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HIDRADENITIS SUPPURATIVA: WHAT'S ON THE HORIZON?

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that has a paucity of effective therapeutic options. In recent years, progress has been made in the understanding of HS pathophysiology which has led to the development of new therapeutic options.

The current HS management algorithm has been outlined in North American treatment guidelines and includes a combination of medical and surgical treatment modalities.[1] The guidelines focus on helping clinicians make optimal treatment decisions while taking an individualized approach in each particular patient case. Medical management recommendations include topical and intralesional therapies, systemic antibiotics, hormonal agents, retinoids, immunosuppressants, and biologics. Immunomodulation has adopted a solid place in HS management and will be the focus of this review.

Various tools have been used for disease assessment and monitoring in clinical practice and clinical trials. Hurley staging[2] has been used to assess disease severity focusing on scarring but lacks in its assessment of disease dynamics. The Hidradenitis Suppurativa Clinical Response (HiSCR) has been validated in clinical trials[3, 4] and is used in clinical practice to assess treatment effectiveness. HiSCR50 is defined as at least a ≥ 50% reduction in total abscess and inflammatory nodule count, with no increase in abscess or tunnel (fistula) count relative to baseline.[3] HiSCR75 is defined as at least a ≥ 75% reduction in total abscess and inflammatory nodule count, with no increase in abscess or tunnel (fistula) count.[4] HiSCR90 is defined as at least a ≥ 90% reduction in total abscess and inflammatory nodule, with no increase in abscess or tunnel (fistula) count.

The HS ALLIANCE working group conducted a systematic review of the literature and provided evidence-based recommendations for disease assessment and monitoring.[5] They suggested that while Hurley staging is useful to assess baseline disease severity, HiSCR is recommended as the dichotomous outcome measure in inflammatory areas under treatment. Additionally, patient-reported outcome measures (e.g. dermatology life quality index [DLQI] and the visual analog scale [VAS]) may provide important insight into patient functioning, quality of life and symptoms and should be included in the disease assessment.[5] Adalimumab is currently the only Health Canada and FDA-approved treatment for HS. The efficacy and safety of adalimumab has

been investigated in two parallel double-blind placebo-controlled phase 3 trials, PIONEER 1 and PIONEER 2[6] with concomitant use of tetracycline class antibiotics permitted in PIONEER 2. The primary endpoint of HiSCR response (HiSCR50) at week 12 was achieved by 42% of patients treated with adalimumab vs 26% of patients treated with placebo (P=0.003) in PIONEER 1 and 59% vs 28%, respectively, in PIONEER 26 **(Figure 1)**. Adalimumab was dosed 160 mg at week 0, 80 mg at week 2 and then 40 mg weekly starting at week 4. Forty percent of patients who failed to achieve the primary endpoint at week 12 achieved HiSCR at week 36 with continuous treatment.[6]

The long term efficacy and tolerability of adalimumab was evaluated by pooling the results of the PIONEER 1 and PIONEER 2 phase 3 studies and the open-label extension (OLE) study.[7] After screening, the patients entered period A and were randomized to receive adalimumab 40 mg weekly or placebo for 12 weeks. In period B, patients who were randomized to receive adalimumab in Period A were reassigned to receive adalimumab 40 mg weekly, adalimumab every other week, or placebo for 24 weeks. Patients who were randomized to receive placebo in period A were reassigned to continue receiving placebo (PIONEER 2) or to receive adalimumab 40 mg weekly in period B (PIONEER 1). In the OLE trial, all patients received adalimumab 40 mg weekly for at least 60 weeks. At week 12 of the pooled analysis, HiSCR was achieved by 52.3% of patients receiving adalimumab weekly who entered the OLE and 73% of patients defined as responders plus partial responders (PRRs) which included those who did not achieve HiSCR but did achieve at least a 25% reduction in abscess and nodule count relative to

