Clinical Implementation of Biologics and Small Molecules in the Treatment of Hidradenitis Suppurativa

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Abstract

Hidradenitis suppurativa (HS) is a chronic, recurrent, auto-inflammatory skin disease originating from the hair follicles. The typical inflammatory nodules, abscesses, and draining sinus tracts (tunnels) are characterized by a massive influx of neutrophils, macrophages, B-cells, plasma cells, T helper (Th)1, Th17 cells and upregulation of pro-inflammatory cytokines such as IL-1, IL-17, IL-12/23, and TNF-α. Over the last decades, several clinical trials evaluated the clinical efficacy of different biologics targeting these pro-inflammatory cytokines, in particular TNF-α and IL-1. However, adalimumab is still the only registered drug for HS. This review discusses biologics and small molecules with high level of evidence for their clinical application, provides guidance on when and how to use these biologics and small molecules in clinical practice, and elaborates on the combination with medical and surgical treatment options beyond the current guidelines. Furthermore this review provides an overview of potential biologics and small molecules currently under investigation for novel targets in HS such as IL-36, C5a, Janus kinase family members, CD-40, LTA4 and CXCR1/2.

Key Points

Adalimumab (anti-TNF-α) is still the only registered agent for the treatment of hidradenitis suppurativa.

The refined Hurley staging is an easy-to-use method to provide clinical guidance on when and how to implement biologics, especially with regard to additional surgery.

Various novel biologics and small molecules targeting IL-17, IL-23, IL-36, CD-40, Janus kinase family members, complement, LTA4 and CXCR1/2 are currently being investigated for HS.

1 Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin disease. Patients present with painful, inflammatory nodules, abscesses, and draining sinus tracts (tunnels), typically in the flexural body sites such as the axillary, inguinal/genital, and gluteal/perianal areas [1]. The overall prevalence of HS has currently been reported to be 0.4% in the pooled data from studies in Western Europe, Scandinavia, and the USA [2]. The first symptoms develop in early adulthood affecting both males and females, with an estimated ratio of 1:3 in North American and European patients [3]. Because of severe pain, itching, malodorous discharge, and the psychological consequences of the disease, HS has a significant impact on patient’s quality of life and professional activity [4]. The impact of HS on health-related quality of life is comparable to cerebrovascular stroke, diabetes mellitus, or severe chronic obstructive pulmonary disease [4].

The etiology of HS is multifactorial with genetic predisposition, environmental factors such as smoking and obesity, hormonal factors, and microbiota being involved in both the onset and maintenance of the disease [5]. It is hypothesized that the interaction of endogenous and exogenous factors leads to activation of predominantly

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the innate immune system around terminal hair follicles [6]. This causes hyperkeratosis and hyperplasia of the follicular epithelium, especially the infundibulum, resulting in follicular occlusion [7]. Rupture of the dilated hair follicle triggers a massive immune response with recruitment of neutrophils, macrophages, B-cells, T helper (Th)1, and Th17 cells into the skin, leading to the formation of an inflammatory nodule or abscess [5]. These pro-inflammatory cytokines play a crucial role in the immune dysregulation of the acute and chronic state of the disease [1].

Our increased understanding of the pathogenesis of HS resulted in targeted therapies using biologics. In 2001, the first case-report of biologic treatment in HS was published in a patient with Crohn’s disease and concomitant HS [12–14]. The clinical symptoms of HS improved drastically during the treatment of Crohn’s disease with infliximab [12]. This report ignited scientific research on the inflammatory pathways involved in the pathogenesis of HS, and the efficacy of other biologics targeting tumor necrosis factor (TNF)-α (infliximab, adalimumab, etanercept) for HS [15].

In this review we will start with biologics and small molecules with level 1 evidence, meaning that at least one double-blind randomized controlled trial (RCT) has been published for HS (Table 1). Secondly, we provide guidance on therapy choice and the implementation of these biologics in clinical practice. Finally, we discuss the clinical potential of novel targets and provide an overview of new agents for HS on www.clinicaltrials.gov as well as agents with a previously published open-label study.

