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Review

Hidradenitis suppurativa: infection, autoimmunity, or both?

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***Abstract*:** Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease mainly affecting areas rich in apocrine glands. Clinically, is characterized by painful subcutaneous nodules and if left untreated to pus secretion, abscess and fistula formation. Its frequency is estimated to be 0.5–4% of the general population, affecting women more often. Pathogenesis of HS is still not clearly defined. It seems to be a combination of genetic factors with alterations in the skin microbiome. Furthermore, at tissue (i.e. skin) as well as at serum level, several inflammatory cytokines are upregulated. The most important of the latter are tumor necrosis factor (TNF), interleukin (IL)-1, IL-17, and IL-23. Adding another level of complexity, it has been suggested that keratinocytes might be intrinsically activated, contributing also to the observed inflammation. Interestingly, it has been noted that frequency of HS is increased in some autoimmune rheumatic diseases, such as spondyloarthropathies (SpA). Of note, both HS and SpA have relatively strong association with metabolic diseases and obesity implying that there are indeed some common underlying pathophysiological pathways. Although no specific microbe has been identified, alterations in the microbiome of the skin of these patients have been reported. Of note, microbes with a capability for biofilm formation are abundant. Treatment of HS among others, include antibiotics as well as biologic drugs targeting TNF and other cytokines and used for autoimmune rheumatic diseases.
Herein, we review the current evidence on links between HS and autoimmune diseases and infectious diseases with a focus on epidemiology and pathophysiology.

***Keywords*:** autoimmunity, Hidradenitis suppurativa, microbiome

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Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by subcutaneous painful nodules[1] affecting areas rich in apocrine glands such as axillary, inguinal, genital, and infra-mammary regions.[2] The inflamed glands result into pus secretion and eventually to scar, fistula, sinuses, or abscess formation.[3,4] Its frequency has a wide range among different ethnic subgroups,[2,5] but on average is estimated to be around 0.5–4%.[2,3,6,7]

Epidemiology

HS remains generally under-recognized,[8] especially if not presented to dermatologists, affecting the overall reported prevalence and incidence figures. This is despite its very distinct clinical presentation and the possibility to achieve a reliable diagnosis even based on simple questioning.[9] Prevalence figures are also affected by the nature of the studies undertaken, population studied, and geographical location.[10] With a prevalence of up to 4%, HS is therefore frequent, especially in post-pubescent women.[8,11] However, the onset of HS has been described also in prepubertal children as well as postmenopausal women.[7,12] The female:male ratio is approximately 3:1, with women showing a greater likelihood of having genitofemoral lesions.[13] The prevalence of HS appears to decline after the age of 50 years.[7] Around a third of patients report a positive family history for HS, with an autosomal dominant pattern of inheritance.[14,15] Family history has been

associated with early onset HS.[16] Many genes have been implicated in the pathogenesis of the disease with these encoding for expression of the subunits of γ-secretase complex being the most well described.[2] Single nucleotide polymorphisms in the promoter region of the tumor necrosis factor (TNF) gene have also been linked with HS.[17]

Associations with metabolic disease, autoimmune rheumatic diseases, and other conditions

