Review paper

Hidradenitis suppurativa: a new therapeutic approach for an old disease

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Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory disease characterised by recurrent painful nodules, abscesses, fistulas and scarring. The primary distinguishing factor in the complex, yet still not fully understood, pathogenesis is an inflammation occurring within the hair follicle, followed by an immune response leading to further development of the skin lesions seen in HS. The treatment of patients with HS is very difficult due to the complexity of the lesions and the frequent tendency to recurrence, which also has a negative impact on the psychological state of patients and directly translates into a reduced quality of life. This review article addresses the pathogenesis, clinical presentation of HS and, in particular, explores the new therapeutic options available.

Key words: hidradenitis suppurativa, acne inversa, biologic therapy, JAK inhibitors.

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory dermatosis characterised by the presence of papules, pustules, and nodules. It usually presents after puberty with painful, deep-seated, inflamed lesions. These manifestations are localized in regions abundant in apocrine glands, including the groin, armpits, submammary areas, and anogenital spaces [1, 2].

Hidradenitis suppurativa is influenced by both genetic predisposition and environmental factors. The primary defect is inflammation within the hair follicles and oil glands, triggering a response that ultimately results in the development of painful nodules, abscesses, and sinus tracts in intertriginous areas [3]. The condition has both physical and psychological effects and can severely impact social functioning and quality of life. Although early diagnosis is essential for achieving optimal outcomes and reducing associated health issues, HS patients often remain undiagnosed for about 7 years after symptom onset [4].

This aim of this paper is to review current literature data regarding the aetiology and clinical aspects of HS, while underlining its severity and the importance of understanding the condition for effective treatment. Ongoing and completed clinical studies are fruitful and provide hope for effective therapies.

Aetiology, pathogenesis and clinical aspects

Hidradenitis suppurativa is characterised by sustained inflammation resulting from infections which occludes and plugs hair follicles, stimulating immune system activation [3]. Macrophages, Th1 and Th17 lymphocytes secrete pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin-1β (IL-1β) and interleukin-17 (IL-17) which cause migration and proliferation of keratinocytes [5–8]. This can result in the formation of painful, deep-seated inflammatory lesions that are prone to fistula formation and scarring [4].

Interleukin-17 (IL-17) is a crucial inflammatory protein primarily produced by CD4+ helper T cells (Th17 cells) and certain innate lymphoid cells. IL-17A plays a significant role in the development of inflammatory conditions such as hidradenitis suppurativa, psoriasis, and atopic dermatitis by inducing cellular responses not only in keratinocytes but also in other cells including neutrophils, endothelial cells, fibroblasts, and osteoclasts. In keratinocytes, IL-17A binding to its receptors (IL-17RA, IL-17RC, or IL-17RD) promotes keratinocyte growth, followed by the release of inflammatory molecules and chemokines, leading to inflammation [9]. Analysis of skin biopsy samples showed elevated levels of IL-17 in HS patients compared to healthy individuals, and IL-17 mRNA levels were also increased in clinically unaffected perilesional skin [10].

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Biopsies are not commonly conducted as part of routine diagnostics, and although the disease is not inherently infectious, bacteria are involved in its pathophysiology. Napolitano *et al*. found *Staphylococcus lugdunensis* to be the most prevalent species in a microbiological examination of 102 lesions from 82 patients; it was identified as a unique or predominant isolate in 58% of studied nodules and abscesses [11].

The course of the disease is characterised by increased production of IL-1β and intensified inflammation; Frings *et al.* suggest that this may be linked to the dysregulation of keratinocyte-dependent gene responses (e.g., genes related to AP-1) and the activation of the JAK/STAT1 (Janus kinase-signal transduction and transcription activation) pathway. Hence, the progression of HS appears to be based on complex stress response, which is currently being used in clinical trials [12].