2 Current Biologics and Small Molecules with High Level Evidence for the Indication Hidradenitis Suppurativa

2.1 Anti-tumor Necrosis Factor-alpha

Tumor necrosis factor-alpha is a pro-inflammatory cytokine, playing essential roles especially in tissue immune cell infiltration, T-cell functional polarization, and systemic inflammation [24]. Lesional HS skin shows a significant

| Target | Therapy | Study | Patients | Efficacy |
|--------|---------|-------|----------|----------|
| TNFa   | Adalimumab | Kimball et al. 2016 [16] | PIONEER I (n=307) Adalimumab 40 mg/wk s.c. (n=153) Placebo s.c. (n=154) PIONEER II (n=326) Adalimumab 40 mg/wk s.c. (n=163) Placebo s.c. (n=163) | 41.8% HiSCR after 12 wk 26.0% HiSCR after 12 wk p = 0.003 58.9% HiSCR after 12 wk 27.6% HiSCR after 12 wk p < 0.001 |
| TNFa   | Adalimumab | Kimball et al. 2012 [17] | Adalimumab 40 mg/wk s.c. (n=51) Adalimumab 40 mg EOW s.c. (n=52) Placebo s.c. (n=51) | 17.6% HS-PGA after 12 wk 9.6% HS-PGA after 12 wk 3.9% HS-PGA after 12 wk p = 0.025 40 mg/wk vs placebo |
| TNFa   | Adalimumab | Miller et al. 2011 [18] | Adalimumab 40 mg EOW s.c. (n=15) Placebo s.c. (n=6) | − 11.3 in Sartorius score after 12 wk + 5.8 in Sartorius score after 12 wk p = 0.07 |
| Infliximab | | Grant et al. 2010 [19] | Infliximab i.v. 5 mg/kg (n=15) Placebo i.v. (n=23) Administered week 0, 2, and 6 | 60% 25–50% HSSI after 8 wk 5.6% 25–50% HSSI after 8 wk p < 0.001 |
| Etanercept | | Adams et al. 2010 [20] | Etanercept s.c. 50 mg EOW (n=10) Placebo s.c. (n=10) | No statistically significant difference between etanercept and placebo groups p > 0.99 |
| IL-1 | Anakinra | Tzanetakou et al. 2016 [21] | Anakinra 100 mg/day (n=10) Placebo s.c. (n=10) | 78% > 50% decrease in DAS after 12 wk 30% > 50% decrease in DAS after 12 wk |
| Bermekimab | | Kanni et al. 2018 [22] | Bermekimab 7.5 mg/kg EOW (n=10) Placebo i.v. (n=10) | 60% HiSCR after 12 wk 10% HiSCR after 12 wk |
| PDE-4 | Apremilast | Vossen et al. 2019 [23] | Apremilast oral 30 mg 2x/day (n=15) Placebo oral (n=5) | 53.3% HiSCR after 12 wk 0% HiSCR after 12 wk p = 0.055 |

DAS disease activity score, EOW every other week, HS hidradenitis suppurativa, HSSI HS severity index, IL-1 interleukin-1, i.v. intravenously, PDE-4 phosphodiesterase 4, s.c. subcutaneously, TNFa tumour necrosis factor alpha, wk week

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increase in TNF-α levels compared with healthy controls [11]. Additionally, concentrations of TNF-α in serum were significantly higher in patients with HS compared with blood serum of healthy controls [25].

2.1.1 Adalimumab

Adalimumab is a fully human IgG-monoclonal antibody targeting TNF-α. Ex vivo experiments of HS lesional skin have shown a reduction of TNF-α, interferon (IFN)-γ, IL-6 and IL-17A in response to adalimumab [26]. In treatment with adalimumab has been shown to decrease the in situ levels of IL-1β, CXCL9, B lymphocyte chemoattractant (BLC), cysteine-cysteine chemokine ligand (CCL)5, IL-6R, IL-16, IL-1RA, soluble TNF-R2, intercellular adhesion molecule (ICAM)-1, IL-10 and CCL3 in HS skin after 12 weeks [27]. To date, adalimumab remains the only European Medicines Agency (EMA)- and Food and Drug Administration (FDA)-approved agent for the treatment of moderate-to-severe HS.