Associations have been reported with various factors and habits that belong in the cardiometabolic spectrum, such as obesity, diabetes mellitus, dyslipidemia, hypertension, and smoking.[7,18,19] Smoking has been linked with worse disease in HS.[20] Similarly, a strong association has been found between body mass index (BMI) and disease severity of HS, with more severe HS seen in obese compared with overweight patients.[20] A possible metabolic loop has in fact been described linking insulin resistance and HS, with altered mammalian target of rapamycin (mTOR), the latter reported in metabolic and autoimmune disorders. More specifically, mTOR has been found to be increased in lesional as well as nonlesional skin of HS patients and mTOR gene expression correlated with the severity of HS. Evidence also implicates mTOR in insulin resistance seen in patients with HS,[21] further supporting the concept of a metabolic loop linking HS, BMI, and insulin resistance. This disease 'behavior' and association with BMI and obesity has also been reported in other inflammatory skin and joint conditions such as psoriasis and rheumatoid and psoriatic arthritis (PsA).[22–26] Common proinflammatory pathways seem to be the culprit in these observed associations.[27] For example, upregulation of conventional cytokines [e.g. TNFα and interleukin (IL)-17] and adipokines (e.g. chemerin, visfatin, leptin, and adiponectin) have been reported in psoriasis and adiposity.[28] Studies have shown a relationship between adiponectin and psoriasis, but a relationship that depends on the presence of obesity.[29] Adiponectin, a cytokine produced by adipose tissue at levels inversely proportional to BMI and waist:hip ratio, induces the release of pro-inflammatory cytokines IL-1 and IL-10 and inhibits the cytokines IL-6 and TNFα, the latter two well-recognized for their role in inflammation for example, in the setting of rheumatoid arthritis (RA). In the case of leptin, another pro-inflammatory cytokine derived from adipocytes, its circulating levels have been correlated directly with body fat mass.[30] Therapeutic strategies targeting all aspects of disease, including skin and joint involvement in the case of psoriasis and PsA as well as obesity, are recommended. Of note, a higher prevalence of metabolic syndrome has also been noted in patients with HS compared with controls, suggesting that metabolic abnormalities may be a contributing factor in the development of HS, particularly in younger patients.[31] Similar associations have been identified in psoriasis possibly due to commonalities in the mechanistic pathways underlying both skin conditions.[32,33] Interestingly, obesity also seems to negatively affect the response to biologic therapy in these conditions.[34] In line with these observations, weight loss has been associated with improved inflammatory states in autoimmune rheumatic diseases such as PsA, supporting the hypothesis of obesity as a promotor of disease activity in PsA.[23] In the case of HS, reports on nonpharmacologic approaches to therapy that include weight loss are limited by the small study size and the general lack of randomized controlled trials.[35] However, a recent multicenter, observational, crossover, pilot study has shown no association of the improvement in disease severity with weight loss.[36]

Inflammatory bowel disease is also a frequent comorbidity in HS.[37] A study has shown that 17% of patients with Crohn's disease are affected by HS.[38] Clinical, histologic and epidemiologic similarities (e.g. sinus tracts, granulomatous inflammation, scarring and post-pubertal onset) support this association.[38] In addition, it has been also suggested that mood disorders such as depression and anxiety are also more frequent in these patients.[1,39,40]

With regard to autoimmune inflammatory joint disease, rheumatoid factor negative, and HLA-B27 negative joint disease appears to be more frequent among patients with HS compared with the general population, often with asymmetrical peripheral joint involvement.[41] Interestingly, however, recent evidence from a cross-sectional study in patients from the Groningen Leeuwarden Axial Spondylarthritis (GLAS) cohort, fulfilling the Assessment of Spondylarthritis International Society (ASAS) criteria for axial spondyloarthropathy (SpA) (79% HLA-B27 positive), shows HS to be more prevalent than in the general population (9.1% *versus* 0.053–4.1%).[42] Reports also exist of the coexistence of HS with other autoimmune

rheumatic diseases such as systemic lupus erythematosus (SLE)[43] and SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome,[44] further supporting the notion of a possible common denominator in disease pathogenesis.

Pathogenesis

General aspects

The pathogenesis of HS is not entirely clear and possibly represents a dysregulated immune response to skin microbiota, in a susceptible genetic background.[1] There is some evidence that keratinocytes may be also intrinsically dysfunctional,[45] while it is unknown whether bacterial infections are *per se* the primary cause or a contributing factor to this clinical condition.[1] It is currently debated which is the initiating event in the pathogenesis of HS. Current hypothesis suggests that infundibular hyperkeratosis, follicular epithelium hyperplasia, and perifolliculitis come first.[46] These lead to possible bacterial biofilm formation,[1] distention and rupture of the terminal hair follicles (HFs), and subsequently to spillage of material (such as keratin or hair-shafts) from pilosebaceous unit to the dermis.[2,4] These act as danger signals initiating the immune response and recruiting various cells including macrophages, B and T lymphocytes, and neutrophils.[2]