The disease manifests in three distinct forms: axillary, follicular, and gluteal. Abscesses can appear beyond these areas, including the neck, trunk, limbs, or retroauricular region. The symptoms mainly affect areas around the apocrine glands and terminal hair follicles and appear to be influenced by low androgen levels. Likewise, anogenital HS can also occur, manifesting as lesions in the anal canal [11].

The onset of HS typically occurs immediately after puberty and is significantly more common in women; however, more severe lesions tend to be observed in men [13]. HS is a multifaceted dermatosis whose course is influenced by genetic factors, environmental influences, lifestyle choices, immune system irregularities, nicotine use, bacterial infections, and endocrine disorders. However, studies have ruled out any correlation with diabetes, acne vulgaris, inadequate hygiene, the use of deodorants, or depilation [14].

Treatment

Unfortunately, treatment can be costly, uncomfortable, and may take months to show results, and the end result is not guaranteed. Therapeutic failures and relapses are common, affecting patient involvement. Even so, various treatment options are available, including antibiotics, corticosteroids, biological therapies, or surgery.

General recommendations for patients include wearing loose, breathable clothing and non-abrasive underwear to help minimize friction-related irritation [15]. Studies indicate that smoking and obesity exacerbate cutaneous inflammation and frequent relapses in HS; lifestyle changes, such as dietary modification and smoking cessation, can improve treatment outcomes [16]. A study of nearly four million tobacco smokers across various demographic groups by Garg *et al.* found a significantly higher incidence of HS among smokers (0.2%) compared to non-smokers (0.11%), indicating that smoking is a risk factor in pathogenesis. The incidence rate was found to be almost twice as high as those among non-smokers [17].

New skin lesions may be caused by the elevated insulin levels associated with obesity. Furthermore, obesity is believed to exacerbate the condition by increasing skin friction, altering the skin microbiome, and prolonging inflammation. Weight loss can alleviate symptoms and improve quality of life [18].

Topical treatment

Clindamycin

Clindamycin is an antibiotic that acts by binding to the 50S subunit of the ribosome. It is recommended as a treatment for HS (localized Hurley stage I or mild stage II) in current European S1 guidelines. In such cases, clindamycin 0.1% should be applied twice daily for 12 weeks and is most effective in treating superficial lesions [8].

Resorcinol

Resorcinol is an aromatic organic compound that shows anti-inflammatory, antimicrobial and keratolytic activity. Molinelli *et al*. assessed the efficacy of topical 15% resorcinol in 61 patients with Hurley stage I and II. A clinical response, indicated by a reduction in HS lesions, was observed in 52.5% of participants at week 4 and 85.2% at week 12. This study suggests that topical 15% resorcinol could be a well-tolerated alternative for patients with established resistance to topical clindamycin [19].

Ruxolitinib

Ruxolitinib (1.5%), a topical JAK1/JAK2 inhibitor, is currently under evaluation in Pennsylvania (NCT04414514) in patients during the early stages of HS. Treatment efficacy is determined by the percentage of patients achieving HiSCR (Hidradenitis Suppurativa Clinical Response) after 16 weeks of treatment. So far, 24 patients have already been enrolled. This study is expected to be completed by January 2025 [20].

Intralesional corticosteroid

An intralesional corticosteroid injection, particularly with triamcinolone acetonide, may be a suitable treatment for patients with isolated but painful abscesses, nodules and sinus tracts. In this study, 54 patients received triamcinolone at a high dose of 20 mg/ml or 40 mg/ml: 92.6% demonstrated a significant improvement in skin condition, and 75.9% in quality of life. Interestingly, no adverse events were reported [21].

Systemic treatment

Tetracyclines

Tetracyclines have been demonstrated to be effective, particularly in disseminated Hurley stage I or mild Hurley stage II. They are used as the first-line therapy

for patients demonstrating no response to topical treatment. The recommended dose is 500 mg daily administered for approximately 4 months or longer, depending on the severity of symptoms [8].