The first RCT investigated the efficacy of adalimumab in HS using the psoriasis dosing regimen (40 mg every other week [EOW]) [18]. This Phase II trial compared the change in Sartorius score between the adalimumab 40 mg EOW and placebo group, 15 patients were enrolled in the treatment group versus six patients in the placebo group. A significant reduction was seen in Sartorius score after six weeks with a change of −10.7 in the treatment group versus +7.5 in the placebo group (p = 0.024). After 12 weeks however, the reduction was not significant with −11.3 in the treatment group versus +5.8 in the placebo group (p = 0.07). In 2012, Kimball et al conducted a Phase II parallel RCT using a minimal change of two in The Hidradenitis Suppurativa Physician’s Global Assessment scale (HS-PGA) as primary outcome, allocating 154 patients in three different groups, 51 patients received placebo, 51 patients received adalimumab weekly, and 52 patients received adalimumab EOW. After 12 weeks, the clinical efficacy, defined as a minimal change of two in HS-PGA, was achieved by 3.9% of the placebo group, 9.6% of the patients in the EOW group, and 17.6% of patients in the adalimumab weekly group (p = 0.025). Hereby a weekly dose of 40 mg weekly was found to be more efficacious than the EOW regimen leading to two substantial Phase III studies, the PIONEER I and PIONEER II [17]. These RCTs with 307 patients in PIONEER I and 326 patients in PIONEER II used Hidradenitis Suppurativa Clinical Response (HiSCR) as primary outcome. Achievement of HiSCR was significantly higher in the adalimumab weekly groups compared with the placebo groups at week 12: 41.8% versus 26.0% in PIONEER I (p = 0.003) and 58.9% versus 27.6% in PIONEER II (p < 0.001), respectively [16]. Recently, long-term data were published in a 3-year Phase III open-label study with the pooled data of the two PIONEER studies and an open-label extension study, which confirmed that adalimumab sustains efficacy and has an acceptable safety profile through 168 weeks [28].

2.1.2 Infliximab

Infliximab is a chimeric monoclonal IgG1 anti-TNF-α antibody and is administered through intravenous infusions [29].

In 2010, one Phase II trial with crossover was published. This study remains the only RCT for infliximab in HS to date [19]. In total, 38 patients were randomized into two groups comparing infliximab (5 mg/kg at weeks 0, 2 and 6) against placebo. Eight weeks after baseline, patients in the placebo group were offered to crossover to the treatment group. In the first eight weeks, 60% of patients treated with infliximab versus 5.6% of patients treated with placebo reached a 25–50% decrease in the Hidradenitis Suppurativa Severity Index (HSSI). Eight weeks after crossing over, patients from the placebo group showed a similar improvement [19].

2.1.3 Etanercept

Etanercept is a dimeric fusion protein, composed by the fragment crystallizable (Fc) portion of human immunoglobulin (Ig)G1 and the extracellular domain of human TNF-R2. Etanercept binds soluble TNF-α. Additionally, it binds lymphotoxin-α (LTα), which is known to be involved in the inflammatory cascade, activating nuclear factor-kappa B (NFκB) pathways that upregulate the expression of inflammatory cytokines, chemokines, and adhesion molecules [30].

One RCT, including a total of 20 patients was conducted in HS administering 50 mg etanercept twice weekly [20]. After 12 weeks, the placebo group received etanercept in an open-label treatment period. No significant difference was seen in the HS-PGA at 12 or 24 weeks between the treatment and placebo groups (p > 0.99). In addition, no significant difference was found in physician-assessed pain, erythema, or drainage after 12 and 24 weeks.

2.2 Anti-interleukin-1

The IL-1 family is a group of 11 cytokines of which IL-1α and IL-1β are targets in inflammatory diseases [31]. They have the potential to induce a complex network of pro-inflammatory cytokines and to regulate and initiate inflammatory responses, predominantly via leukocytes and endothelial cells. Of the IL-1 family, IL-1Ra functions as a natural antagonist and regulator by competitive binding of the same receptor [31]. IL-1β is shown to be highly active in the skin of HS patients, with messenger RNA (mRNA) and protein levels strongly elevated compared with healthy

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controls ($p \leq 0.001$). Furthermore the IL-1β pathway was found to be systemically active in the blood of HS patients [32].

