the-art review series

Back in 2017, I wrote a *BJD* editorial along with Tara Burton, a hidradenitis suppurativa (HS) patient advocate, covering National Institute for Health and Care Excellence (NICE) payer approval in the UK for adalimumab, the first licensed treatment for HS. We posed the question 'was this the end of the beginning for HS therapeutics?'[1] Subsequently, as Editor-in-Chief of the *BJD*, I championed publication of high-quality HS research to encourage further developments. A lot has been achieved since then, including development of the HS core outcomes set by the Hidradenitis SuppuraTiva cORe outcomes set International Collaboration (HiSTORIC), which were the core domains that featured in the *BJD*'s Outcomes and Qualitative Research section in 2018.[2] In 2019, the *BJD* published the first UK guidelines for HS from the British Association of Dermatologists (BAD).[3] In 2021, the SHARPS randomized trial results provided helpful evidence showing that adalimumab could be safely and effectively combined with wide excisional surgery to provide integrated medical and surgical care.[4] Then in 2023 and 2024, large phase III randomized trials of anti-interleukin (IL)-17 biologic therapies for HS were published, demonstrating the effectiveness and safety of secukinumab and bimekizumab for HS.[5,6]

So, lots of progress in the HS space. However, more needs to be done, particularly in the context of an ongoing average diagnostic delay of 7–10 years.[7] There are several guidelines that are in need of an update, and there are still only three licensed therapies for HS. Work is being undertaken to address all these issues and more, including updates to the BAD guidelines and the HS Cochrane review that are currently under way.[8]

Patients and clinicians are rightly impatient for further therapeutic progress. To achieve this, we need a better understanding of the fundamentals of HS pathogenesis in order to develop targeted therapies for HS, rather than relying on retasked treatments used for other chronic inflammatory conditions that may not cover the array of pathogenic pathways implicated in HS. To that end, the review of pathogenesis sole authored by John Frew in the HS supplement accompanying this month's *BJD* provides an expert, nuanced summary of recent developments.[9] New players in HS pathogenesis are highlighted, including SOX9, a transcription factor essential for hair follicle formation and epithelial stem cell fate. The role of fibroblasts is explored, which can amplify inflammation via production of CXCL13, IL-1, IL-6 and interferon-γ. In addition, Frew considers the role of tertiary lymphoid organs in deep HS tissue, which permit T-cell, B-cell, dendritic cell and fibroblast interaction in local tissue without requiring circulation to draining lymph nodes. The endocrine hypothesis in HS pathophysiology is explored further, with increased oestradiol (E2) levels leading to IL-23-independent IL-17 production, which could underpin variable responses to IL-23 inhibition in HS.

Looking ahead, the review of HS pathogenesis identifies markers of rapid disease progression and personalized therapy as key issues to be investigated further. This theme is taken up by the second review paper, which covers how phenotype–genotype correlations can be leveraged to implement precision medicine in HS.[10] Lynn Petukova, Barbara Horvath and colleagues summarize latent class analysis approaches to subclassifying HS phenotypes, pointing out that analyses to date which have focused on physical signs and demographics have had limited utility. The authors recommend addition of comorbidities, molecular phenotyping including transcriptome signatures, and immunophenotyping using flow cytometry data to take this approach to the next level. Ultimately, the success or failure of this field within HS will be judged on whether it can identify those at risk of rapid disease progression and those who are more likely to respond to particular therapies.

The second review article goes on to examine the genetics of HS, pointing out that while we are still at the early stages of gene discovery for HS, three HS disease mechanisms have been identified from genetics. Two were identified by studies of single-gene disorders in affected families. The γ-secretase loss-of-function mechanism was identified in East Asian families; however, it has not been reproduced in HS populations in other parts of the world. Defective inflammasome signalling is a second potential genetic mechanism, typically resulting in rare syndromic forms of HS, although it remains unclear in most cases whether the reported genetic variants are pathogenic. Nevertheless, there are treatment implications in terms of the potential for anti-IL-1 therapeutics for HS. Our knowledge of the third disease mechanism comes from initial HS genome-wide association studies (GWASs), which have implicated the *SOX9* and *KLF5* genes involved in hair follicle development and homeostasis. However, the authors conclude that larger GWASs are required to identify a sufficient number of risk variants to develop robust polygenic risk scores in HS. Given that twin studies estimate heritability of HS to be 70%, a full understanding of HS genetics remains a high priority for future HS research.

