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Therapeutic Notes

Therapeutic Options for Hidradenitis Suppurativa: An Update

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic skin condition with severe, deep inflammatory lesions, also referred to as acne inversa. Intertriginous regions, such as the axillae, groins (genital, anal, and perianal areas), infra- and intermammary skin, and buttocks are typically affected, although other areas (e.g., neck nape and lower abdominal fold) might also be affected. Painful nodules and leaking sinuses often affect patients with serious conditions, exuding fluid that sometimes smells, and many patients fear that these new lesions might burst at any moment, requiring incision and drainage, corticosteroid, or surgical injection. Topical lotion of clindamycin or cream of resorcinol can be useful long-term treatments in mild disease, while tetracycline is a first-line systemic option. While antibiotics can help reduce inflamed lesions, recurrence is common after discontinuation. If patients do not respond well to these standard medical procedures, then using biologics such as adalimumab or infliximab would be the next step. Anti-inflammatory drugs, such as fumarate, dapsone, and cyclosporine, are also prescribed for HS. Surgical procedures are also necessary for healing, particularly when the sinuses or scars are present. The clinical staging system of HS and the desires of patients should be used as the basis for every therapy.

Key words: Hidradenitis suppurativa, acne inversa, clindamycin, rifampicin, infliximab.

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INTRODUCTION

The chronic inflammatory skin disease hidradenitis suppurativa (HS) is also known as acne inversa [1]. The clinical appearance forms the basis for assessment. There are painful nodules and abscesses that can be inflamed or not, often accompanied by sinus development and scarring. HS typically involves the axillae, groins (genital, anal, and perianal areas), and infra- and intermammary skin [2]. The characteristic skin lesions must be present at least twice every 6 months [3].

HS pathogenesis remains unclear. The major hair follicle occlusion pathology is known as infundibulum keratosis and cutaneous follicle hyperplasia. It leads to accumulation of the hyperkeratotic debris and abscess formation, which ultimately ruptures the hair follicle; this results in sinus tract formation and scars [4]. In HS pathogenesis, the role of a deviant immune reaction is of interest [5].

HS typically occurs in adolescents and those in their early 20s, and is unusual in children [6]. The prevalence of the disease is between 0.05 and 4%, with women being more affected than males, by the 3:1 ratio [1,2]. The severity of the disease can be measured using various intensity ratings. The Hurley score (Fig 1) is the most widely established and used [7]. The Sartorius' updated score is more potent. This is due to its comprehensiveness, addressing the number of areas,

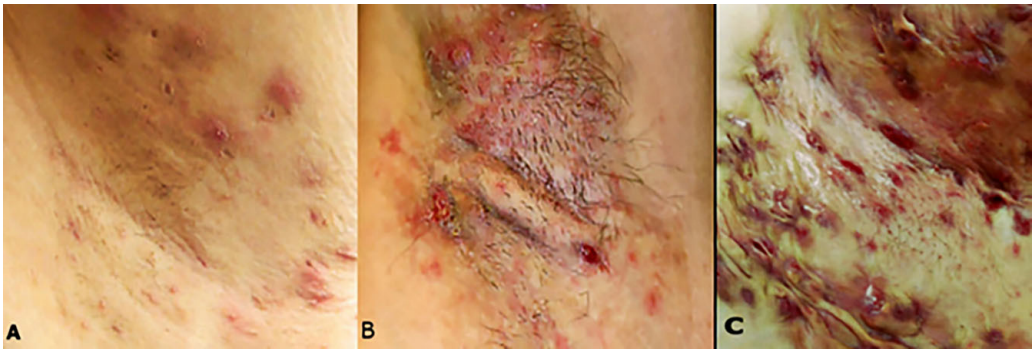

Fig 1. Hurley staging system of hidradenitis suppurativa. A. Hurley stage I (single or multiple abscess formation without sinus tracts); B. Hurley stage II (abscesses with tract formation and cicatrization); C. Hurley stage III (diffuse involvement with multiple interconnected tracts and abscesses).

fistulas, hypertrophic scars, and nodules [8]. However, this means that it takes longer to complete and makes it less appropriate for daily use [9].