2.2.1 Anakinra

Anakinra is a recombinant IL-1 receptor antagonist. It blocks the biological activity of naturally occurring IL-1 by competitively inhibiting the binding of both IL-1α and IL-1β to the IL-1 type 1 receptor [33].

A RCT with 12 weeks’ treatment and 12 weeks’ follow-up enrolled 10 patients in the treatment group and 10 patients in the placebo group [21]. Anakinra was administered subcutaneously daily at a dose of 100 mg. A > 50% decrease in disease activity score was used as the primary endpoint, which was achieved by 78% of the treatment group and 30% of the placebo group ($p = 0.02$). Additionally, in the treatment group a significantly longer time was seen until the first new exacerbation after the treatment period ($p = 0.01$). Therefore, the study deemed anakinra a reasonable alternative for adalimumab with a prolonged efficacy of 12 weeks after the 12-week treatment period.

2.2.2 Bermekimab

Bermekimab is a human monoclonal antibody that neutralizes IL-1α by binding this cytokine with high affinity and thereby acts as a blocker of IL-1α activity [34].

Two trials have been conducted to assess the efficacy, one with intravenous administration and one with subcutaneous injections [22, 34]. The intravenous administration was studied first in a Phase II double-blind RCT including 20 patients with refractory HS or who were ineligible for adalimumab. Bermekimab was administered every 2 weeks at a dose of 7.5 mg/kg. Ten patients were treated with bermekimab, of whom 60% achieved HiSCR compared with 10% of the 10 patients in the placebo group ($p = 0.035$) [22].

In 2020, Gottlieb et al conducted a Phase II open-label study in 24 patients who failed anti-TNF-α treatment (group A) and 18 patients who were naïve to anti-TNF-α treatment (group B) [34]. Initially, 200 mg bermekimab was administered every week, but during the study a switch was made to 400 mg weekly after new insight regarding efficacy and tolerability was obtained. After 12 weeks, 63% of patients reached HiSCR in group A compared with 61% of patients in group B.

In addition, a Phase II RCT with 144 patients is currently being conducted (NCT03019041).

2.3 Selective PDE-4 Inhibitors

2.3.1 Apremilast

Apremilast is a highly specific, small molecule drug designed to inhibit the phosphodiesterase 4 enzyme, to elevate intracellular cyclic adenosine monophosphate levels, and to regulate pro- and anti-inflammatory mediators in inflammatory cells [35].

One RCT has been performed with apremilast 30 mg twice daily [23]. Twenty patients were randomized in a 3:1 ratio resulting in 15 patients with mild-to-moderate disease treated with apremilast and five patients receiving placebo. In the treatment group 53.3% achieved HiSCR after 16 weeks versus no patients in the placebo group. This difference was borderline significant ($p = 0.055$). For the abscess and nodule count, a significant difference was observed with a mean difference of −2.6 ($p = 0.011$). Patients who achieved HiSCR at the end of the study were offered to continue apremilast treatment in a compassionate use program [36]. Of the eight patients who achieved HiSCR, four discontinued before the first year. Of the other four patients, all maintained HiSCR at the 1- and 2-year follow-up.

3 Implementation of Biologics in Clinical Practice

The treatment of HS is challenging due to an unpredictable response to medical treatment and clinical heterogeneity. Regarding treatment choice and efficacy, evaluation determination of disease severity is of vital importance. However, designing a dynamic and reliable measuring tool has been shown to be difficult as RCTs used 16 different physician-reported instruments until 2016 [37]. Here, we will discuss the advantages and disadvantages of the most frequently used severity scoring methods in clinical practice.

The HS-PGA ranges from clear to very severe in 5 stages. However, marked heterogeneity potentially exists among patients in the most severe category, creating the possibility that patients may experience clinically important improvement but not gain a meaningful reduction in their HS-PGA score [38].

The International Hidradenitis Suppurativa Severity Score System (IHS4) score was created by an international consortium of HS experts—members of the European Hidradenitis Supurativa Foundation (EHSF) e.V. as a dynamic objective outcome measure. The IHS4 is a cumulative score of inflammatory nodules, abscesses and draining tunnels, which are given one, two and four points, respectively. A score of three or less corresponds to mild disease, 4 to 10 to moderate disease, and ≥ 11 to severe disease [39]. The IHS4 has a dynamic component as well as a classifying
component, making it usable in both clinical practice and clinical research.