As mentioned above, genetic factors play significant role in the pathogenesis of the disease. Familiar cases are associated with loss of function mutations for genes encoding proteins in the γ-secretase complex.[47] γ-secretase plays a significant role in the Notch signal transduction, as it mediates the intramembrane cleavage of the latter and subsequent release of the intracellular domain of Notch (NICD).[48] Notch plays a significant role in the HF and hair cycle homeostasis[48,49] regulating also keratinocyte (KC) differentiation and proliferation.[49–51] It also seems to be important for the development and function of natural killer (NK) and T-regulatory (Treg) cells.[47,52] It is not known what the exact role of Notch is in pathogenesis for HS. Some investigators have suggested that Notch dysregulation might be an epiphenomenon related to the observed aberrancies in keratinocytes proliferation.[53]

Tregs have been found to promote the proliferation and differentiation of HF stem cells, which is critical for HF maintenance and regeneration.[47,54] A high T-helper-17 (Th17)/Tregs ratio has been observed in the skin of patients with HS. This, was normalized after treatment with anti-TNF reagents.[55] Interestingly, an imbalance in the Th17/Tregs ratio has been found in obesity and other conditions associated with HS, as mentioned previously, such as smoking, depression, and inflammatory bowel diseases.[47]

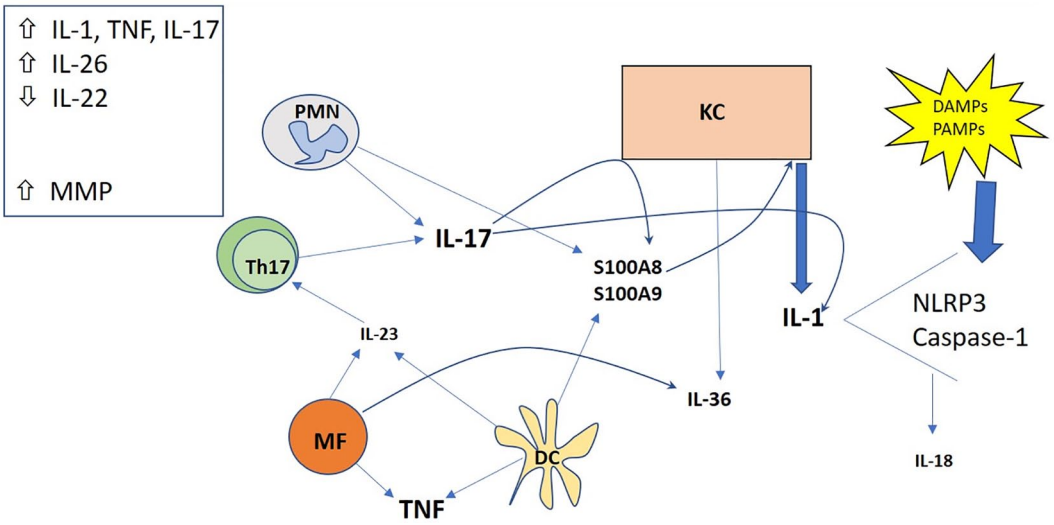
What happens at the lesion?

Histopathology. Lesions of HS are characterized by infiltrates of white blood cells. It has been suggested that in early lesions, neutrophilic abscesses along with macrophages, monocytes, and dendritic cells predominate, whereas in chronic lesions one can note more B lymphocytes and plasma cells.[56]

Cytokines-role of TNF, IL-17, and IL-1. Pro-inflammatory (IL-1β, TNF, IL-17) as well as anti-inflammatory cytokines (IL-10) are found to be increased in HS lesional and per-lesional skin compared with healthy donors or patients with psoriasis[56,57] (Figure 1). Interferon (IFN)-γ is also increasingly expressed in the skin of HS patients compared with healthy individuals.[1,50] However, this finding has not been confirmed by all investigators.[55]

TNF is produced by dendritic cells and macrophages and its levels are associated with HS severity.[1] IL-17 is produced by neutrophils,[58] Th17 cells,[59] or other cells capable for its production.[47] In agreement, high levels of IL-23 (which drives IL-17 production) have been also found to be increased in HS lesions[59] produced by macrophages and dendritic cells.[1]

