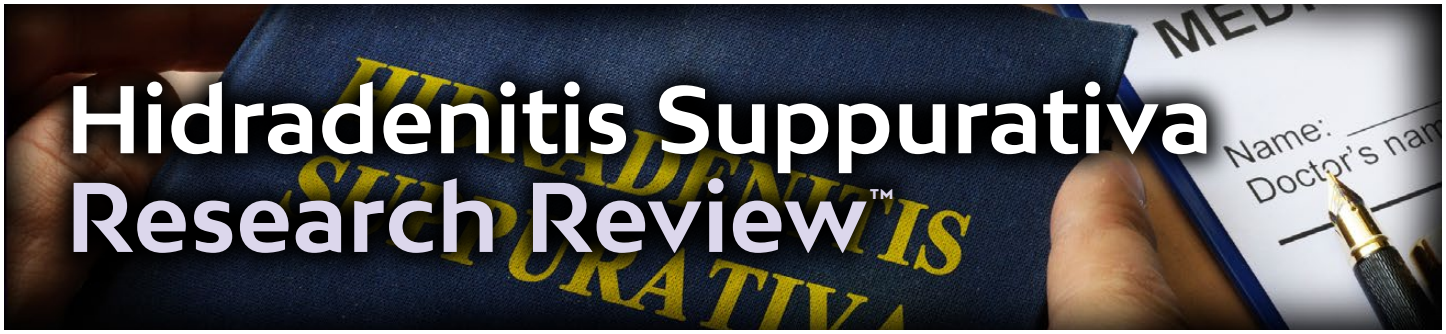

Hidradenitis Suppurativa Research Review™

Making Education Easy

Issue 12 - 2021

In this issue:

Abbreviations used in this issue:

AD = atopic dermatitis; **BMI** = body mass index; **CI** = confidence interval; **DLQI** = Dermatology Life Quality Index; **HiSCR** = Hidradenitis Suppurativa Clinical Response; **HiSQOL** = Hidradenitis Suppurativa Quality of Life; **HR** = hazard ratio; **HS** = hidradenitis suppurativa; **IL** = interleukin; **JAK** = Janus kinase; **PtGA** = patient global assessment; **TNF** = tumour necrosis factor.

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Welcome to the latest issue of Hidradenitis Suppurativa Research Review.

The first article we look at in this issue underscores the urgent need to reduce delays in diagnosing hidradenitis suppurativa (HS) in paediatric patients with the international, multicentre study finding a median two-year delay between disease onset and clinical diagnosis, by which time a large proportion already have scarring and disease complications. A systematic review published in *Dermatology* summarises the current literature regarding the safety and efficacy of radiotherapy for HS. Radiotherapy was investigated in the 1950s for HS and has only just begun to be investigated again for this indication. Whilst the current evidence to support radiotherapy is sparce, it may be a viable option for patients with treatment-resistant disease who are not suitable for surgery and we look forward to greater clarity regarding its safety and efficacy when results are published for the ongoing Montefiore Medical Centre, New York, USA, phase 1 trial of low-dose radiotherapy for advanced HS (ClinicalTrials.gov Identifier: NCT03040804). There are some exciting new therapeutic targets being investigated for HS and John Frew and colleagues provide a systematic review of interleukin (IL) and Janus kinase (JAK) inhibition as well as a critical evaluation of their clinical relevance. We also look at some real-world evidence for the survival of biologic agents in HS and an Italian retrospective study supports the use of adalimumab earlier in the disease course, finding increased odds of nonresponse in patients treated further from disease onset.

We hope you enjoy this HS research update, and look forward to receiving any feedback you may have.

Kind Regards,

Associate Professor Erin McMeniman

erin.mcmeniman@researchreview.com.au

Hidradenitis suppurativa in the paediatric population: an international, multicentre, retrospective, cross-sectional study of 481 paediatric patients

Authors: Liy-Wong C et al.

