

Current and Emerging Nonsurgical Treatment Options for Hidradenitis Suppurativa

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■ Abstract

Several nonsurgical strategies for managing hidradenitis suppurativa (HS) are used that are successful in many patients. The overall goals of pharmacologic therapy are to clear or reduce the number and extent of current lesions and to prevent new lesions from forming. No pharmacologic agent is universally effective in all patients with HS, and, to date, none has been approved for this indication by the US Food and Drug Administration. Among the agents most commonly used are topical and systemic antibiotics and intralesional and systemic corticosteroids. Within the past decade, clinical experience with biologic agents—principally, tumor necrosis factor inhibitors—has been described, and the results of clinical trials with these agents in patients with HS have been promising.

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The treatment options for patients with hidradenitis suppurativa (HS) include both surgical and medical modalities. The severity, extent, chronicity, and anatomic location of HS lesions determine which treatment—or combination of modalities—is most appropriate for a given individual case. Even a cursory scan of the medical literature on HS treatment suggests that surgery is the only curative method of choice. Articles abound reporting the use of various surgical techniques and their short-term outcomes. Certainly, patients with advanced disease may do well with surgery, but these procedures can be extensive and associated with high morbidity. In addition, depending on the operative site and the extent of dissection, surgery can result in disfigurement and loss of function. Moreover, long-term follow-up data are not available that demonstrate cure without recurrence, quality-of-life results, or patient satisfaction. Thus,

surgery should not be the treatment of first choice in every case but should be considered along with medical therapy in developing an individualized treatment plan.

In addition to conventional surgical modalities (including deroofing and excision procedures) and photodynamic therapy, the use of laser therapy—especially the long-pulse neodymium yag laser—has shown promise in some patients, resulting in clearance of nodules and sinuses, including deep lesions.¹

A variety of pharmacologic treatments have been used, with varying degrees of success (Figure). To date, no medical treatment has been approved by the US Food and Drug Administration (FDA) specifically for the treatment of HS. This article provides an overview of the medical therapies currently in use, including the most recent addition to the roster of options, the biologic anti-inflammatory agents.

The overall goals of pharmacologic therapy are to clear or reduce the number and extent of lesions and to prevent new lesions from developing. Theoretically, success in achieving these goals also should result in reduced scarring and other complications and sequelae. Some of the medications commonly used are helpful for many patients, but no therapy is universally effective for all patients. Effective management often requires multiple trials of agents and combinations. The categories of medications most commonly used are antibiotics (usually with topical chlorhexidine or similar skin washes), retinoids, hormones, corticosteroids, immunosuppressants, metformin, and, most recently, biologic anti-inflammatories.

Antibiotics

For many clinicians, the mainstay of initial therapy for mild to moderate HS comprises topical or systemic antibiotics, a strategy initially based on the clinical similarities between HS lesions and acne conglobata. Antibiotics do not clear HS lesions, but they are administered to treat and prevent secondary infection and the associated inflammation in existing lesions, and to prevent new breakouts. Very few studies have been done in recent years to assess the efficacy of antibiotics in HS, and published double-blind and comparative trials are even more sparse.

Clindamycin is commonly used. The benefit of topical clindamycin was demonstrated in an early, small, double-blind placebo-controlled study in HS in which the medication was statistically superior ($P < 0.01$) to placebo in reducing the number of abscesses, inflammatory nodules, and pustules.² A study of topical clindamycin and oral tetracycline failed to demonstrate superior efficacy of the systemic medication.³

Oral clindamycin plus rifampicin was evaluated in two retrospective studies published in 2009. One involved 34 patients who took 600 mg/day of clindamycin and 600 mg/day of rifampicin.⁴ Total remission was seen in 16 patients (47%) at 10 weeks; an additional 12 patients experienced at least some improvement. Thus, in this study, a total of 28 patients—or 82%—had at least some benefit from using this combination. In the other study, patients had taken 300 mg of clindamycin

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twice daily and 600 mg/day of rifampicin.⁵ At 10 weeks, the 70 patients (of the original 116) for whom data were available had significant improvement ($P<0.001$) in disease severity (measured by the Sartorius scale) and quality of life (measured by the Dermatology Life Quality Index [DLQI]).

