Emerging medical treatments for hidradenitis suppurativa

Alexis B. Lyons, MD,[a] Nadine Shabeeb, MD, MPH,[b] Cynthia L. Nicholson, MD,[c] Taylor L. Braunberger, MD,[a] Anjelica Peacock, BS,[c] and Iltefat H. Hamzavi, MD[a]
Detroit, Michigan and Madison, Wisconsin

Hidradenitis suppurativa (HS) is a chronic inflammatory disease affecting intertriginous skin areas, and it is characterized by recurrent painful episodes of inflammatory drainage. Although the pathophysiology of HS is not fully understood, recent research points to an imbalance of cytokines as a contributing factor to the associated symptoms of purulent drainage and sinus tract formation. HS lesions are often characterized by a superimposed pathogenic/commensal bacterial infection that can improve with targeted antibiotic therapy. New medical treatments have emerged in recent years, many of which specifically work against a variety of proinflammatory mediators associated with HS. These newer, specified treatment options, in conjunction with surgery and lasers, are thought to provide positive outcomes and an overall improvement in quality of life in patients with HS. (J Am Acad Dermatol 2020;83:554-62.)

Key words: hidradenitis suppurativa; inflammatory disorders; medical therapies; treatment.

Hidradenitis suppurativa (HS) is a chronic inflammatory disease affecting apocrine gland–bearing skin.[1] Despite recent advances, there is still much to learn about the pathophysiology of this disease. Recent research has uncovered targeted treatment options (Table I).[2,3] The Hurley staging system is most commonly used to assess HS severity, with Hurley stage I classified as recurrent nodules and abscesses, stage II as a limited number of sinus tracts or scarring, and stage III as many sinus tracts and scarring.[4] Additional publications addressing well-established medical and surgical treatments,[5] and why some treatments have been discontinued, also offer additional background beyond the scope of this discussion.[6] A particularly notable advance has been the introduction of biologic medications targeting inflammatory messengers that may help control the inflammatory milieu.[7] Research has led to a deeper understanding of the cytokine imbalance that may be involved in perpetuating this recurrent inflammatory disease, and with additional research, new medical treatment options for HS will continue to emerge (Fig 1).

EMERGING ANTIBACTERIAL TREATMENTS

Dysbiosis was recently proposed as a pathogenic concept in HS and is defined as the derangement of the normal microbiome, with fewer normal bacteria and an abundance of pathogenic bacterial populations.[8,9] It is hypothesized to be the result of a synergistic interaction between a dysregulated innate immune system and the microbiota of the skin.[10] The ability to alter the microbiome of patients with HS offers a new therapeutic target.

In addition, biofilms have been implicated in the pathogenesis of HS. Biofilms are formed when bacteria attach to a substrate or to one another and then become embedded in a matrix of extracellular polysaccharides that provide protection and

From the Department of Dermatology, Henry Ford Hospital, Detroit[a]; Department of Dermatology, University of Wisconsin Hospital and Clinics, Madison[b]; and Department of Dermatology, Wayne State University, Detroit.[c]

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Correspondence to: Iltefat H. Hamzavi, MD, Department of Dermatology, Henry Ford Hospital, 3031 West Grand Blvd, Detroit, MI 48202. E-mail: lhamzav1@hfhs.org.

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stability, making them difficult to clear with antibiotics or through host defense mechanisms.[10-12] Biofilm disorders are ultimately refractory to treatment and are characterized by a chronic course with acute exacerbations; features consistent with HS.[11,13,14] In a study of 42 patients with chronic HS, biofilms were present in 67% of chronic lesions and in 75% of perilesional samples.[11]

Ertapenem

Ertapenem is a potent intravenous antibiotic with a broad spectrum of coverage, including aerobic Gram-positive, Gram-negative, and anaerobic activity.[15] A study of 30 patients treated for 6 weeks with intravenous ertapenem daily resulted in a mean decrease in Sartorius score from 49.5 to 19.0.[15] Another study of 36 patients with HS who were treated with ertapenem found that 97% showed improvement of HS severity and that 86% experienced increased quality of life.[16]

Rifampin

Combination antibiotic therapy including rifampin is often used as a first-line treatment for HS.[17] Rifampin monotherapy should be avoided to prevent the rapid development of bacterial resistance.[18] Rifampin is thought to have antibacterial, antibiofilm, and anti-inflammatory properties, among others.[17] In addition, a recent study by Ardon et al[19] found that rifampin was the most effective antibiotic in eradicating *Staphylococcus epidermidis* biofilms found in HS lesions.