The third review article in the HS supplement, written by Chris Sayed, Amit Garg and colleagues, considers the progress and ongoing challenges in the design of clinical trials for HS.[11] High placebo response rates are highlighted as a threat to bringing new treatments for HS to market, which may in part relate to the challenge of identifying different lesion types

**Accepted:** 15 November 2024

in HS lesion scoring systems. There remains a debate regarding omission of draining skin tunnel counts by the Hidradenitis Suppurativa Clinical Response (HiSCR) instrument, compared with a weighted score of 4 assigned to draining skin tunnels by the International Hidradenitis Suppurativa Severity Scoring System (IHS4) instrument. Furthermore, there is a lack of consistency regarding skin tunnel counting in clinical trials, in which tunnel openings or tunnel networks could be counted. In addition, the utility of portable ultrasound devices to count tunnels more accurately has not been fully assessed. Finally, higher efficacy endpoints, for example HiSCR 75 rather than HiSCR 50, which requires a reduction of at least 75% rather than 50% from baseline in the abscess and inflammatory nodule count, could become the norm in future, in keeping with rising patient and clinician expectations. Could higher efficacy endpoints also reduce placebo response rates? Watch this space.

The review also reflects on the relative lack of diversity in HS trial populations to date, which is particularly important given the higher rates of HS in Black Americans, for example. Efforts to correct this imbalance are supported by the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act passed by the US Congress in 2022, mandating the US Food and Drug Administration to require sponsors of pivotal trials to submit Diversity Plans to improve the diversity of trial populations. Other trial topics covered include concomitant medications and rescue therapy, inclusion criteria, statistical analysis plans and the timing of the primary endpoint. HiSTORIC's work in developing a core set of outcome measures spanning both physician-reported and patient-reported domains is highlighted.[2] Innovative and efficient trial designs are discussed, including platform trials which allow multiple drugs to be tested against a shared placebo arm.

I hope you enjoy reading these review articles as much as I did. I don't think we are at the 'beginning of the end' for HS management yet, but substantial progress has been achieved and the *BJD* continues to showcase some of the best research in the HS field.

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Acknowledgements: John McGrath, King's College London, the *BJD* Editor-in-Chief, kindly reviewed an earlier version of this manuscript.

Funding sources: This editorial received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. This paper was published as part of a supplement financially supported by independent funding from Novartis Pharma AG.

Conflicts of interest: J.R.I. has received a stipend as immediate past Editor-in-Chief of the *BJD* and an authorship honorarium from UpToDate. He is a consultant for AbbVie, Boehringer Ingelheim, ChemoCentryx, Citryll, Incyte, Insmed, Kymera Therapeutics, MoonLake, Novartis, UCB Pharma, UNION Therapeutics and Viela Bio. He is cocopyright holder of the Hidradenitis Suppurativa Quality of Life (HiSQOL), Investigator Global Assessment and Patient Global Assessment instruments for hidradenitis suppurativa. His department receives income from copyright of the Dermatology Life Quality Index and related instruments. He is a founder of the Hidradenitis SuppuraTiva cORe outcomes set International Collaboration (HiSTORIC).

Data availability: Not applicable.

Ethics statement: Not applicable.

Patient consent: Not applicable.

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Co-primary endpoints PASI 90 and IGA 0/1 at Week 16 were met.**Secondary endpoints. †N= mNRI, missing data were imputed with mNRI (patients with missing data following treatment discontinuation due to lack of efficacy or a TRAE were counted as non-responders; multiple imputation methodology was used for other missing data). ‡43.9% (n=189/431), and 43.4% (n=116/267) of biologic-naïve and TNFi-IR PsA patients achieved the primary endpoint of ACR 50 at Week 16 in BE OPTIMAL and BE COMPLETE, respectively (vs 10.0% [n=28/281] and 6.8% [n=9/133] placebo, p<0.0001); 54.5% (n=235/431) and 51.7% (n=138/267) maintained it at Week 52 (NRI).[4–6]

**ACR 50,** ≥50% response in the American College of Rheumatology criteria; **AS**, ankylosing spondylitis; **CRP**, C-reactive protein; **DMARD**, disease-modifying antirheumatic drug; **HS**, hidradenitis suppurativa; **IGA**, Investigator's Global Assessment; **(m)NRI**, (modified) non-responder imputation; **MRI**, magnetic resonance imaging; **nr-axSpA**, non-radiographic axial spondyloarthritis; **NSAID**, non-steroidal anti-inflammatory drug; **PASI 75/90/100**, ≥75/90/100% improvement from baseline in Psoriasis Area and Severity Index; **PsA**, psoriatic arthritis; **PsD**, psoriatic disease; **PsO**, psoriasis; **TNFi-IR**, tumour necrosis factor-α inhibitor – inadequate responder; **TRAE**, treatment-related adverse event.

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