Interestingly, a statistically significant reduction in the number of lesions was observed after 12 weeks of therapy with tetracyclines (from 9.0 to 5.0) and the combination of clindamycin and rifampicin (from 13.0 to 6.0) [22].

Tetracycline and clindamycin

Combined clindamycin (300 mg) and rifampicin (600 mg daily in one or two divided doses) for 10 weeks is a recommended oral therapy for Hurley stage I or mild stage II, in the event of inadequate response to treatment with tetracyclines [8]. Dessinioti *et al.* analysed the clinical responses of 26 patients after therapy with 600 mg clindamycin and 600 mg rifampicin daily. At baseline, patients had varying stages of HS. Most of the study group showed a clinical response, with 73% experiencing a 50% reduction in lesions. Importantly, after 1 year, 47% of patients showed no further symptoms or exacerbations [23]. The same combination at the recommended dose, i.e. 300 mg clindamycin and 600 mg rifampicin, was tested in another study. Only 70 of 116 patients reported for the follow-up after initiation of treatment. Significant reductions in pain severity, improvement in psychological well-being and in the median Sartorius score were noticed [24].

Systemic corticosteroids

Systemic corticosteroids can be included in HS therapy thanks to their anti-inflammatory, immunosuppressive and anti-proliferative properties. It is suggested that they should be administered for the shortest possible period to avoid systemic adverse effects. The typical recommended dosage regimen is 0.5–0.7 mg/kg of oral prednisolone for a short course to ease exacerbation of HS. If skin lesions reappear when the steroid dose is reduced, additional anti-inflammatory or immunosuppressive drugs should be included in the treatment plan [8, 25].

Biologic therapy

It has been proposed that the pathogenesis of HS may be influenced by an inadequate immune response to an unidentified antigen. Research has revealed increased levels of various proinflammatory cytokines in patients, pinpointing potential targets for biological interventions [6, 7].

Adalimumab

Adalimumab is the only FDA-approved treatment for moderate to severe HS. It is a recombinant human IgG1 monoclonal antibody that targets and inhibits proinflammatory TNF-α [26]. Adalimumab has been found to be effective in two phase 3 studies – PIONEER I (n = 307) and PIONEER II (n = 326). The majority of patients in the treatment groups achieved HiSCR at week 12 [27]. Further analysis showed that adalimumab also relieved skin pain, especially in the first 2 weeks of treatment [28]. The total length of PIONEER I and II was 3 years; 52.3% of patients receiving adalimumab weekly maintained HiSCR levels up to week 168, demonstrating a sustained clinical response [29].

Infliximab

Infliximab is a monoclonal antibody that selectively binds to soluble and membrane-bound TNF-α, neutralizing its pro-inflammatory effects. It may also induce elimination of affected cells, possibly through complement activation, antibody-dependent cellular cytotoxicity, or apoptosis. Infliximab may be administered at a dosage of 5 mg/kg of body weight in preparation for surgery. For extended or long-term therapy, the recommendations involve administering infliximab at a dose of 5 mg/kg of body weight on day 0, day 2 and day 6, and then subsequently every 8 weeks.

A selection of case reports involving 73 patients with moderate to severe disease found infliximab administration to elicit a cumulative response rate of 58%, with a significant improvement of at least 50% in 42 patients. In a retrospective comparative study involving 20 patients (1 : 1 ratio), 5 mg/kg infliximab administered intravenously at weeks 0, 2, and 6 achieved a notably greater reduction in mean Sartorius score (by 56%) compared to 40 mg adalimumab subcutaneously every other week (by 34%). In a long-term treatment study (4 years), involving 10 patients with moderate to severe HS, infliximab demonstrated an impressive 80% response rate [8].

Ustekinumab

Ustekinumab blocks the effects of interleukin-12 (IL-12) and interleukin-23 (IL-23). A study examined the effect of three subcutaneous 45 mg injections given at weeks 0, 4, and 16, on moderate-severe HS in 3 patients. Treatment led to a cumulative response rate of 33%, with 1 patient achieving ≥ 50% improvement. However, two out of 3 (66%) patients experienced relapses after stopping treatment [8].