Summary: Liy-Wong et al provide a cross-sectional medical chart review of HS presentation and diagnosis in a paediatric cohort. Analysis was based on 481 patients aged less than 19 years (80% girls) accrued from ten dermatology clinics in the US, Canada, Israel, Australia and Italy between 1996 and 2017. There was a significant delay between disease onset and clinical diagnosis, median 2.5 years. The mean age at diagnosis was 14.4 years. Cysts/abscesses were the first symptom of disease in almost half of patients (48%) while pain/tenderness or papules/pustules were the first symptom in 25% and 24% of patients, respectively. At the first clinical assessment 48% of patients had scarring. Comorbid conditions were common, found in 85% of patients, most commonly obesity (65%) or acne vulgaris (29%). Complications such as scars or contractures were also present in 80% of patients. Of the 60% of patients for whom disease severity was known, Hurley stage 1 disease was found in 47%, stage 2 in 45% and stage 3 in 8%. A family history of HS was documented in 41%.

Comment: This is a valuable contribution to the literature on HS looking at paediatric (age 1-18) patients. We should be especially cognisant of improving early diagnosis and management in children in order to prevent long-term physical and mental effects of the disease. This is a multicentre study across five countries that examined retrospective data, and found an approximate two-year delay to diagnosis from onset. From my own personal discussions with patients this delay leads to frustration, fear and the pain and recurrent nature of the abscesses has a major impact on a child's social and mental health. Obesity was a common comorbidity, in 65% and a multi-disciplinary approach is needed in order to achieve a healthy weight, which may need to be tailored to be mindful of their skin disease. If running flares their groin lesions and their scarring makes them too embarrassed to be seen swimming then the team will need to be inventive in suggesting exercise programs. It was reassuring that only 8% were Hurley stage 3, however 45% were already stage 2 meaning they have already developed scarring sinus tracts. Major efforts need to be made to improve delay to diagnosis so that effective multidisciplinary management can be started, along with repeated education about lifestyle factors such as the importance of never starting smoking.

Reference: JAMA Dermatol 2021;157(4):385-91

Abstract

Contribution of genetics to the susceptibility to hidradenitis suppurativa in a large, cross-sectional Dutch twin cohort

Authors: van Straalen K et al.

Summary: This cross-sectional twin study aimed to elucidate the heritability of HS. The authors analysed self-reported data from 2,343 twin pairs (978 female monozygotic twin pairs, 344 male monozygotic twin pairs, 426 female dizygotic twin pairs, 167 male dizygotic twin pairs and 428 dizygotic twin pairs of the opposite sex) who participated in the nationwide Netherlands Twin Register between 2011 and 2016. The prevalence of HS was 1.2% (58 of 4,686). An age-adjusted model that assessed additive genetic factors and unique environmental factors found the narrow-sense heritability (susceptibility due to additive genetic factors) of HS to be 77% (95% confidence interval [CI], 54%-90%). The authors concluded that the genetic basis of HS may be stronger than previously understood but that the study supported a multifactorial cause of disease and a genome-wide association study in patients with HS is warranted.

Comment: This study found a higher-than-expected heritability of HS between twins in the Netherlands. The overall prevalence was similar to other population wide studies, at 1.2%. Previous studies report a positive family history in 30-50% of patients with HS, and the question of whether this is primarily 'nature/genetics' or 'nurture/shared environment' has been pondered. They find a 77% narrow sense heritability, or 77% of effect is due to additive genes. The concordance in monozygotic twins was 0.31 and in dizygotic only 0.08 reflecting a much stronger genetic link than anticipated. It may be quite complex to identify a single gene though, and we may see a polygenic risk model developed as so far no clear gene targets have been found.

Reference: JAMA Dermatol 2020;156(12):1359-62
Abstract

Adalimumab and infliximab survival in patients with hidradenitis suppurativa: a daily practice cohort study

Authors: Prens L et al.

Summary: This retrospective analysis of biologic drug survival provides data regarding real-world survival of the tumour necrosis factor (TNF)-α inhibitors in patients with HS. A total of 104 patients who received treatment with either adalimumab or infliximab between 2008 and 2020 at the University Medical Centre Groningen or Erasmus University Medical Centre, Rotterdam, both in the Netherlands, were included in the study. The median age of the patients was 38 years with a median disease duration of 14.8 years. Most of the population had moderate-to-severe disease (Hurley stage 2, 38.8%, Hurley stage 3, 47.8%) and obesity and smoking were both prevalent (mean body mass index [BMI] 30.6 kg/m^2 and 80.5%, respectively). Kaplan–Meier survival curves revealed a median drug survival of 18.1 months for adalimumab and 19.5 months for infliximab. Twelve-months drug survival rates were similar between the biologics at 56.3% and 58.3% but higher with infliximab at 24-months, 30.5% and 48.6%. The main reason for discontinuation of either biologic was ineffectiveness followed by side effects such as fatigue, shortness of breath and itch, remission following surgery or switching to another biologic. Univariate Cox regression analysis revealed prolonged biologic survival in patients with more severe disease while adalimumab survival was extended in older patients (hazard ratio [HR] 0.97), those with longer disease duration (HR 0.95) and higher BMI (HR 0.93). Surgical intervention significantly improved infliximab drug survival (HR 0.32). Survival of adalimumab or infliximab was not impacted by previous biologic exposure or concomitant antibiotic use.