The Hurley classification is the oldest tool subdividing HS into three stages [40]. Stage I is a mild disease, defined as abscess formation (single or multiple) but no sinus tracts or cicatrisation/scarring. Stage II is a moderate disease and is defined as recurrent abscesses with sinus tracts and scarring, single or multiple separated lesions. Stage III is a severe disease and is defined as diffuse or almost diffuse involvement, or multiple interconnected sinus tracts and abscesses across the entire area. Although the Hurley classification is simple to use, it was developed for surgical treatment and therefore the extent of inflammation is not measured.

The refined Hurley (Fig. 1) classification was specifically created as a treatment guide for daily clinical practice and incorporates guidance on both anti-inflammatory treatment and surgery (Fig. 1) The refined Hurley subdivides the classic Hurley I and II stages into A, B and C, which correspond with mild, moderate and severe disease. Hurley III is always considered as severe [41]. The two most noteworthy stages with regard to treatment choice are Hurley I C and IIA, Hurley 1C is characterized by migratory inflammatory nodules and abscesses, which appear and disappear at multiple sites. This type of HS is highly inflammatory. In contrast to the traditional Hurley classification, which would stage such a patient as Hurley I (mild disease), the refined Hurley will indicate Hurley 1C as severe. The other important refined Hurley stage is Hurley IIA, which is characterized by the presence of low or non-inflammatory tunnels and is therefore considered mild disease. The refined Hurley classification accurately correlates with HS severity assessed by both patients and clinicians [42].

3.1 Which Patients are Biologically Eligible?

The two most prominent HS guidelines are the 2015 European S1 Guideline and the more recent 2019 North American Guideline [43–45]. The European guideline however, offers only little guidance on the use of the biologics as both adalimumab and infliximab are recommended only in the unspecified more severe disease. The North American guideline is clearer and advises adalimumab or infliximab for treatment of Hurley stage II and III.

To assess biologic eligibility in daily practice, we prefer the refined Hurley classification, since it was specifically designed for this purpose and incorporates advice on both anti-inflammatory treatment as well as surgical intervention. Since most benefits from biologic therapy in terms of clinical response and quality of life are to be expected in patients with high inflammation, biologic treatment should be considered in patients classified as IB, IIC, IIB, IIC and III according to the refined Hurley classification.

3.2 Which Biologic to Initiate?

In 2018, the HS ALLIANCE, a consortium of HS experts from 25 countries, provided treatment guidance based on systemic literature search as well as clinical experience beyond the guidelines [46]. There was a consensus that adalimumab should be considered as the biologic agent of first choice. Second in line was infliximab with a consensus of 81%. Anakinra can be considered a third-line biologic with a consensus of 84%. Ustekinumab was deemed potentially effective for the treatment of HS as only one non-RCT open-label study has been performed. Etanercept was regarded not to be an effective treatment and should therefore not be used [46].
Although early treatment has been suggested to be a predictive factor for response to adalimumab, no other clinical predictors regarding efficacy of biologic treatments have been found to date [47]. A post hoc analysis on the data from the PIONEER 1 and 2 studies aimed to assess the influence of patient characteristics on clinical efficacy in a multivariate logistic regression model [48]. However, the population used for logistic regression model was biased due to participant selection and the model included adalimumab as covariate and therefore adjusted for its effect on the outcome. Therefore, no conclusions on predictors for the efficacy of treatment with adalimumab could be drawn from this study.

Drug survival and associated predictors have been studied for adalimumab and infliximab [49]. Adalimumab has a 12-month drug survival in HS of 56.3% and a 24-month survival for adalimumab and infliximab [49]. Adalimumab has a comparable drug survival, of 58.3% and 48.6%, respectively. Remission contributed to the discontinuation of adalimumab and infliximab in 13.5% and 20%. Predictors of drug survival for adalimumab were older age, increased disease duration, moderate HS according to Hurley staging, and severe HS according to IHS4 staging. Two predictors for a longer drug survival were found for infliximab, namely severe disease compared with mild disease and concomitant surgical intervention.