Photodynamic therapy

Photodynamic therapy (PDT) is a commonly used cancer therapy and has also shown efficacy in the treatment of several infectious diseases. Because the biofilms in HS lesions are often resistant to antibiotics, PDT is an option for disruption of these biofilms. A study of intralesional PDT in patients with HS showed that 5 out of 7 patients had remission of the disease in the treated area after 6 months.[20] However, topical PDT has shown equivocal results.[21-23]

AGENTS TARGETING DYSREGULATED IMMUNITY

The immune response is a complex system. The 2 pillars of the immune system, innate and adaptive, are known to interface.[24] Immune dysregulation, including cytokine expression, is thought to contribute to the pathogenesis of HS. Inappropriate immune response to bacterial flora of the skin is hypothesized to play a role.[25] High levels of neutrophils in the deep infiltrate of HS lesions lead to suppuration, which significantly affects the quality of life of patients with HS.[25] In addition, a recent study found that interleukin (IL) 26 in patients with HS may play a role in decreased skin antimicrobial activity.[26] More research is needed to identify biomarkers in patients with HS to correlate disease severity and response to treatment.

CAPSULE SUMMARY

- Although hidradenitis suppurativa is still an understudied disease, recent research has uncovered targeted treatment options.
- New medical treatments have emerged that specifically work against a variety of pathogens and proinflammatory mediators associated with hidradenitis suppurativa.

IL-17 inhibitors

IL-17 is an inflammatory cytokine that causes immense inflammation.[27] A recent systematic review of inflammatory cytokines involved in HS found a large degree of variance between measured levels of cytokines between studies but did find a strong and significant IL-17 component.[28] IL-17 has been found to be elevated in the serum of patients with HS, with levels positively correlated with disease severity.[25,29] There are also increased levels of IL-17 in both lesional and perilesional skin of patients with HS.[25,30] Increased levels of IL-17 in perilesional skin suggests that IL-17 may appear early on and may also explain the recurrence of lesions after surgical excision.[31]

Anti—IL-17 antibodies have emerged as a possible treatment for HS.[29] In a man with recalcitrant Hurley stage III disease, 12 weeks of treatment with secukinumab, an anti—IL-17a monoclonal antibody, led to improved patient-reported outcomes, including lesion count and pain; however, physician-reported outcomes did not show any significant improvements.[32] In addition, CJM112, a new fully human anti—IL-17 monoclonal antibody, acts by blocking the binding of IL-17A to its receptor, which then prevents inflammation by inhibiting the release of inflammatory cytokines and chemokines.[33] A phase 2 clinical trial is currently investigating its safety and efficacy in treating moderate to severe HS.[33] Bimekizumab, another anti—IL-17 antibody to both IL-17A and IL-17F, has shown promise for the treatment of psoriasis.[34] It is also currently undergoing clinical trials to test its efficacy, safety, and pharmacokinetics in patients with moderate to severe HS (NCT03248531). Further studies are needed

Abbreviations used:

HS:	hidradenitis suppurativa
IL:	interleukin
JAK:	Janus kinase
PDT:	photodynamic therapy
PG:	pyoderma gangrenosum
STAT:	signal transducer and activators of transcription
TNF:	tumor necrosis factor

to elucidate the role of these medications in the treatment of HS.

IL-12 and IL-23 inhibitors

IL-23 has been associated with the development of autoimmune disease in animal models and is also expressed in humans with autoimmune diseases.[35] Activated macrophages in HS lesions express IL-23 and IL-12.[36,37] Ustekinumab is a human IgG1 monoclonal antibody that binds to the common p40 subunit of IL-12 and IL-23.[38] In a prospective study of 17 patients with Hurley stages II and III HS treated with ustekinumab, 82% of patients showed marked or moderate improvements in their modified Sartorius scores after 40 weeks of treatment.[38]

Apremilast is a phosphodiesterase 4 inhibitor with anti-inflammatory effects that works by inhibiting the production of proinflammatory cytokines such as tumor necrosis factor (TNF), IL-12, and IL-23.[39,40] In a case series of 9 patients with refractory HS, 6 patients completed treatment, and 5 showed significant decreases in Sartorius, pain, and Dermatology Life Quality Index scores.[39]

Additionally, guselkumab, a novel anti—IL-23 monoclonal antibody, is being studied as a treatment for patients with moderate to severe HS (NCT03628924). More information from larger studies is needed to draw conclusions and make recommendations.