Etanercept

Etanercept is a recombinant fusion protein that combines the TNF receptor, effectively disrupting the actions of TNF-α. In a group of 34 patients with moderate to severe HS, subcutaneous injections of 25 mg twice weekly over a period of 3 to 10 months, yielded a cumulative response rate of 44%, with 15 patients experiencing improvement of ≥ 50% [8].

Secukinumab

Secukinumab is a fully human monoclonal antibody that selectively neutralizes IL-17A by binding to the IL-17 receptor and preventing it from interacting with the cytokine [30–33].

SUNSHINE and SUNRISE [32, 33] were multicentre, randomized, placebo-controlled, double blind phase 3 trials assessing the efficacy and safety of secukinumab against placebo for up to 52 weeks. Patients were randomly assigned to receive subcutaneous secukinumab 300 mg every 4 weeks (Q4W) or every 2 weeks (Q2W) until week 16, or placebo.

The treatment was found to be effective during the first 4 weeks of the study, i.e. the induction phase. HiSCR response was maintained in both SUNSHINE and SUNRISE until week 52, with Q2W and Q4W secukinumab compared with placebo.

In both SUNSHINE and SUNRISE, Q2W secukinumab was more successful than placebo in terms of percentage change from baseline regarding abscess and inflammatory nodule count (AN) and incidence of flares by week 16.

Interestingly, patients originally assigned to the placebo group demonstrated rapid improvements in response rates after reassignment to the secukinumab group, with similar treatment effects. Based on the reliability of phase III program data, secukinumab has been approved by the European Commission for the treatment of adults with active moderate-to-severe HS unresponsive to conventional systemic therapy [34].

Bimekizumab

Bimekizumab, a monoclonal antibody targeting two forms of interleukin 17 (IL-17A and IL-17F), is indicated for the management of active moderate to severe hidradenitis suppurativa in adults with an insufficient response to traditional systemic therapy. The efficacy and safety of bimekizumab were evaluated in the BE HEARD I and II 48-week phase 3, randomized, double-blind, placebo-controlled, multicentre studies. In total, there were 1014 patients (of at least 18 years of age). Participants were diagnosed with HS for at least 6 months, presenting with Hurley stage II or III disease, and with ≥ 5 inflammatory lesions (a sum of abscesses and inflammatory nodules), along with a prior history of insufficient response to systemic antibiotics for HS treatment.

Bimekizumab achieved a high degree of clinical efficacy (75% lesion reduction on average) and improved health-related quality of life by week 16 compared with placebo, with consistent effectiveness until week 48 [35, 36]. Consequently, bimekizumab was officially endorsed by the European Medicines Agency (EMA) for HS patients in April 2024. For adults the recommended dose is 320 mg (two injections of 160 mg each) every 2 weeks until week 16, then every 4 weeks. With this dosing regimen in the BE HEARD I and II, more than half of patients (52%) achieved HiSCR50 by week 16, with over 63% (63.8%) maintaining efficacy until week 48 [35–37].

Izokibep

Izokibep is a potent and selective inhibitor of interleukin 17A (IL-17A) currently in development for HS treatment (NCT05355805). This trial is currently in phase 2 [38].

Sonelokimab

Sonelokimab is a bi-specific nanobody designed to counteract interleukins IL-17A, IL-17F, and IL-17A/F. Its effectiveness and safety profile is under evaluation in clinical trial NCT05322473. The trial has recently proceeded to phase 2b [39].

Lutikizumab

Clinical trial NCT05139602 aims to evaluate both the effectiveness and safety of lutikizumab, an anti-interleukin-1α/β (anti-IL-1α/β) dual variable domain immunoglobulin in patients not responding to anti-TNF therapy. Existing data indicate higher response rates with lutikizumab (300 mg every other week or 300 mg weekly) compared to placebo with regard to achieving HiSCR at week 16. Given these promising results, the trial has progressed to phase 3 [40].