There is no known cure for HS, but there are several suggested treatments. The incorporation of drug treatment and surgery is often important to achieve remission. Recently, the European guidelines on HS therapy were published [10]; guidance should be provided on the treatment of HS prevention measures. Here we review the HS literature and provide a summary of current HS therapies.

METHODS

A systematic analysis of the PRISMA literature was conducted to identify HS patient clinical findings. The scope of the review included studies published between 1998 and 2019, and written in English. The Cochrane, MEDLINE, and PubMed databases were searched. In conjunction with keyword treatment, HS, acne inversa, or Verneuil's disease are key search items. The Google search results were filtered and grouped by the form of study design so that the findings were appropriately presented from case reports, case series, and clinical observational studies.

Quality assessment and data analysis

A five-point Jadad index for clinical tests measured the consistency of each of those studies. A positive answer to the question was scored as 1, whereas a negative response was scored as zero. If the overall score was ≤ 2, the analysis was classed as "low quality", whereas if the overall score was ≥ 3, it was considered "high quality" [11]. Evidence quality was evaluated on the basis of the grading criteria in the Dermatology Archives 4 and the guidance on evidence quality for structural evaluations. Tests categorized by type (surgical, medical, or miscellaneous) were reported for evidence quality, the number of patients to be treated, treatment protocols, and outcomes.

RESULTS

Medical treatment

Hidradenitis suppurativa is most commonly treated with a combination of therapies. Therapy can reduce the bacterial load, decrease inflammation, decrease the immune response, decrease pain, and increase the satisfaction of the patients. Conventional HS medications include antibacterial washings (e.g., benzoyl peroxide wash), topical clindamycin, various combined antibiotics, systemic retinoids, and intralesional steroid injections (typically as antibiotic adjuvants) with or without azelaic acid adjuvant [12-14]. Some of these therapies have demonstrated their efficacy in deterring HS flares. Unfortunately, the patients cannot take oral antibiotics for a long period due to the risk of developing hypersensitivity, as well as the risk of other adverse effects. Additionally, some patients have trouble using topical treatments twice daily to prevent flares. Modifications in topical therapy and lifestyle are also appropriate for mild HS. Using a topical antibiotic along with a local anti-inflammatory agent to overcome and prevent follicular obstruction and combat secondary infection will produce the best results.

Topical clindamycin

Topical clindamycin is an effective and commonly used HS treatment [12,13]. In the daily topical application, clindamy-

cin (1%) was shown to be more efficient in the early stages of HS. Significant reductions were observed in the pustules, inflammatory nodules, and abscesses after 3 months of clindamycin treatment [13]. The most common side effect after treatment is a slight feeling of burning. Clindamycin is nevertheless considered an efficient and useful treatment choice for solitary nodules.

Resorcinol cream

Owing to its keratolytic properties at high concentrations, resorcinol cream is an effective topical treatment for HS. The follicular keratin plug is presumed to be targeted and regarded as the main event in HS pathogenesis [4]. It also has an added antiseptic effect. Resorcinol efficacy was 10–15% in a clinical study of 12 patients, and the amount of time that the nodules and abscesses continued following routine treatment decreased in patients [15]. However, patients should be advised to use resorcinol in restricted areas of the skin to avoid systemic absorption and damage to the skin and clothing. Likewise, resorcinol use should be avoided during pregnancy because of insufficient data on pregnancy outcome [15,16].

Other topical agents

A variety of topical antiseptic solutions are also used for HS, including chlorhexidine and iodine [17]. This approach can be beneficial as it prevents bacterial secondary lesion infections. The effectiveness of these agents in the treatment of HS has never been investigated in depth. For mild cases, azelaic acid was also used. Its antifungal and bacteriostatic properties were observed *in vitro*, and the proliferation of keratinocytes was inhibited [16-18]. Azelaic acid can have beneficial characteristics in HS, but this appears to be complex, and no work is available about how it is properly used in HS [19].