IL-1 inhibitors

IL-1 plays a major role in local and systemic inflammatory processes.[41] IL-1B leads to the induction of chemokines and the stimulation of inflammatory cells.[31,42] IL-1B and TNF are both upregulated in the lesional skin of patients with HS and are correlated with Hurley stage.[31] Levels of IL-1B are also significantly increased in perilesional skin.[31]

Anakinra is a recombinant IL-1 receptor antagonist that competitively inhibits IL-1A and IL-1B from binding to the IL-1 type 1 receptor.[43] A randomized trial assessing the use of anakinra in the treatment of severe HS showed a decreased disease activity score in 67% and 20% in the anakinra and placebo groups, respectively.[43] At 12 weeks, the Hidradenitis Suppurativa Clinical Response was attained in 78% and 30% in the anakinra and placebo groups, respectively.[43]

Additionally, canakinumab is a humanized monoclonal antibody against IL-1B.[44] One patient with moderate HS and treatment-refractory pyoderma gangrenosum (PG) was treated with canakinumab with resolution of the HS lesions after the first injection.[44] Furthermore, MABp1/bermekimab, a true human anti—IL-1 alpha antibody, is undergoing phase 2 clinical trials for the treatment of HS (NCT02643654, NCT03512275).

TNF inhibitors

TNF is a proinflammatory cytokine that is upregulated in lesional skin of patients with HS.[31] Adalimumab is a fully human IgG1 monoclonal antibody to TNF and is the only medication approved by the US Food and Drug Administration for HS.[45] Infliximab is another anti-TNF agent that has also shown efficacy in the treatment of HS.[46,47] The dosing of infliximab is weight based, while the dosing of adalimumab is not. This is an important distinction and could play a role in obese patients with HS and response to treatment. Traditionally, infliximab has been dosed at 5 mg/kg at weeks 0, 2, and 6, followed by the maintenance dose every 8 weeks.[47] However, a recent prospective study by Ghias et al[48] suggested that 7.5 mg/kg every 4 weeks with dose escalation to 10 mg/kg every 4 weeks (if necessary) was effective for decreasing HS disease activity as measured by at least a 2-grade improvement in Physician Global Assessment. This study found that 20 of 42 (47.6%) patients receiving 7.5 mg/kg and 6 of 16 (37.5%) patients receiving 10 mg/kg achieved the 2-grade improvement in Physician Global Assessment at week 4. Similarly, a recent study by Oskardmay et al[49] found that infliximab 10 mg/kg every 6 to 8 weeks was well tolerated and resulted in significant improvements in abscess and nodule count, as well as draining sinuses. For patients who develop human antichimeric antibodies to infliximab, the addition of methotrexate (7.5-10 mg/week) has been used as a rescue therapy.[50]

In addition to adalimumab and infliximab, other anti-TNF treatment options including golimumab are emerging. In a patient with a history of HS, ulcerative colitis, and pyostomatitis vegetans treated for 2 months with golimumab, there was subsequent resolution of dermatologic and oral lesions and complete colonic mucosal healing.[51]