Other antibiotics, including dapsone, also have been tried in patients with HS, although studies of these agents are limited and have yielded mixed results.⁶

Retinoids

Because of the clinical resemblance between HS and nodular cystic acne, as well as their similar pathophysiologic mechanism—namely, follicular occlusion— isotretinoin has been studied in HS, but without good results. For example, in a retrospective study of 358 patients, Soria and colleagues⁷ showed that only 16.1% of patients experienced an improvement; most of the patients (77%) had no improvement, and 6.9% had a worsening of their HS.

Hormones

In some women with HS, symptoms seem to correlate with hormonal fluctuations during the menstrual cycle. Indeed, a hormonal connection with HS is suggested by the gender and age distribution pattern—HS is three times more common among women than men, and onset rarely is seen after menopause. Anecdotally, some patients with HS have reported symptom improvement during the use of combination estrogen/progesterone oral contraceptive use. Also, some clinicians have used spironolactone, although no studies of this agent in HS have been reported.

In men with HS, finasteride has been used with some success,⁶ and recently Randhawa and colleagues⁸ reported good results with this agent in three children and adolescent patients with HS.

Corticosteroids

Intralesional injection of a topical corticosteroid such as triamcinolone acetonide commonly is done to reduce the pain and swelling of individual lesions and to achieve drainage of an abscess. Systemic corticosteroids such as prednisone reduce inflammation and may help clear existing HS lesions and prevent additional lesions from forming. Because of the increased risk for side effects with sustained use over time, corticosteroids are not a long-term therapeutic option.

Immunosuppressants

Amelioration of HS—presumably, through reduction of inflammation—has been reported with the use of methotrexate or cyclosporine in patients using these medications for other reasons (such as prevention of rejection of a transplanted organ). These agents have not been widely studied in HS.

Metformin

Metformin, the glucose-lowering biguanide agent approved for the treatment of type 2 diabetes mellitus, has shown some benefit in female patients with HS.⁶ No formal studies have been done to evaluate the safety and efficacy of metformin in HS.

Biologic Agents

The study of inhibitors of tumor necrosis factor (TNF) for HS was prompted by the finding that some patients with HS who were treated with the anti-TNF agent infliximab for Crohn's disease experienced improvement in HS lesions. More than 20 articles have been published reporting this benefit in the clinical context of Crohn's disease therapy.

As has been demonstrated in the treatment of numerous immune-mediated inflammatory diseases—including Crohn's

disease, rheumatoid arthritis, and psoriasis—interruption of the underlying inflammatory processes can yield significant long-term therapeutic benefits. It is postulated that, although the inciting event in HS is follicular occlusion (albeit from an as-yet-unidentified underlying cause), the resulting inflammatory response may be the process responsible for the disease progression, chronicity, associated morbidity, and, ultimately, the permanent tissue damage and associated disability that many patients with HS experience. Therefore, use of potent anti-inflammatory biologic agents seems a rational approach to control or prevent these inflammatory responses and their disfiguring and disabling sequelae in HS.

In a study of the long-term effects of one course of treatment with infliximab in 10 patients with severe, recalcitrant HS, Mekkes and Bos⁹ found that all patients improved within 2 to 6 weeks on both an acne score and the DLQI. After 2 years of follow-up, three of these patients had no recurrence of HS lesions and maintained substantial improvements. The other seven patients experienced recurrence within 4.3 to 13.4 months (mean, 8.5 months).

More recently, the first double-blind prospective study of infliximab in moderate to severe HS (N=38 patients) was published.¹⁰ The trial consisted of three phases; the first was an 8-week double-blind phase, in which patients were given infliximab, 5 mg/kg (n=15), or placebo (n=23) at weeks 0, 2, and 6. After 8 weeks, the study was unblinded, and patients in the placebo group were offered infliximab treatment (induction therapy was given at weeks 8, 10, and 14, and then two additional doses every 8 weeks—ie, at weeks 22 and 30). During this second, open-label phase, patients who had received infliximab since the start of the study received infliximab every 8 weeks through week 22. The third phase involved observation without additional treatment through week 52, during which patients were assessed monthly for adverse events and signs of relapse.