Systemic antibiotics

Although the earlier stage of HS pathogenesis is not specifically associated with bacterial infections, the first treatment choice is antibiotics, mainly due to the anti-inflammatory effects [20]. HS lesion cultures are usually sterile and show normal skin flora [21–24]. *Staphylococcus aureus* is mainly developed from chronic suppurative lesions that suggest a superinfection with a chronic lesion [22-25]. More recently, it has been shown that *Staphylococcus lugdunensis* is frequently present in Hurley stage I lesions, while a mixed anaerobic flora is more typical in Hurley stage II and III [26]. However, antibiotics are rarely curative in the advanced stages of HS, although they might reduce swelling, and enhance surgical intervention.

Tetracyclines

Antibiotic tetracyclines are among the first line of HS systemic therapies [27, 30]. Tetracyclines are wide spectrum antibiotics that operate by reversible binding to the ribosomal 30S subunit, thereby inhibiting bacterial protein synthesis [28]. Tetracycline also has mild anti-inflammatory properties in which chemotaxes and neutrophil migration are suppressed, and nitric oxide synthesis is inhibited [29]. In addition, it can also hinder angiogenesis [30]. However, preventing HS exacerbations by tetracyclines is relatively less successful.

Matusiak *et al.* [20] cultivated isolates in HS patients with bacterial infection and found that 64% were tetracycline resistant. Moreover, in a randomized, double-blind controlled trial monitoring the number of abscesses, the number of nodules, and pain scores, 1% topical clindamycin was shown to be as successful as 500 mg twice daily systemic tetracycline [31]. The typical adverse reactions of tetracyclines tend to be gastrointestinal problems, photosensitivity, and permanent childhood dental stains [32-35]. Tetracyclines are not to be used with antacids or milk, as an insoluble product can be created, thus lowering its absorption. Furthermore, during pregnancy, tetracyclines are contraindicated due to the risk of teratogenic effects [36].

Clindamycin and rifampicin combination

Clindamycin is a wide-spectrum antibiotic, but most Gram-negative aerobic bacteria are clindamycin resistant [37]. Clindamycin binds to the 50S ribosomal subunit, and thus inhibits the synthesis of bacterial proteins. Rifampicin is an active chemical compound that is used against most Gram-positive cocci, Gram-negative cocci and bacilli, and most anaerobic cocci [38]. The bactericidal activity is accomplished by inhibiting the DNA-dependent polymerase RNA [39]. Rifampicin has an immunosuppressive effect and substantially reduces T-cell activity, and there has been evidence of decreased metamorphosis of the *in vitro* lymphocytes [40].

Clinamycin (300 mg) twice daily plus rifampicin (600 mg) once per day or (300 mg) twice per day for 10 weeks is a typical therapeutic regimen in several trials [38–40]. One-hundred-sixty-four patients were enrolled in three clinical studies, 88 of whom received 300 mg of clindamycin twice daily and 600 mg once daily or 300 mg twice daily every 10 weeks [39–42]. Twenty-one patients were removed from completing the therapies due to medication side effects, primarily diarrhea and nausea. For 55 patients, there were no results of efficacy from 10 weeks or specific dosing regimens. Of the remaining 88 patients, 25 were completely cured (28.4%), and 57 had partial (64.8%) responses. However, after the therapy ended, recurrence rates of up to 61.5% were recorded [40-42]. Approximately 20 out of 23 patients completed their 10-week treatment course during the currently available single prospective trial, 17 of whom had a 25% reduction in Sartorius ratings. One patient stopped early because of gastrointestinal problems [43].

Studies showed that somehow, when combined with rifampicin [37-39], the plasma clindamycin concentration decreases significantly, up to 82% of the average. Rifampicin is a powerful cytochrome P450 inducer, while clindamycin is metabolized by the cytochrome P450 enzyme CYP3A4, which results in reduced clindamycin serum levels [38].

Gastrointestinal symptoms, such as diarrhea, vomiting, and nausea, are, by far, the most adverse effects of the combination of clindamycin and rifampicin [41,45]. Rifampicin can also cause red-orange urine discoloration. During pregnancy, clindamycin is regarded as extremely safe [44]. However, little information is available on the use of rifampicin during pregnancy, so that it should be avoided under certain circumstances [44]. Given that rifampicin interacts with oral contraceptive medications, additional methods of birth control should be considered in women [45].