Janus kinase (JAK) inhibitors

The exact pathogenesis of hidradenitis suppurativa remains incompletely understood; however, epidermal stress is known to play a role. Various genes, including *DEFB4B, DEFB4A, TNIP3* and *CXCL8*, are upregulated in the epidermal stress response, leading to overactivation of AP-1 (Activating protein 1). Moreover, interferon γ (IFN-γ) promotes overexpression of JAK/STAT1 signalling, which may contribute to the heightened expression of certain immune response genes, such as *TLR2*, *TNIP3* and *cGAS*, observed in HS lesions. Therefore, JAK inhibitors can be beneficial in suppressing epidermal stress and ultimately reducing inflammation [12].

INCB054707

The safety and tolerability of INCB054707, a JAK1 inhibitor, has been assessed in two phase trials (registered as NCT03569371 [41] and NCT03607487 [42]).

In trial NCT03569371, 10 patients were enrolled and received 15 mg of INCB054707 daily. Among these, seven successfully completed the study, with 43% of the study group achieving HiSCR at week 8 [41].

Trial NCT03607487 comprised 35 patients divided into four groups; these received INCB054707 30 mg daily, 60 mg daily or 90 mg daily, with the final group receiving placebo. Seventeen patients achieved HiSCR after 8 weeks of treatment. In addition, 80% of patients in the 30 and 60 mg groups and 50% of patients treated with

90 mg reported grade 1-2 adverse events (i.e. non-life-threatening). However, 37% of patients receiving 90 mg experienced grade 3 adverse events, defined as requiring hospitalization [42].

As neither clinical trial included a lot of patients, the authors are currently conducting a similar second phase study which has already enrolled 209 patients (NCT04476043) [43].

Upadacitinib

Another JAK1 inhibitor, upadacitinib in under investigation for HS in clinical trial NCT04430855: a phase II study with 68 patients enrolled. However, the results have not been published yet [44].

Tofacitinib

Tofacitinib, an oral JAK inhibitor, reduces inflammation by inhibiting the action of the JAK1 and JAK3 enzymes [45]. Savage *et al.* describe 2 cases who achieved a clinical response and improved quality of life during tofacitinib treatment after failing to respond to prior standard and biologic therapy [46]. Additionally, 2 other cases presented successful outcomes with reduced pain and fewer skin lesions [47]. Currently, the safety and efficacy of tofacitinib in patients with HS and Down syndrome are under evaluation in a clinical trial (NCT04246372), with 47 patients enrolled and ongoing recruitment. The estimated completion date of the study is December 2024 [48].

Surgical treatment

Surgical treatment for HS is complex, as the technique depends on disease stage and lesion location. Relapses are more frequent in the anogenital and submammary regions post-surgery, and lower rates associated with wide excisions; in addition, incision and drainage of abscesses in the acute phase significantly increase the rate of recurrence, apart from reducing pain [49, 50]. Deroofing has a lower risk of recurrence, of about 17% [51], it is used to manage single and localized lesions in one area of the body in Hurley stages I–II.

Less invasive surgical interventions, such as incision and drainage or deroofing, are preferred in the acute phase, while more extensive surgical procedures are typically deferred until the remission phase. Severe lesions require excision of the affected area with primary closure of the lesion, or closure by secondary healing. The reconstructive technique should be tailored to the required extent of the excision and the specific needs of the patient [52].

Conclusions

Multiple therapeutic options exist for the management of patients with HS, including antibiotics, corticosteroids, biologic therapy, retinoids and non-pharmacological procedures. However, treatment remains challenging due to the chronic nature of the disease and frequent relapses. The selection of an appropriate treatment modality should be based on an assessment of the disease severity. An individualized approach is a key for patients affected by HS.

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Conflict of interest

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