A post hoc analysis¹⁰ of composite response on the Hidradenitis Suppurativa Severity Index (HSSI) showed that 60% (n=9) of patients treated with infliximab had improvements in the HSSI ranging from 25% to 50% compared to 5.6% in the placebo group ($P<0.001$). Most patients treated in the placebo group (88.9%) had decreases from baseline in the HSSI of less than



■ **FIGURE** Severe Axillary Hidradenitis Suppurativa. This patient has severe disease, with friable, ulcerated tissue, scarring, and draining sinus tracts. The goals of pharmacologic therapy include clearing or reducing the number and extent of lesions and preventing new lesions from developing. Photo courtesy of Robert G. Micheletti, MD.

25%; only 13.3% of patients in the infliximab group had decreases in the HSSI of less than 25% ($P < 0.001$). In addition, substantial improvements were seen in secondary endpoints, including the DLQI, physicians' global assessment, and pain. Significant improvement was seen with infliximab treatment on a visual analog scale (VAS) of self-reported magnitude of pain. The mean VAS at baseline was 53.3 in the infliximab-treated group; at week 8, the mean change from baseline was 39.8 (down to 13.5). In contrast, the mean VAS at baseline was 49.7 in the placebo group, and, after 8 weeks, the mean VAS was 49.2 ($P < 0.001$ versus the infliximab group).¹⁰

Etanercept also had been reported to have some benefit in HS. However, two prospective studies of etanercept versus placebo failed to demonstrate significant improvement.^{11,12}

A third TNF inhibitor, adalimumab, also showed promise in early studies. Although early case reports and series demonstrated mixed results, a phase II parallel, randomized placebo-controlled trial demonstrated a clear benefit in a group of 154 adult patients with moderate to severe disease who had failed a trial of oral antibiotics.¹³ At the beginning of the study, patients were randomized (1:1:1) to receive adalimumab 40 mg/week, adalimumab 40 mg every other week, or placebo for 16 weeks (the blinded period), after receiving loading doses of 160 mg of adalimumab at week 0 and 80 mg at week 1. At the beginning of period 2 of the study (the 36-week open-label period), all patients were given adalimumab 40 mg every other week; those with a suboptimal response at week 28 or 31 were switched to weekly dosing. At week 16, 9 of 51 (17.6%) patients in the weekly-dose active treatment group had achieved a clinical response compared with 5 of 52 (9.6%) patients in the group who received adalimumab every other week and 2 of 51 (3.9%) patients who received placebo. Importantly, substantial improvements in pain intensity also were seen with adalimumab use.

Subsequently, two large phase III clinical trials were launched in 2013 to evaluate adalimumab in HS. The multicenter, multinational phase III trials (PIONEER I and PIONEER II) involved about 600 patients with moderate to severe HS. Enrollment was limited to patients who had had moderate to severe HS for at least 1 year, with stable disease for the 2 months prior to beginning the study; a total abscess and inflammatory nodule count of three or more, the location of lesions in two distinct anatomic areas, and an inadequate response to a trial of an oral antibiotic agent for a minimum of 3 months were also inclusion criteria. The trials were completed in early 2014, so results were not available at the time of publication of this article.

Two other biologic agents, the interleukin (IL)-1 receptor antagonist anakinra and the IL-12/23 inhibitor ustekinumab, also have been reported to be helpful in HS. An open-label, nonrandomized phase II efficacy study of anakinra in HS showed promising results¹⁴; a randomized, placebo-controlled phase II study of a similar compound is nearing completion at this time. A proof-of-concept phase II study of ustekinumab in HS currently is under way.

Disease Severity Affects Treatment Choices

Patients with mild disease (Hurley stage I) often respond to topical therapy. In addition to topical antibiotics such as clindamycin or mupirocin, topical treatment includes reducing skin bacteria populations with soaps, detergents, and antibacterial skin washes such as those used for acne vulgaris. In addition, overweight or obese patients should receive education

about how excess weight corresponds to increased HS activity and should be counseled about the benefits of weight reduction in managing HS. Also, as cigarette smoking is associated with HS, smoking cessation should be strongly encouraged.

For patients with more severe disease (Hurley stage II), the topical measures described above should be employed, but long-term oral antibiotic regimens—such as clindamycin plus rifampicin or a tetracycline (minocycline or doxycycline)—should be considered. Patients with chronic outbreaks of HS in a particular anatomic area may want to consider laser hair removal in those regions as a preventive measure.