It has been suggested that IL-17 might drive production of IL1-β by KCs *via* activation of the nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain containing (NLRP3) protein of inflammasome and caspase-1.[58,60] Both are increased in the epidermis of HS patients. IL-18 regulated by caspase-1 and NLRP3 was also found increased in HS skin.[57] It has been hypothesized that keratin fibers and other debris as well as damage-associated molecular pattern molecules (DAMPS) or pathogen-associated molecular pattern molecules (PAMPS) can also activate the inflammasome.[1,56] It has also been suggested that IL-17 induces the production of S100A8 and S100A9 by KCs, which are increased in lesional but not perilesional skin in HS[58] and are also expressed by macrophages and neutrophils.[50] Of note, they are also increased in



Figure–1. Molecules involved in the lesions of hidradenitis suppurativa, at a glance. At the upper right corner are summarized the main alterations observed.
DAMP, damage-associated molecular pattern; DC, dendritic cells; KC, keratinocytes; IL, interleukin; MF, macrophages; MMP, matrix metalloproteinases; PAMP, pathogen-associated molecular pattern (e.g. keratin, debris); PMN, polymorphonuclear; TNF, tumor necrosis factor; Th, T-helper.

the serum of HS patients.[58] These proteins, in turn, can augment KC proliferation and expression of pro-inflammatory cytokines and chemokines.[58] In addition, there are data supporting that KCs intrinsically produce increased levels of IL-1.[50] It is possible that there is a positive feedback loop between IL-1 and IL-17.[1] To add another level of complexity, IL-36 family members which belong to the IL-1 family are also increased systemically and locally expressed by KCs and macrophages.[61] These are able to mediate Th1 and Th17 responses as well as KC proliferation.[61,62] Finally, a recent study demonstrated that IL-26 is increased in plasma and skin of HS patients.[63] IL-26 is a cytokine expressed mainly by Th17 cells but also from other cell types such as innate lymphoid cells 3 (ILC3), and belongs in the IL-20 subfamily.[63,64] It leads to the production of pro-inflammatory cytokines through ligation to its receptors (IL-10R2 and IL-20R1) but it can also bind to cell-free DNA and subsequently activate Toll-like receptors pathways. In addition, it exerts direct antimicrobial properties having the ability to open pores in bacterial membranes.[63,64] Scala *et al.* showed that inhibition of IL-26, decreased IL-1β, IL-6 as well as human β-defensin-2 (HBD-2) and human β-defensin-3 (HBD-3) genes expression, in skin, leaving unaffected those encoding for IL-17 and IL-23.[63] Interestingly, antimicrobial, cytotoxic, and phagocytic ability from peripheral blood mononuclear cells (PBMCs) obtained from HS patients was impaired, implying that IL-26 might be dysfunctional in these patients.[63]

In contrast, IL-22 is relatively decreased in HS.[50,65] KCs from HS patients produced less IL-22 compared with those of healthy donors.[45] IL-22 deficiency has also been linked to increased IL-10 production,[65] which might be induced, among others by IL-1β.[65] It is also worth mentioning that IL-22 production is enhanced by Notch signaling, which is defective in some HS patients.[50] In human intestinal epithelial cells, it has been shown that IL-22, through the forced expression of the Notch target gene Hes1 and subsequent phosphorylation of signal transducer and activator of transcription (STAT)-3, induced the genes encoding for antimicrobial peptides (AMPs) such as REG1A, REG3A, and REG3G.[66]