Rifampicin, moxifloxacin, and metronidazole triple therapy

An effective treatment option is the use of rifampicin, moxifloxacin, and metronidazole in severe and resistant cases [46]. Metronidazole is an antiprotozoal agent developed originally for anaerobic bacteria. Metronidazole forms an intermediate redox metabolite that induces breakup of DNA, repair inhibition, and, eventually, disruption of transcription or cell death [47]. Metronidazole also has immunosuppressive activity. Leukocytes' migration is also reduced [47]. Moxifloxacin is a broad-spectrum fluoroquinolone that inhibits bacterial DNA topoisomerase and affects DNA replication, recovery, and recombination [48]. Moxifloxacin is effective against various Gram-positive organisms, including *Staphylococcus aureus* [49].

Co-administration of rifampicin does not significantly affect the moxifloxacin kinetics within the body. In the randomized trial by Lamber *et al.,* 28 patients received rifampicin (10 mg/kg one time daily), moxifloxacin (400 mg once daily), and metronidazole (500 mg three times daily) [46]. Seventeen patients had a full recovery after the trial, and another 13 had mild reactions. Metronidazole was discontinued after 6 weeks to avoid neurological effects but re-introduced following recurrence in four patients.

Metronidazole side effects included vomiting, nausea, and a metallic taste sensation. Toxicities in the peripheral and central nervous system are significant issues but are very rare side effects of metronidazole. Kuriyama *et al.* [50] recently documented 84 cases of neurotoxicity caused by metronidazole. The central nervous system was involved in most (90.5%) cases, and most of these cases involved ataxia, encephalopathy, or convulsions. Polyneuropathy was also identified in 26 cases. The risk of developing toxicity with the CNS does not appear to be greater in patients with longer or higher doses of treatment [51]. The most common issues with moxifloxacin tend to be dizziness, vomiting, and nausea. If used along with formulations of antacids, sucralfate, or iron, moxifloxacin's binding affinity is significantly reduced. All three antibiotics have typically been prescribed throughout pregnancy and during breastfeeding. Because of the interaction between rifampicin and oral contraceptives, women receiving rifampicin should use extra contraceptive measures.

Biological treatment

Biological therapies are widely used for inflammatory disorders, such as asthma, Crohn's disease, and psoriasis [61]. HS, first recorded in a patient with Crohn's disease, was treated with infliximab in 2001 [52]. This paper brought about a groundbreaking understanding of the disease, and further research has led to a breakthrough in pathogenesis and hidradenitis therapy. TNF-α is a pro-inflammatory cytokine with a critical role in HS pathogenesis, and the pro-inflam-

matory cytokines IL-1 and IL-17 [53–59]. IL-23 also plays a significant role. The need for armamentarium drugs in HS management has become an essential objective for reducing inflammatory responses [60–66]. TNF-α antagonists, such as adalimumab, infliximab, and etanercept, were the first biological agents tested in the treatment of HS. Adalimumab has more robust trials and stronger evidence for effectiveness in HS.

Adalimumab

Adalimumab is a fully genetically modified, TNF-α soluble monoclonal antibody drug [67]. Adalimumab is the only biological drug approved for the treatment of HS [67–68]. In Phase 3 clinical trials, known as PIONEER I and PIONEER II, the effectiveness of adalimumab was documented, which is superior to placebo for treating HS. In PIONEER I, approximately 312 (146 for placebo and 156 for adalimumab) and 340 (167 for placebo and 173 for adalimumab) were selected and 173 in PIONEER II. At week 12, the HiSCR (Hidradenitis Suppurativa Clinical Response) rate of outcome for randomized adalimumab weekly patients was significantly higher (41.8% vs. 26.0% in PIONEER I, $P = 0.003$, and 58.9% vs. 27.6% in PIONEER II, $P < 0.001$) [68].

During the 36th week (phase B), the HiSCR output was higher for all adalimumab patients weekly in the A and B phases (42.7% in PIONEER I and 48.3% in PIONEER II) compared to patients who were randomized for application every 2 weeks for weekly adalimumab in period A (29.6% in PIONEER I and 44.7% in PIONEER II) or placebo (25.7% in PIONEER II) [69]. The quality of life of HS patients was also significantly improved by adalimumab. The HiSCR levels were sustained for a long period, and the safety profile was close to that recorded for the medication for moderate-to-severe HS patients. The dose of adalimumab for HS treatment, as developed in PIONEER II, is 160 mg on day 1, 80 mg on day 14, and 40 mg weekly from day 29. The areas of residual infection or scarring can be excised once the inflammation is managed [70,71].