Table I. Emerging treatments for HS

Treatment agent	Mechanism of action	Outcome measures	Studies
Antibacterial			
Ertapenem	Antibiotic	Sartorius score, Hurley stage	2 studies for HS treatment[15,16]
Targeted immune modulators			
Adalimumab*	Anti-TNF	Sartorius score, HS-PGA	RCTs,[2,7,45] case series[3]
Golimumab	Anti-TNF	Wound healing	Case report[51]
Infliximab	Anti-TNF	HS Severity Index, VAS, QOL	Studied originally for Crohn's disease[46] One RCT for HS[47]
Secukinumab	Anti—IL-17a	Patient-reported outcome measures including number of lesions, pain on VAS; physician-reported outcomes including HS-PGA and modified Sartorius score	One case report[32]
CJM112†	Anti—IL-17	Efficacy for treating moderate to severe HS—no results yet	Phase 2 clinical trial is currently underway[33]
Bimekizumab†	Anti—IL-17	Efficacy for treating moderate to severe HS—no results yet	Phase 2 clinical trial is currently underway
Ustekinumab	Anti—IL-12 and anti—IL-23	Modified Sartorius score	One open-label study[38]
Apremilast	Phosphodiesterase 4 inhibitor	Sartorius score, VAS score, DLQI score	One case series[39]
Guselkumab	Anti—IL-23	Efficacy for treating moderate to severe HS—no results yet	Phase 2 clinical trial is currently underway
Anakinra	IL-1 receptor antagonist	Disease activity score, HiSCR, Sartorius, VAS, DLQI	One RCT[43]
MABp1/ bermekimab†	Anti—IL-1 alpha	Efficacy for treating moderate to severe HS—no results yet	Phase 2 clinical trial is currently underway
Canakinumab	Anti—IL-1B	Wound healing	One case report[44]
Tofacitinib	JAK inhibitor	N/A	No studies published for HS treatment yet
Baricitinib	JAK inhibitor	N/A	No studies published for HS treatment yet
INCB054707†	JAK kinase inhibitor	Efficacy in treating HS—no results yet	Phase 2 clinical trial is currently underway
IFX-1†	Anti C5a	Efficacy for treating moderate to severe HS—no results yet	Phase 2 clinical trial is currently underway
Traditional immune modulators			
Methotrexate	Prevents DNA synthesis	Self-reported symptoms, dermatologic assessment	Case report and case series[66,67]
Cyclosporine	Calcineurin inhibitor	HS severity, wound healing	Case reports and case series[68-72]
Corticosteroids	Anti-inflammatory	VAS	Case series[74] and prospective, multicenter study[75]
Hydroxychloroquine	Anti-inflammatory	Efficacy for treating HS—no results yet	Phase 2 clinical trial is currently underway
Antidiabetic agents			
Liraglutide	Glucagon-like peptide-1 agonist	HS-PGA	Case report[76]

DLQI, Dermatology Life Quality Index; *HiSCR*, Hidradenitis Suppurativa Clinical Response; *HS*, hidradenitis suppurativa; *IL*, interleukin; *JAK*, Janus kinase; *N/A*, not applicable; *PGA*, Physician Global Assessment; *QOL*, quality of life; *RCT*, randomized controlled trial; *VAS*, Visual Analog Scale.

*Adalimumab has been approved by the US Food and Drug Administration for HS since 2015.

†Not currently clinically available.