Matrix metalloproteinases and AMPs. Overexpression of matrix-metalloproteinases (MMP; especially MMP-2 and MMP-8) has been observed in lesional skin of patients with HS[3,67,68] partly explaining the derangement of extracellular matrix and the respective morphological changes.[3] In a recent study, it was found that MMP-8 was secreted in HS skin by accumulating granulocytes, driven by TNF.[69] The latter was found to also increase the expression of MMP-8 by dermal

fibroblasts. Providing another hint for the link between HS and metabolic diseases, Tsaousi *et al*. found a negative correlation between MM8 blood levels (which were also increased) and high-density lipoprotein (HDL) blood levels.[69] For the former, a positive correlation with resistin is also reported.[69] To be mentioned, resistin is one of the key adipokines increased in obese patients. It is considered as an inflammatory mediator and has been reported to be increased in patients with inflammatory arthritis similarly to PsA and ankylosing spondylitis.[25] In addition, IL-17 could be related with augmented MMPs production, as it has been shown previously for fibroblast-like synoviocytes from patients with enthesitis-related arthritis.[70]

AMPs seem to also have a role in HS. There is relative deficiency of AMPs in HS lesions, compared with skin from psoriasis or atopic dermatitis patients.[65] This could be related to the lower IL-22 and IL-20 levels in HS lesions, both regulating along with other factors (e.g. IL-17) AMP production.[65] It has been shown that there are alterations in the pattern of the AMP produced by isolated KC from HS patients compared with healthy donors, further supporting the notion for an intrinsic defect of these cells.[50] Transcriptome analyses have shown that expression of the AMPs dermcidin and ribonuclease-7 were downregulated in HS lesional skin compared to skin form healthy donors.[71,72] The role of dermcidin was further highlighted in another transcriptome analyses, in which the gene encoding for this AMP was one of the top downregulated genes in HS lesions compared with nonlesional skin from the same patients.[73] On the other hand, in HS lesions compared with healthy skin from the same patients, mRNA levels of several AMPs such as HBD-2, S100A7 (psoriasin), S100A7A (koebnerisin) and LL-37 were found to be increased.[73–75] LL-37 (cathelicidin) can be produced by many different cell types including resident cells such as keratinocytes and immune cells. Its levels were correlated with presence of immune cells such as neutrophils, macrophages, and T cells.[4] It acts as chemo-attractant, augmenting also pro-inflammatory responses, upregulating costimulatory molecules expression by DCs and increasing the production of pro-inflammatory cytokines [4] Expression of AMPs might also vary, with regard to the severity of HS. Hofmann *et al*.[72] found that HBD-3 was upregulated in HS but not in patients with Hurley grade III.

Serum

At a peripheral blood level, inflammation markers such as C-reactive protein (CRP) and several cytokines, most of them are pro-inflammatory, are found to be elevated in HS patients. In fact, it is generally observed that IL-1, IL-6, IL-8, IL-12p70, IL-17, soluble TNF receptor II (sTNF-RII), TNF-a, and IL-10 are found to be elevated in the peripheral blood of these patients.[18,76–79] Recently, it was suggested that IL-26 is also increased.[63] Various studies have shown that levels of the pro-inflammatory cytokines and CRP go in parallel with disease[18,76,77,79] and mirror response to treatment.[18] In addition, a small study has suggested that baseline IL-6 and CRP levels can serve as negative predictors for response to infliximab;[80] and the frequency of T cells secreting IL-17 and IL-22 is increased in the peripheral blood of patients with HS compared with that of healthy donors.[50] IL-17 leads to chemokine production, which, in turn, recruit leukocytes (e.g. macrophages, neutrophils) at the site of inflammation.[81] In addition, they augment the production of IL-1β and IL-6 providing a positive feedback loop for Th17 cells development and subsequent IL-17 production[81] and regulate AMP production. On the other hand, it has to be mentioned that there are some possibly contradictory data.[82,83] Kanni *et al*. have shown that isolated PBMCs produced lower levels of the above-mentioned cytokines compared to healthy controls, which is also in line with the fact that no differences were observed in the whole blood mRNA expression between patients and controls.[83,84] These discrepancies require further investigation but might represent differences in the environment (*in vivo versus ex vivo*) in that the cytokines were measured, in epigenetics modifications, or both.[84]

A recent study demonstrated that complement might have some role in HS.[3] Kanni *et al*. showed that C5a and membrane attack complex C5b-9 were increased in plasma of HS patients compared with healthy individuals.[3] In addition, in *ex vivo* experiments they showed that blocking c5a was able to inhibit TNF production by patients' PBMCs. These findings imply a central role of the complement in HS and possibly explain, at the same time, recruitment and activation of neutrophils at skin lesions.[3]

