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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.

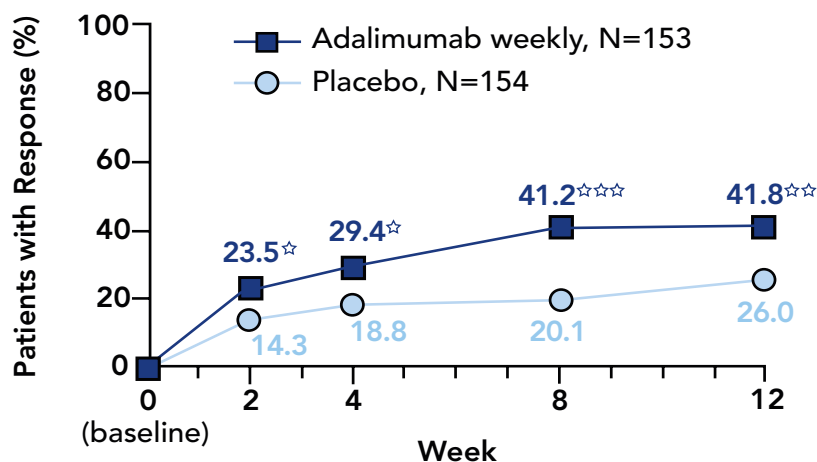
Various tools have been used for disease assessment and monitoring in clinical practice and clinical trials. Hurley staging² has been used to assess disease severity focusing on scarring but lacks in its assessment of disease dynamics. The Hidradenitis Suppurativa Clinical Response (HiSCR) has been validated in clinical trials^{3, 4} and is used in clinical practice to assess treatment effectiveness. HiSCR50 is defined as at least a $\geq 50\%$ 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 $\geq 75\%$ 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 $\geq 90\%$ 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 2⁶ 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

A PIONEER I, Period 1: All Patients



B PIONEER II, Period 1: All Patients

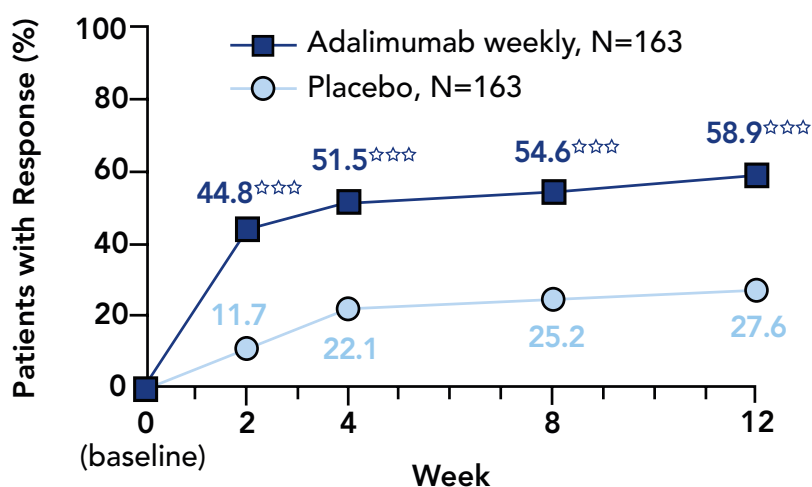


Figure 1. PIONEER 1 (A) and PIONEER 2 (B) results for all patients at Week 12; adapted from Kimball et al, 2016

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 series¹⁹⁻²² 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 serum²³ as well as lesional and perilesional HS skin.²⁴ Several case reports and case series utilizing secukinumab²⁵⁻³⁰, ixekizumab³¹⁻³² and brodalumab³³ 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 presents 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 reports³⁶⁻³⁸ 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 bimekimab. 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-1 α 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-1 α 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)

References:

1. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: Topical, intralesional, and systemic medical management. *J Am Acad Dermatol* 2019; 81:91-101.
2. Hurley H. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa and familial benign pemphigus: surgical approach. *Dermatologic Surgery New York: Marcel Dekker*. 1989:729-739
3. Kimball AB, Jemec GB, Yang M et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. *Br J Dermatol* 2014; 171: 1434-1442
4. Kimball AB, Sobell JM, Zouboulis CC et al. HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from placebo-controlled portion of a phase 2 adalimumab study. *J Eur Acad Dermatol* 2016. 30: 989-994.
5. Zouboulis CC, Bechara FG, Dickinson-Blok JL et al. Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization-systematic review and recommendations from the HS ALLIANCE working group. *JEADV* 2019. 33: 19-31.
6. Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Eng J Med* 2016; 375: 422-434.
7. Zouboulis CC, Okun MM, Prens EP et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. *J Am Acad Dermatol* 2019. 80(1): 60-69.e2, available online <https://doi.org/10.1016/j.jaad.2018.05.040>
8. Gulliver W, Alavi A, Papp, KA et al. Improvement of the quality of life of patients with moderate to severe hidradenitis suppurativa treated with adalimumab: The Solace study final analysis. Presented at the 9th conference of the European Hidradenitis Suppurativa Foundation, 5-7 February 2020, Athens, Greece.
9. Hafner A, Ghislain PD, Kovacs R, et al. Improvement in Hidradenitis Suppurativa and Quality of Life in Patients Treated with Adalimumab: Real-World Results from the HARMONY Study. Presented at the 9th Conference of the European Hidradenitis Suppurativa Foundation, 5-7 February 2020, Athens, Greece.