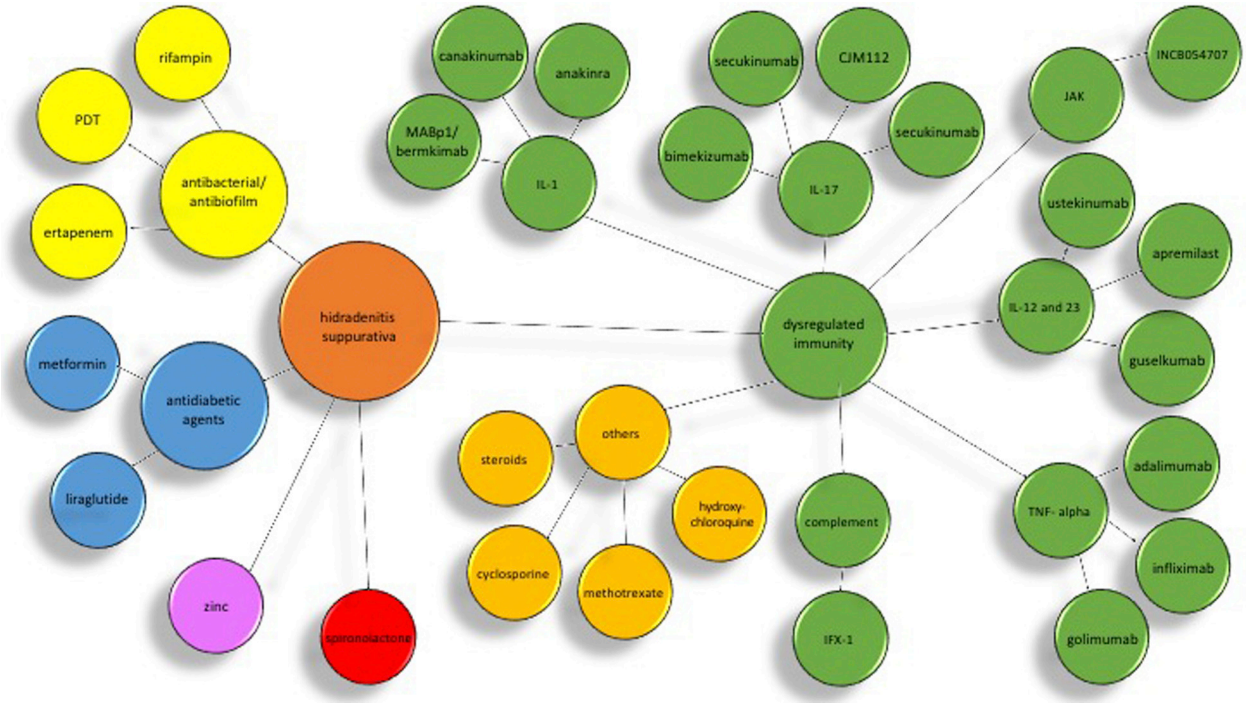

Fig 1. The complex interplay among potential targets for hidradenitis suppurativa therapy.

It is important to note that not all TNF inhibitors have shown efficacy in HS. Etanercept, a dimeric human TNF receptor that binds TNF with higher affinity than natural monomeric receptors to TNF, failed to show clinical improvement in HS lesions.[52] Although adalimumab and infliximab have shown promise, additional clinical studies are needed to determine the best criteria for patient selection to optimize treatment response.

Janus kinase inhibitors

Many inflammatory cytokines use Janus kinase (JAK)/signal transducers and activators of transcription (STATs) for signaling.[53,54] The JAK/STAT pathway is involved in inflammatory diseases including rheumatoid arthritis and inflammatory bowel disease.[55] Certain proinflammatory cytokines involved in HS act through the JAK/STAT pathway, and inhibition of this pathway may help reduce inflammation.[56] Tofacitinib has shown efficacy in the treatment of a variety of dermatologic diseases, including dermatomyositis, graft-versus-host disease, and psoriasis.[55,57] In addition, baricitinib has been efficacious in the treatment of psoriasis, rheumatoid arthritis, alopecia areata, and atopic dermatitis.[55,56,58-61]

Inhibition of the JAK/STAT pathway is an important therapeutic target for HS treatment because many proinflammatory cytokines that are instrumental in HS function either directly or indirectly through this pathway. A recently published case series showed that tofacitinib was effective in 2 patients with recalcitrant ulcerative HS.[62] Both patients had previously failed infliximab therapy and had improvement and healing of ulcerations with 5 mg tofacitinib twice daily. One patient concomitantly received 5 mg/kg cyclosporine and amoxicillin, and the other received mycophenolate mofetil, topical corticosteroids, and a combination of antibiotics. INCB054707, a JAK inhibitor, is currently being tested for efficacy in patients with HS (NCT03607487).

Complement inhibitors

Complement C5a is involved in many inflammatory processes including HS. Monoclonal antibodies against C5a may prove to be a therapeutic target for HS. For this reason, IFX-1, an anti-C5a monoclonal antibody, is currently being tested in patients with HS (NCT03001622, NCT03487276).[63-65]

Methotrexate

Methotrexate is a folate antimetabolite that prevents DNA synthesis with possible immunomodulatory effects.[66,67] There are few reports in the literature on the use of methotrexate to treat HS, with conflicting results. In a series of 3 patients with treatment-resistant HS, no clinical improvement was reported with 12.5 mg or 15 mg.[66] Larger studies are

needed to evaluate the efficacy of this nonspecific immunomodulatory medication.