Microbiome and biofilms

Despite the clinical presentation of HS that resembles bacterial infection and the efficacy of

antimicrobials as a treatment modality, the role of bacteria remains controversial. To understand their role in the pathogenesis of HS and possibly identify new therapeutic targets, researchers tried to isolate bacteria from skin lesions in HS patients. No specific bacterial agent has been found so far, contrariwise a variety of microorganisms mostly part of the skin normal flora were identified. Gram-positive cocci and rods,[85] including *Staphylococcus aureus*, coagulase-negative *staphylococci* (CoNS), and *Corynebacterium spp* have been isolated from deep tissue samples. CoNS were the most common species found in cultures from deep lesions obtained by carbon dioxide laser treatment.[86,87] *Staphylococcus lugdunensis*, a CoNS species, was associated with early stages of HS lesions (Hurley I).[88] Anaerobic bacteria, predominantly Gram-negative rods *Prevotella* and *Porphyromonas*, were also identified in various early and chronic HS lesions.[88,89] Using next-generation sequencing, it was demonstrated that there is a significantly different microbiome in patients with HS, either lesional or nonlesional, compared with that in healthy controls: *Corynebacterium* species (type I) or *Porphyromonas* and *Peptoniphilus* species (type IV) were the predominant species identified from HS lesions, whereas type IV was not detected in healthy controls. This significant difference between both lesional and nonlesional HS skin microbiota and that in healthy controls, drives the hypothesis of a link between a dysbiotic cutaneous microbiome and HS.[90]

The formation of biofilm in chronic and acute HS lesions is not a surprising finding knowing that CoNS and the other commonly found in HS bacteria are known for their capability of biofilm formation.[91,92] The presence of the latter has implications both in the pathogenesis of HS, as well as in the choice of treatment. The chronic course with acute exacerbations in between, the need of prolonged treatment with the slow healing process of the lesions, the need for surgical debridement in severe stages, and the relative resistance towards classic antimicrobials are compatible with a biofilm-driven disease.[93]

Severity and scores of HS

In the last three decades, multiple scoring systems have been introduced in order to evaluate the severity of HS. The Harley staging system was proposed first in 1989 and it is still widely used in research and clinical practice. It uses clinical features such as the presence of abscesses, scarring, and sinus track formation to categorize HS patients into three distinct stages: stage I is characterized by abscess formation, single or multiple, without scarring or sinus tracts; stage II by recurrent abscesses single or multiple, widely separated lesions with scarring and tract formation; and stage III by diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.[94] Hurley severity staging is helpful in therapeutic decisions, but it is not suitable for treatment evaluation during follow up. Thus, more dynamic HS scoring systems such as Sartorius score (later modified) and Physician Global Assessment (PGA) were proposed in order to assess treatment response better; an overwhelming need especially after the introduction of biologics into the treatment options.[20,95] A more recent scoring system, Hidradenitis Suppurativa Clinical Response (HiSCR), is defined as at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess and draining fistula count when compared with baseline[96] and has been used to assess the effectiveness of treatment with biologics. Furthermore, scale scores that consider the degree of pain, the number of flares, and the impact on quality of daily life in HS patients, such as the Dermatology Life Quality Index (DLQI) and Pain Visual Analog Scale, have been used to assess treatment effectiveness in both research and clinical settings.[97] It is worth noting that not all the staging scores use biomarkers in the assessment of either the severity or the treatment response. However, a study proposed that soluble interleukin-2 receptor (sIL-2R) serum level could be used as a valuable marker for disease staging in patients with HS.[98] Finally, is worth mentioning that efforts have been made to establish a core outcome set in HS clinical trials.[99]

Treatment

Antibiotics

Systemic antibiotics used to be the cornerstone of HS treatment for decades. Both European[100] and North American[97] guidelines continue to recommend as a considerable option the use of antimicrobial agents alone or in combinations at different stages of HS. Tetracyclines, clindamycin, rifampicin, moxifloxacin, metronidazole, and ertapenem are the agents that have proved their efficacy in HS treatment. Not surprisingly, the regimens that have been proposed seem to share

more or less the same attributes: they are active against aerobic and anaerobic bacterial agents most commonly found in HS lesions, they penetrate and show antimicrobial activity in biofilms, and importantly possess significant anti-inflammatory and immunomodulatory properties.