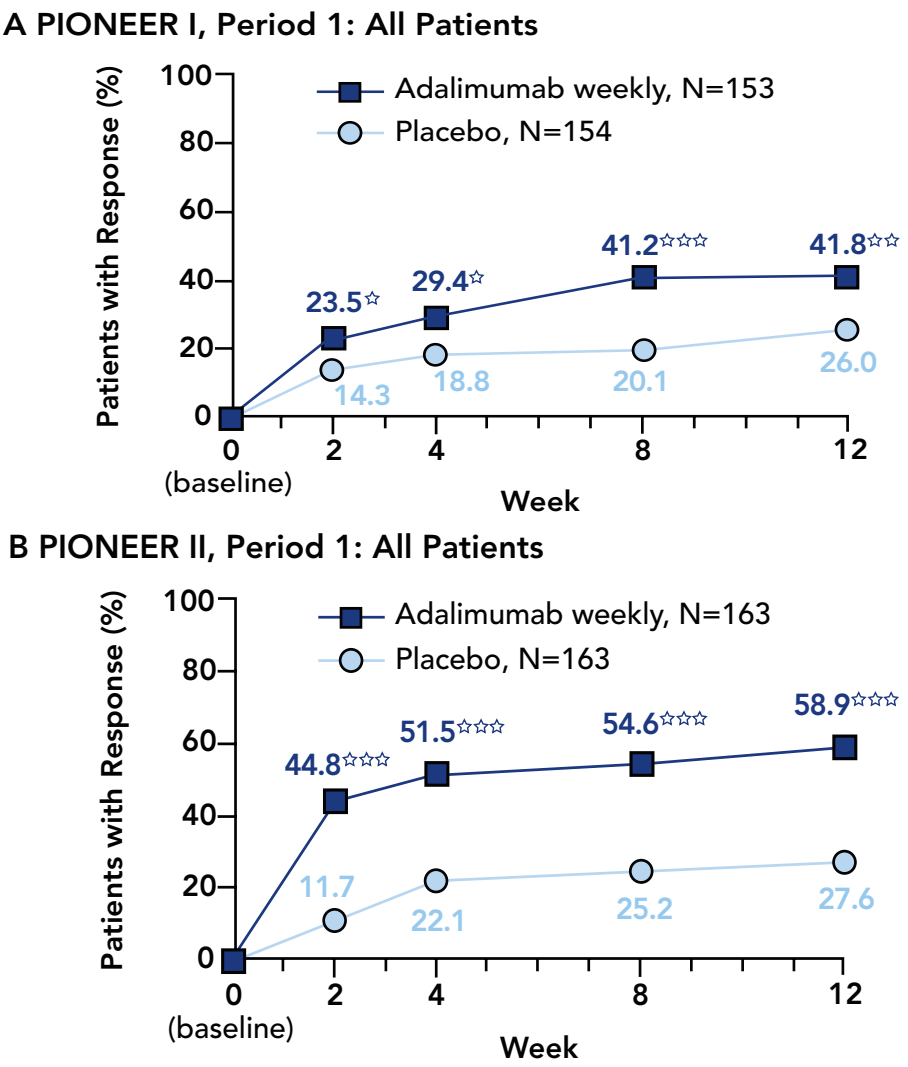

Figure 1. PIONEER 1 (A) and PIONEER 2 (B) results for all patients at Week 12; adapted from Kimball et al, 2016

baseline. HiSCR was maintained through week 168 in 52.3% receiving adalimumab weekly and 57.1% of patients defined as PRRs. Inflammatory lesion count, draining fistula count, total fistula count and pain, all improved from baseline in both populations. Sustained improvement was seen through week 168.[7]

The Canadian Humira Post Marketing Observational Epidemiological Study: Assessing Humira® Real-life Effectiveness and Impact on Moderate to Severe HS Burden of Illness and Health Care Resources Utilization (SOLACE) evaluated adalimumab efficacy and safety in a prospective cohort of patients with moderate-to-severe HS in a real-world clinical setting.[8] Overall, 69% of patients achieved HiSCR at week 24 (primary endpoint) which was maintained out to week 52. The HARMONY study is another real-world prospective, multicenter, post-marketing observational study conducted in Europe and Middle East that included patients with moderate- to-severe HS. In the HARMONY study, 70.2% of patients achieved HiSCR at week 12 (the primary endpoint) which was maintained out to weeks 24 (HiSCR 75.7%) and 52 (HiSCR 72.1%).[9] These studies confirm adalimumab's efficacy in a real-world clinical setting and suggest that treatment optimization with the addition of medical and surgical therapeutic modalities achieve further improvements in HS management.