In severe disease, biologic agents should be considered. As noted above in the section on biologics, the TNF inhibitors infliximab and adalimumab (although not etanercept) have shown benefit in some patients. In addition, surgical intervention may be required to halt progression of the disease and mitigate scarring and subsequent disability.

Conclusion

Because HS is a relatively rare disease, large clinical trials of many of the treatments currently in use have not been conducted. Therefore, clinicians must rely on what data are available and use their best medical judgment in determining treatment strategies. Ideally, earlier diagnosis and treatment of HS will become more common, and the most severe stages of the disease and its comorbidities and sequelae will be prevented in more patients. In addition, the availability of evidence demonstrating efficacy of at least one anti-TNF agent will allow earlier effective management of moderate to severe disease, making potentially disabling surgery unnecessary.

References

- Ramghatla PV, Lim HW, Hamzavi I. A systematic review of treatments for hidradenitis suppurativa. *Arch Dermatol*. 2012;148:439-446.
- Clemmensen OJ. Topical treatment of hidradenitis suppurativa with clindamycin. *Int J Dermatol*. 1983;65:303-315.
- Jemec GB, Wendelboe P. Topical clindamycin versus systemic tetracycline in the treatment of hidradenitis suppurativa. *J Am Acad Dermatol*. 1998;39:971-974.
- van der Zee HH, Boer J, Prens EP, Jemec GB. The effect of combined treatment with oral clindamycin and oral rifampicin in patients with hidradenitis suppurativa. *Dermatology*. 2009;219:143-147.
- Gener G, Canoui-Poittrine F, Revuz JE, et al. Combination therapy with clindamycin and rifampicin for hidradenitis suppurativa: A series of 116 consecutive patients. *Dermatology*. 2009;219:148-154.
- Scheinfeld N. Hidradenitis suppurativa: A practical review of possible medical treatments based on over 350 hidradenitis patients. *Dermatol Online J*. 2013;19(4):1.
- Soria A, Canoui-Poittrine F, Wolkenstein P, et al. Absence of efficacy of oral tretinoin in hidradenitis suppurativa: A retrospective study based on patients' outcome assessment. *Dermatology*. 2009;218:134-135.
- Randhawa HK, Hamilton J, Pope E. Finasteride for the treatment of hidradenitis suppurativa in children and adolescents. *JAMA Dermatol*. 2013;149:732-735.
- Mekkes JR, Bos JD. Long-term efficacy of a single course of infliximab in hidradenitis suppurativa. *Br J Dermatol*. 2008;158:370-374.
- Grant A, Gonzalez T, Montgomery M, 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;62:205-217.
- Lee RA, Dommasch E, Treat J, et al. A prospective clinical trial of open-label etanercept for the treatment of hidradenitis suppurativa. *J Am Acad Dermatol*. 2009;60:565-573.
- Adams DR, Yankura JA, Fogelberg AC, et al. Treatment of hidradenitis suppurativa with etanercept injection. *Arch Dermatol*. 2010;146:501-504.
- Kimball AB, Kerdel F, Adams D, et al. Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: A parallel randomized trial. *Ann Intern Med*. 2012;157:846-855.
- Leslie KS, Tripathi SV, Nguyen TV, Pauli M, Rosenblum MD. An open-label study of anakinra for the treatment of moderate to severe hidradenitis suppurativa. *J Am Acad Dermatol*. 2014;70:243-251.

Additional Reading

- Chinniah N, Cains GD. Moderate to severe hidradenitis suppurativa treated with biological therapies. *Australas J Dermatol*. 2014;55:128-131.
- Kimball AB, Gu Y, Okun M. Treatment of moderate to severe hidradenitis suppurativa. *Ann Intern Med*. 2013;159:72-73.
- Martin-Ezquerro G, Masferrer E, Masferrer-Niubò M, et al. Use of biological treatments in patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venerol*. 2014 Mar 13. doi: 10.1111/jdv.12438. [Epub ahead of print]
- Prasad V. Treatment of moderate to severe hidradenitis suppurativa. *Ann Intern Med*. 2013;159(1):72.