Comment: This is a small retrospective series, so of course we should be mindful not to over interpret from these results, however, it is valuable to make one point. The survival of both TNF inhibitors used to treat HS (adalimumab and infliximab) is significantly less than in psoriasis and can be improved by actively offering surgery to chronic sinus tracts whilst the patient is on the biologic agent. At the one-year mark 56% of adalimumab patients were still taking it and 58% of infliximab, with most discontinuations due to ineffectiveness. This survival dropped at two years to 30% for adalimumab and 48% for infliximab. Many clinicians treating HS have discussed this 'wearing off' effect, and this is why we need to manage chronic areas with surgery, and manage lifestyle factors as best as possible while we have a potential window of control. Of course, we hope that there will be a growing number of approved therapies in the future such that there are other options to move to also.

Reference: Br J Dermatol 2021; Feb 5 [Epub ahead of print]
Abstract

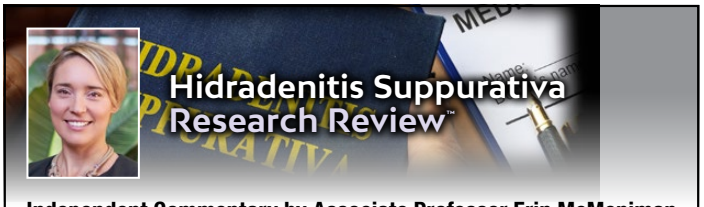
Validation of global item for assessing impact on quality of life of patients with hidradenitis suppurativa

Authors: Kirby J et al.

Summary: Kirby and colleagues from Penn State University, USA, report the development and validation of a single-item patient global assessment (PtGA) tool to evaluate health-related quality of life in HS. A reliable PtGA with five levels was identified through a cross-sectional study and cognitive debriefing interviews of patients with HS from the USA and Denmark. Concurrently administered candidate items were evaluated for validity and responsiveness in comparison to patient-reported scales such as the Hidradenitis Suppurativa Quality of Life (HiSQOL), Dermatology Life Quality Index (DLQI) and numerical rating scale for pain. The authors reported that the single-item PtGA demonstrated validity (significant correlation with both HiSQOL score and DLQI, r=0.79 and r=0.78, respectively; p<0.001), reliability (intraclass correlation coefficient, 0.82; 95% CI, 0.78-0.85) and was capable of detecting changes in improvement.

Comment: Whilst many dermatologists are familiar and comfortable using the DLQI it really does not capture the impact of HS on a patient's daily life. The DLQI works better for eczema and psoriasis but fails to reflect the impact of pain and oozing of pus on the function of a patient. After extensive focus group work, the HiSQOL was developed, and I have found it to be an excellent tool for measuring impact of this disease. It is easy to do, and a patient can fill it out as I write notes or print scripts. It serves as a good way for me to focus on what aspects bother the patient the most, and we can discuss the aims of treatment and what I am hoping will improve. For example, we will discuss that a biologic agent will be used to try to reduce pain, and number of new nodules, but will not remove scarring. The HiSQOL is 17 questions asking how the disease impacts exercise, work, sexual function, mental health and about pain, itch, drainage and odour. This latest paper is offering a simplified version of the HiSQOL which asks one question, "In the past seven days how much has HS influenced your quality of life?" and is rated 0-4 to represent not at all to extremely impacted. Although the study reports this correlated with HiSQOL my reservation is that this was done in a population who had been through consent, all the lead up questions and who are primed and ready to think about impact on day-to-day life. In my experience patients are sadly so used to coping with their pain, ooze, impact on mental health, that they may not answer this one-off question in a reliable way in the real world of clinical medicine. This an academic centre, and the results of this study may be biased by the concurrent administering of the more thorough tools which specifically ask the patient to reflect on 17 ways their disease impacts their daily choices and function.