Other TNF-α inhibitors have been investigated as potential therapeutic options and are currently used off label.[1] Infliximab has the most published experience with the most benefit seen in higher dosing regimens (5-10 mg/kg every 4 -8 weeks).[10-12] Etanercept (50 mg twice weekly) was evaluated in 20 patients in a single center, randomized, prospective, double-blind, placebo controlled study and failed to achieve its primary endpoint of physician global assessment clear or mild at week 12. There were also no statistical differences between the active arm and placebo in patient global assessment and DLQI.[13] Certolizumab pegol has also been reported to be beneficial in achieving clinical response in case reports.[14-16]

Anakinra, an IL-1 inhibitor has been shown to achieve HiSCR in a small randomized controlled trial of 20 patients and an open label study of 6 patients.[17,18] Anakinra was dosed at 100 mg daily. The North American clinical management guidelines recommend considering anakinra only after failure to TNF inhibition.[1] Unfortunately, the use of anakinra for HS is limited in Canada due to accessibility issues.

Ustekinumab, an IL-12/23 p40 inhibitor was investigated in a small open label study in 17 patients with moderate-to-severe HS and demonstrated improvements in Sartorius scores and inflammatory lesion count.[19] There is no robust evidence confirming ustekinumab's efficacy in this patient population and no data evaluating its efficacy using higher doses similar to Crohn's disease. However, ustekinumab has been successful in achieving clinical response in case reports and small case series[19-22] and might be a useful therapeutic option for patients with HS and other comorbidities or HS patients with inadequate response to TNF-α inhibitors.

New therapeutic targets in HS management include inhibition of IL-17 and IL-23 pathways. IL-17 cytokines have been shown to be elevated in serum[23] as well as lesional and perilesional HS skin.[24] Several case reports and case series utilizing secukinumab[25-30], ixekizumab[31-32] and brodalumab[33] have demonstrated improvements in HS clinical outcomes. Therapeutic agents in clinical development for the treatment of HS are outlined in **Table 1**.

A recent bimekizumab phase II clinical trial (NCT03248531) had demonstrated clinically meaningful improvements across all outcome measures.[34] This trial included patients with diagnosis of HS for 1 year, abscess and inflammatory nodule count of 3 and inadequate response to a 3 month course of oral antibiotics (used for HS treatment) and HS lesions present in 2 distinct anatomical areas (one of which must be at least Hurley stage II or III) and excluded patients with prior anti-IL-17 or anti-TNF experience. Eighty-eight patients were randomized 2:1:1 to bimekizumab 320mg (q2w; 640 loading dose), placebo, or adalimumab (as per product monograph). Primary endpoint was HiSCR50 at week 12. Exploratory endpoints included: HiSCR75, IHS4, PGA skin pain, DLQI.

At 12 weeks, 56.9% of patients treated with bimekizumab achieved HiSCR response compared to 23.7% of patients treated with placebo. In this study, 59.8% of patients treated with adalimumab had achieved a HiSCR response, similar to the proportion of patients achieving HiSCR50 on bimekizumab. More patients treated with bimekizumab achieved HiSCR75 compared to placebo (50% vs 11.1%), and adalimumab (38.9%) at week 12. In addition, at week 12, bimekizumab performed better than placebo and adalimumab in exploratory endpoints of PGA skin pain. Bimekizumab performed similar to adalimumab in quality of life measures (DLQI) and IHS4 and better than placebo. The overall incidence of treatment emergent adverse events at week 12 was similar between placebo, adalimumab and bimekizumab with no unexpected safety findings.