Tetracyclines. Tetracycline and its second-generation semisynthetic analogs doxycycline and minocycline are recommended as monotherapy for mild stages of HS.[97,100] They have a broad-spectrum bacteriostatic activity against a variety of Gram-positive and Gram-negative bacteria by binding to the 30S ribosomal subunit, thereby halting bacterial protein synthesis. Doxycycline, the most commonly used tetracycline in HS, has been shown to have also the ability to penetrate *S. aureus* biofilm in high-enough concentrations to maintain its antibacterial activity.[101] In addition, doxycycline, as with other tetracyclines, has a variety of anti-inflammatory and immunomodulatory properties.[102] It can reduce the production of IL-1, IL-6, TNF-α, and IL-8, downregulate chemotaxis, promote lipo-oxygenase, MMP and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling inhibition.

Clindamycin, rifampicin. Clindamycin is the only antibiotic that has been studied for topical treatment and can be used in mild localized stages of HS.[103] It has also shown the same efficacy compared with oral tetracycline.[104] The systemic combination of clindamycin and rifampicin is the most studied and its efficacy is well established.[105,106] It is widely offered in cases of tetracycline failure in mild to moderate stages of HS.[97,100] Clindamycin has a bacteriostatic activity against both aerobic and anaerobic Gram-positive bacteria by binding irreversibly to 50S ribosomal subunit, thereby inhibiting bacterial protein synthesis. It has no potent antibiofilm effect[101] and its anti-inflammatory properties are suggested in topical treatment against *Acne vulgaris*.[107] However, the lack of both properties is balanced by the excellent antibiofilm activity of rifampicin as it has been proven in periprosthetic joint infections.[101,108] Rifampicin binds to the 50s ribosomal subunit where it disrupts transpeptidation and thereby halts protein synthesis in a similar manner to macrolides. It has a broad-spectrum activity mostly against Gram-positive and some Gram-negative bacteria as well. In addition, it is suggested that rifampicin possesses anti-inflammatory and immunomodulatory properties. There is evidence that it can reduce inducible nitric oxide synthase (iNOS) transcription and NF-κB activity, inhibit excessive Th17 responses, and thereby reduce their differentiation and secretion.[109,110]

Moxifloxacin, rifampicin, and metronidazole. This triple combination is appeared to be effective in reducing HS activity in moderate to severe cases that were refractory to other treatment.[111] Moxifloxacin is a synthetic fluoroquinolone with a broad spectrum of activity against aerobic Gram-positive and Gram-negative bacteria and has a potent activity against most of the anaerobic enteric pathogens. It is suggested that possesses anti-inflammatory properties as well, by reducing IL-1ß, IL-8, TNF-α, stabilizing IXb protein, suppressing NF-κB signaling, and reducing IL-17A.[112,113] Metronidazole was added to increase the activity spectra; to cover some Gram-negative anaerobic bacteria that are naturally resistant or have intermediate susceptibility to moxifloxacin. In addition, combination of moxifloxacin with rifampicin alters the pharmacokinetics and the efficacy of moxifloxacin.