Reference: Br J Dermatol 2021;184(4):681-7
Abstract



Independent Commentary by Associate Professor Erin McMeniman

BSc MBBS FRACGP MPH FACD PhD, Princess Alexandra Hospital Department of Dermatology, University of Queensland Medical School

A/Prof McMeniman is a dermatologist with an interest in public health, skin cancer, and medical dermatology. She completed a Master of Public Health with a dissertation project in skin diseases in indigenous children and recently completed her PhD on the phenotypic and genotypic correlations in a cohort of patients with multiple primary melanoma. Dr McMeniman conducts a medical dermatology clinic two sessions per week at The Princess Alexandra Hospital, treating a broad range of auto-immune, auto-inflammatory and reactive dermatoses. She has developed Queensland's first multi-disciplinary clinic treating Hidradenitis Suppurativa and has a special interest in this disease. She is a member of the Academic Research committee of the Australasian College of Dermatology, and Chair of the Aboriginal and Torres Strait Islander Committee.

Evidence for a 'window of opportunity' in hidradenitis suppurativa treated with adalimumab

Authors: Marzano A et al.

Summary: This retrospective, real-life multicentre cohort study published in the *British Journal of Dermatology* confirms the efficacy of adalimumab in an Italian real-world cohort of patients with HS and examines factors predicting response. A total of 389 patients (median age 34 years) with moderate-to-severe HS (Hurley stage ≥ 2 or International Hidradenitis Suppurativa Severity Score System ≥ 4) resistant to standard first-line treatments who underwent adalimumab treatment between 2016 and 2018 at one of 21 Italian centres were included in the analysis. Efficacy was measured using the Hidradenitis Suppurativa Clinical Response (HiSCR) and a response (defined as ≥ 50% reduction in nodule and abscess count and no increase in draining fistula count) was achieved by 43.7% of patients at week 16 and 53.9% of patients at week 52. There were also significant improvements at both time points in quality of life as measured using DLQI and Visual Analogue Scale for pain (all $p<0.0001$). Patients with a therapeutic delay of greater than 10 years (time between disease onset and adalimumab initiation) had almost double the odds of not responding to adalimumab treatment compared to patients treated within 10 years (at week 16, odds ratio [OR] 1.92; 95% CI, 1.28-2.89; $p=0.0016$). Reduced odds of achieving a response to adalimumab was also seen in patients with previous systemic immunosuppressive or immunomodulating agent exposure (at week 52, odds ratio 1.78; 95% CI, 1.08-2.95; $p=0.0250$). The authors concluded that this data supports the use of adalimumab earlier in the disease course. A safe toxicity profile was reported with mild adverse events, most commonly asthenia, headache, arthralgia, upper respiratory tract infection, dizziness and nausea.

Comment: This study over 21 centres included 389 patients treated with adalimumab. It has provided some evidence to back up the hunch many of us have from our clinical experience that patients are better off if their disease is managed earlier from disease onset, and earlier in disease progression from Hurley stage 1 to 3. I have now seen many patients presenting early in the process with Hurley 1 or 2 with small localized sinus tracts that do amazingly well with topicals, limited deroofing surgery to chronic sinus tracts and they may or may not need long-term antibiotics or biologics. The good news is the disease does not seem to be on a relentless march forward in all cases. There are, of course, the very severe patients who despite treatment, progress, however, the average patient with localised disease should expect to enjoy very good control with simple and safe treatment. They do need to be diagnosed and treated as soon after onset as possible!

Reference: Br J Dermatol 2021;184(1):133-40
Abstract

Radiotherapy for hidradenitis suppurativa

Authors: Thompson A et al.