In addition, the IL-23/Th17 pathway has been shown to be an important player in the inflammatory milieu in HS lesions.[35] A small retrospective chart review and 2 case reports[36-38] of HS patients treated with guselkumab (using psoriasis dosing of 100 mg q 8 weeks) suggest that it might present a new therapeutic option for HS. Guselkumab and risankizumab are currently being investigated in clinical trials as potential HS therapies.

Other emerging HS therapeutic options include Janus kinase (JAK) inhibitors and bermekimab. JAK inhibitors are made up of a family of intracellular tyrosine kinases that transduce cytokine-mediated signals to further activate transcription. Inhibition of JAK can simultaneously block transcription of multiple cytokines. The JAK family includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK 2). Most cytokine receptors use a combination of JAKs. Therapeutic agents inhibiting JAK can possess high or low selectivity for a particular JAK target and some earlier compounds may possess multi-JAK inhibition. Pan-JAK inhibition is not clinically desirable due to a higher risk of severe adverse events. JAK inhibition is of particular interest in management of HS due to various cytokines involved in disease pathogenesis and the lack

of one therapeutic target.[39] In this instance a phase 2 clinical trial is currently underway to investigate three different kinase inhibitors (PF-06650833, PF-06700841 and PF-06826647) as potential therapeutic targets in adults with HS. Bermekimab, an IL-1α inhibitor represents a novel therapeutic option showing efficacy in a phase II open label study.[40] Bermekimab efficacy was assessed in both HS patients who had previously failed TNF-α therapy and patients who were TNF-naïve. Regardless of the patient's prior TNF failure history, 61% of TNF-naïve patients and 63% of TNF-failed patients achieved HiSCR at week 12, suggesting that the bermekimab therapeutic target is of interest in HS management.

In conclusion, HS is a complex inflammatory condition with an established therapeutic algorithm, yet there exist a paucity of effective approved therapeutic options. Many therapeutic agents currently used in the management of other inflammatory conditions like psoriasis are of high clinical interest as potential therapeutic options for HS. Immune modulation remains an area of high scientific and clinical interest with many agents being investigated in ongoing clinical trials.

Compound	Mechanism of action	Phase in development	Registered trials
Anakinra	IL-1 antagonist	2	NCT01558375, NCT01516749
Bermekimab	IL-1α antagonist	2	NCT03512275, NCT04019041
PF-06650833	IL-1 receptor associated protein kinase 4 (IRAK4) inhibitor	2	NCT04092452
Secukinumab	IL-17 antagonist	3	NCT03099980, NCT03713632 NCT03713619, NCT04179175
Brodalumab	IL-17 antagonist	1, 2	NCT03960268, NCT03910803
Bimekizumab	IL-17 antagonist	2	NCT03248531, NCT04242498 NCT04242446
CJM112	IL-17 antagonist	2	NCT02421172
Guselkumab	IL-23 antagonist	2	NCT04061395, NCT03628924
Risankizumab	IL-23 antagonist	2	NCT03926169
INCB054707	JAK-1 inhibitor	2	NCT03569371, NCT03607487 NCT04476043
Upadacitinib	JAK-1 inhibitor	2	NCT04430855
Ruxolitinib 1.5% Cream	JAK1/JAK2 inhibitor	2	NCT04414514
PF-06700841	Dual JAK1/TYK2 inhibitor	2	NCT04092452
PF-06826647	TYK2 inhibitor	2	NCT04092452
IFX-1	C5a inhibitor	2	NCT03487276 NCT03001622
Apremilast	PD-4 inhibitor	2	NCT03049267 NCT02695212
CSL324	Granulocyte colony-stimulating factor (G-CSF) receptor antagonist	1	NCT03972280
Iscalimab (CFZ533)	CD-40 antagonist	2	NCT03827798
LYS006	Not reported	2	NCT03827798
LY3041658	Not reported	2	NCT04493502

Table 1. Therapeutic agents under investigation for the treatment of HS (clinicaltrials.gov, accessed 04-October-2020)

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