Infliximab

Infliximab is a monoclonal antibody consisting of humanoid and hippocampal neurogenesis proteins that target soluble TNF-α and the transmembrane [60]. A number of case studies have shown the value of infliximab for HS management. Thirty-eight patients were given either infliximab (5 mg/kg in weeks 0, 2, and 6 and every 8 weeks later) or placebo in a randomized, double-blind, HS-controlled clinical trial; an open-label duration followed after 8 weeks in which people receiving the placebo could then receive the treatment [72]. Around 26% of the patients in the treated group benefited by 50%, compared with 5% in the placebo group. Infliximab monotherapy was also well-tolerated, but with far more adverse effects than in the placebo group [84]. The best results were obtained monthly at the beginning of the week, at week 2, and week 6, with 5 mg/kg doses after 5 mg/kg initiation [84]. In patients with spondyloarthropathy associated with HS, methotrexate could be applied to increase the effectiveness of infliximab therapy [72].

Etanercept

Etanercept is a widely used biological TNF-α inhibitor. It is a soluble receptor that binds TNF-α and TNF-β to prevent inflammation [60]. Some studies have suggested that etanercept can be used for treating HS. It has been shown that the regular use of etanercept (50 mg) prevented the progression of HS disease in some studies [73,74].

Ustekinumab

Ustekinumab is a human monoclonal antibody that binds to IL-12 and IL-23 cytokines with high specificity and affinity. The IL-12/23 pathway is involved in HS pathogenesis, and thus ustekinumab suppresses the inflammatory process mediated by these cytokines [75]. In isolated cases, ustekinumab was shown to be successful in treating HS [76,77]. Blok *et al.* [78] confirmed the use of ustekinumab in 17 patients with mild to moderate HS in an open-label study with validated outcomes. The study was completed by twelve patients; moderate to significant outcomes were observed in about 82%. The drug has been prescribed at dosages of 45 mg and 90 mg for body weight greater than 100 kg.

Anakinra and canakinumab

The first biological agent approved for blocking the pro-inflammatory effects of IL-1 was anakinra, the recombinant human IL-1 receptor antagonist [60]. Canakinumab, an IL-1β inhibitor, has also been successfully used in the HS treatment [79-81].

Secukinumab

Secukinumab is a recombinant human monoclonal immunoglobulin G1 that specifically targets IL-17A and inhibits its interaction with the IL-17 receptor. Multiple studies have implicated this cytokine in the pathogenesis of HS [60]. Secukinumab has been used in those cases that are highly resistant to many therapies, showing considerable improvement [82].

Apremilast

Apremilast is a phosphodiesterase-4 inhibitor and is a tiny oral molecule which has shown satisfactory results in the treatment of HS in small case studies [60].

Surgical treatment

For years the treatment for severe HS with surgical resection operations has been definitive. An alternative to conventional medical operations was identified by Blok *et al.* [83]. By directly visualizing the sinus tracts on HS [85], the surgeon could measure the size of the region that needs surgically removing. Cryoinsufflation, an adapted spray cryotherapy obtained by direct injection of liquid nitrogen into HS tunnels through a needle, might be useful if a patient refuses or cannot undergo surgical treatment for Hurley stage II or III disease. This procedure has already been validated in two patients with symptoms and successfully managed sinus scarring [86].

The use of laser techniques has been lauded for chronic lesions. Nodules and tunnels may be targeted by carbon dioxide laser (CO2) vaporization, leaving healthy tissue between treatments. This allows the surrounding healthy tissue to be repaired, with suitable hemostasis and speedy cure. CO2 laser therapy was less painful and more relaxed after surgery than traditional operations [87]. Intense pulsed light, even in cases of Hurley II and III, can have positive effects [88]. Nd:YAG 1064-nm beam therapy might help for the removal of hair, surface lesion treatment, or in moderate-to-severe cases.

Conflict of interest

The author declares that he has no conflict of interest.

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