10. Grant A, Gozalez T, Montgomery MO, et al. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol* 2010; 61:205-217.
11. Paradela S, Rodriguez-Lojo R, Fernandez-Torres R. Long-term efficacy of infliximab in hidradenitis suppurativa. *J Dermatolog Treat* 2012; 23:278-283.
12. Moriarty B, Jiyad Z, Creamer D. Four-weekly infliximab in the treatment of severe hidradenitis suppurativa. *Br J Dermatol* 2014; 170: 986-987.
13. Adams D, Yankura JA, Fogelberg AC et al. Treatment of hidradenitis suppurativa with etanercept injection. *Arch Dermatol* 2010. 146(5):501-504.
14. Tampouratzi E, Kanni T, Katsantonis J. Case report: treating a combination of hidradenitis suppurativa and psoriasis with different therapeutic approaches 2019. *F1000research.com*
15. Abad SJ, Palacios MM, Pastor MV. A case report of hidradenitis suppurativa treated with certolizumab. *J Am Acad Dermatol* 2019, available online <https://doi.org/10.1016/j.jaad.2019.10.098>
16. Porter ML, Golbari NM, Lockwood SJ et al. Overview and update on biologic therapy for moderate-to-severe hidradenitis suppurativa. *Semin Cutan Med Surg* 2018. 37(3):182-189.
17. Tzanetakou V, Kanni T, Gitrakou S, et al. Safety and efficacy of anakinra in severe hidradenitis suppurativa: a randomized clinical trial. *JAMA Dermatol* 2016; 152:52-59
18. Leslie KS, Tripathi SV, Nguyen TV, et al. An open-label study of anakinra for the treatment of moderate to severe hidradenitis suppurativa. *J Am Acad Dermatol* 2014. 70: 243-251.
19. Blok JL, Li K, Brodmerkel C. Ustekinumab in hidradenitis suppurativa: clinical results and a search for potential biomarkers in serum. *Br J Dermatol* 2016. 174: 839-846.
20. Sharon VR, Shirakawa Garcia M, Bagheri S. Management of recalcitrant hidradenitis suppurativa with Ustekinumab. *Acta Dermatol Venereol* 2012. 92: 320-335
21. Gulliver W.P, Jemec GBE, Baker KA. Experience with ustekinumab for the treatment of moderate to severe hidradenitis suppurativa. *J Eur Acad Dermatol* 2011, available online <https://doi.org/10.1111/j.1468-3083.2011.04123.x>
22. Montero-Vilchez T, Pozo-Román T, Sánchez-Velicia L, et al. Ustekinumab in the treatment of patients with hidradenitis suppurativa: multicenter case series and systematic review, *J Dermatol Treat* 2020. Available online <https://doi.org/10.1080/09546634.2020.1755008>
23. Matusiak L, Szczech J, Bieniek A et al. Increased interleukin (IL)-17 serum levels in patients with hidradenitis suppurativa: Implications for treatment with IL-17 agents. *J Am Acad Dermatol* 2017. 76:670-675.
24. Kelly G, Hughes R, McGarry T. Dysregulated cytokine expression in lesional and nonlesional skin in hidradenitis suppurativa. *Br J Dermatol* 2015. 173: 1431-1439.
25. Casseres R, Prissiak L, Zancanaro P. Secukinumab in the treatment of moderate to severe hidradenitis suppurativa: Results of an open label trial. *J Am Acad Dermatol* 2020. 82:1524-1526
26. Reguai Z, Fougerousse AC, Maccari F. Effectiveness of secukinumab in hidradenitis suppurativa : an open label study (20 cases). *J Eur Acad Dermatol* 2020, available online <https://doi.org/10.1111/jdv.16605>
27. Thoriaci L, Theut Riis P, Jemec GBE. Severe hidradenitis suppurativa responding to treatment with secukinumab. *J Eur Acad Dermatol* 2017, available online <https://doi.org/10.1111/bjd.15769>
28. Schuch A, Fischer T, Boehner A et al. Successful Treatment of Severe Recalcitrant Hidradenitis Suppurativa with the Interleukin-17A Antibody Secukinumab. *Acta Dermatol Venereol* 2017. 98: 151-152
29. Jorgensen AHR, Yao Y, Thomsen SF. Therapeutic response to Secukinumab in a 36-year-old woman with hidradenitis suppurativa. *Case reports Dermatol Med (hindawi.com)* 2018 <https://doi.org/10.1155/2018/8685136>
30. Giuseppe P, Nicola P, Valentina C et al. A case report of Moderate Hidradenitis Suppurativa and psoriasis treated with Secukinumab. *Ann Dermatol* 2018. 30: 462-464
31. Megna M, Ruggiero A, Di Guida A et al. Ixekizumab: An efficacious treatment for both psoriasis and hidradenitis suppurativa. *Dermatol Ther* 2020. Available online, <https://doi.org/10.1111/dth.13756>
32. Kirsten N, Augustin M. Two cases of hidradenitis suppurativa successfully treated with ixekizumab. Poster 0066, 28th EADV Congress, Madrid, Spain
33. Frew JW, Navrazhina K, Grand D et al. The effect of subcutaneous brodalumab on clinical disease activity in hidradenitis suppurativa: An open label study. *J Am Acad Dermatol* 2020. In press, <https://doi.org/10.1016/j.jaad.2020.05.007>
34. Jemec G, Sayed C, Schmieder G et al. Efficacy and safety of bimekizumab, a dual interleukin (IL)-17A and IL-18 inhibitor, for the treatment of moderate to severe hidradenitis suppurativa (HS): a 12-week, randomised, double-blind, placebo controlled, Phase 2 study. *Exp Dermatol* 2020; abstract 79
35. Schlapbach C, Hanni T, Yawalkar N et al. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol* 2011. 65: 790-798.
36. Casseres R, Kahn J, Her MJ, et al. Guselkumab in the treatment of hidradenitis suppurativa: a retrospective chart review. *J Am Acad Dermatol* 2019. 81: 265-267
37. Berman HS, Villa NM, Shi VY et al. Guselkumab in the treatment of concomitant hidradenitis suppurativa, psoriasis and Crohn's disease. *J Dermatol Treat* 2019. Available online, <https://doi.org/10.1080/09546634.2019.1654067>
38. Kearney N, Byrne N, Kirby B, et al. Successful use of guselkumab in the treatment of severe hidradenitis suppurativa. *Clin Exp Dermatol* 2020. Available online, <https://doi.org/10.1111/ced.14199>
39. Solimani F, Meier K, Ghoreschi K. Emerging topical and systemic JAK inhibitors in dermatology. *Front Immunol* 2019, available online <https://doi.org/10.3389/fimmu.2019.02847>.
40. Gottlieb A, Natsis N, Kerdel F et al. A phase II open-label study of Bermekimab in patients with hidradenitis suppurativa shows resolution of inflammatory lesions and pain. *J Invest Dermatol* 2020. Available online <https://doi.org/10.1016/j.jid.2019.10.024>