Summary: This systematic review published in *Dermatology* summarises the current literature regarding the safety and efficacy of radiotherapy for HS. The researchers identified nine articles published between 1950 and 2020 from a search of PubMed and Embase that included 122 patients with treatment-resistant HS. All articles were either a case report or case series. The bulk of patients (n=105) were in reports published prior to 2000. While radiotherapy dosing schedules and total doses varied, results were reported as generally favourable, achieving high rates of lesion resolution, partial responses or substantial improvements with few adverse effects, especially in later studies where radiotherapy was delivered in fractions over multiple doses. The authors concluded that radiotherapy may be an option for patients with treatment-resistant disease who are not suitable for surgical intervention due to disease location or comorbidity. They also commented on the paucity of consensus regarding patient selection, dosing and long-term effects such as secondary malignancy.

Comment: This systematic review found nine articles (involving treatment of 122 patients) which met inclusion criteria. It was interesting to read some very positive responses with up to four-years of data showing ongoing complete or partial response in many. Radiotherapy was only considered in those who had failed all other options and were poor surgical candidates. There is currently a phase 1 clinical trial recruiting for treatment using low-dose radiotherapy. Of course, the long-term risk is malignancy of structures including skin, bowel and ovary. A review on this risk states that it is two per 1000 patients treated, and this is higher if the patient is younger. It is not known if controlling the HS will reduce the risk of squamous cell carcinoma in the diseased area, or contribute, making this life-threatening complication more likely. I have seen three patients now who have developed squamous cell carcinoma in their HS, all were men and all had severe buttock disease with the squamous cell carcinoma developing deep in the sinus tract. I look forward to the outcome of the trial on this potential treatment option for our most complex patients.

Reference: Dermatology 2021;237(3):357-64
Abstract

A systematic review of promising therapeutic targets in hidradenitis suppurativa: a critical evaluation of mechanistic and clinical relevance

Authors: Frew J et al.

Summary: John Frew and colleagues provide a summary of new therapeutic targets in HS identified primarily from observational studies. They discuss recent clinical trials that evaluate/ are evaluating inhibition of IL-1, IL-23, IL-17, complement or JAK and the problems encountered including elevated placebo responses. The authors also suggest high-fidelity inflammatory endotype profiling to help eradicate knowledge gaps in HS pathogenicity.

Comment: This work summarises some very exciting work on the cytokine targets in HS. In recent years there has been an explosion of work aiming to understand the pathogenesis of HS and elicit which inflammatory pathway is to blame and should be blocked. Unfortunately, animal models do not seem to be reliable, so most efforts have focused on inflammatory mediator levels in blood and tissue and on observational clinical studies. This paper discusses hopeful pathways of IL-1 (A and B), IL-17, (A, RA, A/F) and IL-23 alone and IL-12/23, IL-36 and JAK inhibitors. The future for management of HS is very promising!!! Be prepared that we may also need multiple agents or higher doses, we may need to combine topicals, orals, surgery and lifestyle management along with this exciting new cutting-edge immunomodulation.

Reference: J Invest Dermatol 2021;141(2):316-24
Abstract

Hidradenitis suppurativa and atopic dermatitis: A 2-way association

Authors: Sherman S et al.

Summary: Data from a retrospective population-based cohort study in Israel published in *Journal of the American Academy of Dermatology* supports the existence of a bidirectional association between HS and atopic dermatitis (AD). Comparison of a cohort of 6,779 patients with HS to a cohort of 33,260 age-, sex- and ethnicity-matched control individuals revealed a more than double likelihood of developing AD in HS patients (2.51 vs 1.25 per 1000 patient years; HR 2.06; 95% CI, 1.64-2.58) and a significantly higher prevalence of pre-existing AD (2.5% vs 1.8%; $p<0.001$). Conversely, patients with a history of AD had increased odds of HS (OR 1.41; 95% CI, 1.19-1.67). Patients with concomitant diagnoses of HS and AD were more likely to be younger, female, non smokers and have a lower BMI than patients with HS alone.

Comment: This study examined the records of over 6,700 patients with HS compared with 33,000 controls. Patients with HS were twice as likely to develop AD compared with controls. Many patients with HS report itch associated with their lesions, and it can be a very distressing part of their disease. It would be interesting to know if this symptom is more common in HS patients who do have AD. Certainly the itch of HS can be treated in a similar way with topical steroids. The value of this paper is in further supporting HS as an auto-inflammatory disease, with known association with other immune deregulation states. I will look forward to trying IL-4/13 pathway inhibition in HS, to date I have not had the chance.

Reference: J Am Acad Dermatol 2020; Dec 27 [Epub ahead of print]
Abstract