Cyclosporine

Cyclosporine is a calcineurin inhibitor that prevents the expression of inflammatory cytokines and decreases T-cell activity.[68] There is limited knowledge on the use of cyclosporine in HS, with a few published case reports and case studies (2-6 mg/kg daily).[68-72] These reports show promise but have several limitations, including small sample size, lack of a control group, concomitant treatments, lack of validated outcome measures, and a variety of doses and treatment durations.

Corticosteroids

The use of systemic and intralesional corticosteroid therapy in the treatment of HS has also been explored. Prednisone blocks the effects of inflammatory mediators and upregulates anti-inflammatory mediators.[73] In a retrospective study of 13 patients with recalcitrant HS started on oral prednisone 10 mg/day, 6 significantly improved, and 5 showed remission after 4 to 12 weeks of prednisone combination therapy.[74] In addition to systemic corticosteroids, treatment with intralesional corticosteroids is used for the management of acute HS flares. In a prospective multicenter study consisting of 36 patients treated for flares with intralesional triamcinolone (10 mg/mL), there was a significant reduction in pain 1 day after treatment, as well as a reduction in edema, erythema, and suppuration assessed by physicians after 7 days.[75]

Hydroxychloroquine

Hydroxychloroquine is currently used routinely in the treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda, with its mechanism of action through the reduction of inflammation by blocking toll-like receptor 9. Because of these anti-inflammatory effects, it is also being studied in patients with HS as a potential treatment option (NCT03275870).

ANTIDIABETIC AGENTS

Liraglutide

Liraglutide is a glucagon-like peptide-1 agonist with anti-inflammatory effects that is commonly used to treat type 2 diabetes mellitus and obesity.[76] Because HS is associated with chronic inflammation, obesity, and metabolic syndrome, liraglutide may be beneficial in the treatment of HS.[76] One case report showed the successful use of liraglutide (0.6 mg titrated to 1.8 mg weekly) in a patient with refractory HS who lost weight with treatment.[76]

Metformin

Metformin is used in the treatment of diabetes mellitus by inhibiting gluconeogenesis and increasing insulin sensitivity.[77] In 1 study, 25 patients with HS with poor response to antibiotics were treated with metformin (500 mg daily titrated up to 500 mg 3 times daily) for 6 months, with 72% showing clinical improvement.[78] Metformin may work in HS by decreasing androgen production or by decreasing the sensitivity of the androgen receptor; however, past studies have shown that androgen levels are normal in many patients with HS.[78-83]

ZINC

Discussions on diet and supplementation are beyond the scope of this article, but nevertheless, these may play a role in affecting immune pathways and, in turn, inflammation and antibiotic resistance in HS. Zinc gluconate has been studied, and with its anti-inflammatory and antiandrogenic properties, it is often used as an adjuvant treatment for HS.[84] In a study of 22 patients with mild to moderate HS who received zinc supplementation, 14 had partial remission, and 8 had complete remission.[84]

SPIRONOLACTONE

Spironolactone is an androgen antagonist medication used for the treatment of some hormonal conditions including polycystic ovary syndrome, acne, and hirsutism. Some have suggested the presence of hormonal influences in patients with HS, particularly in female patients, due to the onset of the disease at puberty, improvement after menopause, and fluctuations in disease severity during pregnancy and menses.[85] A recent study by Golbari et al[86] found that 75 mg spironolactone daily improved the severity of HS in 67 female patients after 6 months. Another smaller case series of 20 women with HS observed improvement after use of spironolactone for 3 months.[87] Eighteen of the 20 women were treated with 100 mg, and 2 of the patients were started on 100 mg, which was increased to 125 mg or 150 mg.[87]

CONCLUSION

Although HS continues to be difficult to manage, new information about its pathogenesis, pathomechanism, and inflammatory mediators has given rise to new treatment options. Most of the emerging treatment options are currently available for a host of other systemic diseases. Broad-spectrum antibiotics may treat biofilm formation and modify the bacterial

burden. Biologic medications, immune modulators, and diabetic treatments have also shown promise. However, developing a coherent strategy to develop drug targets remains difficult. There is no animal model for HS; thus, the understanding of how the immune system affects the disease is based on clinical studies. Further basic and clinical studies are ongoing to better elucidate the optimal medical treatment modalities for this complex inflammatory disease.

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