Ertapenem. Ertapenem is an intravenous broad-spectrum β-lactam antibiotic that can be used to treat complicated skin and soft tissue infections[114] and is highly efficient in improving the clinical aspects of severe HS.[115] However, it is recommended to be used for a single 6-week course as rescue therapy or during surgical planning.[97]

Biologics

Given the role of TNF, IL-23, and IL-17 in the pathogenesis of HS, as outlined above, treatment with biologic disease-modifying antirheumatic drugs (DMARDs) has been successfully tried and are included as therapeutic options in moderate to severe HS, in the relevant European and North American guidelines.[97,100] In fact, after several trials, adalimumab has been approved for moderate to severe (Hurley stage II and III) HS. Of note, the dosing differs from schemes approved for other diseases such as RA, being 40 mg every week, after a loading dose of 160 mg and 80 mg at weeks 0 and 2, respectively.[116]

In the two largest phase-III trials (Pioneer I and II) for adalimumab in HS, involving 307 and 326 patients, HiSCR was achieved at week 12 in 41.8% and 58.9% of patients treated with adalimumab compared with 26.0% and 27.6% for placebo.[117] Infliximab has also proven to be effective

in the treatment of HS,[118] although more studies are needed. Interestingly, in a small retrospective study, infliximab in a dosing scheme of 5 mg/kg at weeks 0 and 2 performed better than adalimumab given at 40 mg every other week.[119] That said, It has been suggested that a dosing scheme of infliximab every 4 instead of every 8 weeks might be beneficial for HS patients.[120] Results for other TNF inhibitors, such as certolizumab[121] or etanercept, are either negative or inconclusive.[116]

Anakinra, an IL-1 receptor antagonist, is also a promising drug for this disease. The largest, thus far, trial for this regime has shown superiority *versus* placebo at week 12. HiSCR was achieved in 78% and 30% of the patients ($p = 0.04$), respectively. This difference wore off after 12 weeks without treatment.[122]

IL-23 is also a significant player in HS. That given, ustekinumab, which is a monoclonal antibody against the p40 subunit of IL-12 and IL-23, has been tried as a treatment modality. In the largest, thus far, open-label trial, 47% of HS patients treated with ustekinumab achieved HiSCR at week 40 and moderate to marked improvement was seen in 82% according to the modified Sartorius score.[82] Furthermore, in a small retrospective study, guselkumab, which is a monoclonal antibody against p19 subunit of IL-23, at a dose of 100 mg at weeks 0 and 4 and every 8 weeks thereafter, proved to be effective in more than half (63%) of the HS patients treated.[123] Importantly, 7 out of 8 patients in the study had previously been treated with other antibiotics. The authors of this study suggested that higher doses might be even more effective. A phase-II multicenter trial is currently underway to test this drug in moderate to severe HS.[121]

Monoclonal antibodies against IL-17 have been also tried. A recently published open-label trial for patients receiving 300 mg of secukinumab weekly for 5 weeks, then every 4 weeks reported that 78% of the patients achieved HiSCR at week 24.[124] In addition, clinical trials are underway to test the safety and efficacy of this secukinumab and bimekizumab (monoclonal antibody against IL-17a and IL-17F) in moderate to severe HS.[121]

Finally, apremilast, which is an inhibitor of phosphodiesterase-4 (PDE4) approved for psoriasis and PsA, has shown some efficacy in HS. In a placebo-controlled trial, 53% of HS patients at 30 mg of apremilast, twice a day, achieved HiSCR at week 16 compared with none of placebo ($p = 0.055$).[125]

In general, treatment for HS is not clearly defined and is based on anecdotal evidence and expert opinion.[126] As a general approach, systemic or topical antibiotics are used. However, in moderate to severe disease or when antibiotics discontinuation leads to disease flares, treatment with biologic drugs or other immunosuppressives is suggested.[126] Short-term glucocorticoids can also be used as a bridging or adjuvant therapy.[97] Surgical treatment is used alone or usually in combination with medical treatment, as outlined previously.

Conclusion

HS is not as rare as previously thought, affecting 0.5–4% of the general population. Its pathogenesis is still largely unclear. However, it seems that a combination of genetic factors and skin microbiome alterations play a role. TNF, IL-23/IL-17 axis, and IL-1 seem to also play a significant role, which is mirrored in the efficacy of TNF inhibitors and other biologics in the treatment of HS. Links between HS and autoimmune conditions have been demonstrated, with an increased prevalence of HS in some antirheumatic drugs and common associations with comorbidities of the metabolic spectrum. Future epidemiologic studies in large HS or antirheumatic drug cohorts will clarify this issue and might elucidate more the pathogenesis of the former.

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