### 3.3 How to Evaluate Biologic Efficacy?

One has to realize that the efficacy of the current biologics in HS is significantly less effective compared to the efficacy in other inflammatory diseases, such as psoriasis. Therefore, realistic treatment goals should be formulated with the patient before biologic initiation. Both objective physician-reported as well as subjective patient-reported outcome measures should be used to evaluate treatment efficacy. We prefer to use the parameters HiSCR and IHS4 as physician-reported efficacy and the DLQI and VAS pain as patient-reported measures. These parameters are validated and relatively easy to incorporate in daily clinical care [38, 39, 50, 51].

The HS ALLIANCE provides guidance on the decision whether to continue or stop biologic treatment: at week 12 patients with < 25% improvement in abscess and inflammatory nodule count (AN count), treatment with adalimumab should not be continued [46]. Patients who achieve a 25–50% improvement in AN count (partial response) can continue treatment and should be re-evaluated after an additional 3 months. However it has been demonstrated that HiSCR could still be achieved after 6 months in patients with dermal tunnels, with a median of 32.6 weeks [52].

Treatment efficacy could be influenced by antibody formation. Abdalla et al demonstrated that antibodies were detected in the serum from 9 of 38 patients with suboptimal clinical response during adalimumab treatment [53]. We therefore advise therapeutic drug monitoring in patients with sub-optimal treatment response or loss of efficacy after initial response. In case of unexpectedly low serum levels, antibodies should be ruled out.

Zouboulis et al published a case series of 14 patients who responded sub-optimally or lost response on the treatment of adalimumab 40 mg per week [54]. Dose intensification to 80 mg per week significantly improved the IHS4, Pain Index, HS-PGA, pain, and DLQI. However, two patients with HS and Crohn’s disease developed psoriatic lesions.

With regard to infliximab, the question of what dosing regimen is most beneficial has arisen. Initially the psoriasis dosing regimen was used that administered 5 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter. In 2014 however, Morigarty et al suggested 5 mg/kg every 4 weeks [55]. Since then, a dose of 10 mg/kg every six to eight weeks has been proven to achieve significant improvement and was well tolerated by patients. Additionally, a regimen of 7.5–10 mg/kg every four weeks provided optimal mitigation of HS-related disease activity [56, 57]. However, we do recommend therapeutic drug monitoring before administering these intensified regimens.

### 3.4 Combining Biologics with Antibiotics?

There are no studies on the efficacy of concomitant antibiotic treatment to biologic therapy. However, some evidence on combining biologics and antibiotics has been derived from the adalimumab PIONEER trials. In PIONEER I, no adjuvant antibiotics were allowed, whereas in PIONEER II patients were allowed to continue antibiotics of the tetracycline class. In PIONEER I, 41.8% of the patients in PIONEER I achieved HiSCR compared to 58.6% in the PIONEER II study. Kimball et al conclude that this difference in responsiveness is likely to be the result of a higher disease burden in the PIONEER I trial, but this difference may be amplified by the effect of concomitant antibiotic use [52].

In our experience, the concomitant treatment of antibiotics (tetracylines or clindamycin and rifampicin combination therapy) with biologic or small molecule therapy improves efficacy.

### 3.5 Combining Biologics with Surgery?

The management of HS often consists of a combination of medical therapy and surgery (Fig. 2). Biologics have the potential to reduce the inflammatory load in HS lesions. However, in our clinical experience when tunnels and (deep-seated) nodules on fixed locations remain present, these chronic lesions will, in most cases, result in local recurrence. We therefore advise performing surgery, i.e. deroofing or (wide) local excision on chronic lesions, e.g.
Biologics and Small Molecules for Hidradenitis Suppurativa

There is an increasing interest in HS, reflected by the exponential growing number of trials and publications. In this section we will discuss new immunological targets in HS with corresponding biologics and small molecule therapies, which are currently studied for HS according to www.clinicaltrials.gov (Table 2) as well as other biologics without level 1 evidence.

4 Upcoming Biologics and Small Molecule Therapies for Hidradenitis Suppurativa

4.1 Anti-interleukin-23 and Anti-interleukin-12

Interleukin 23 is a pro-inflammatory member of the IL-12 cytokine superfamily, with a potent ability to enhance the production of Th17 cells [59]. Interleukin-23 is mainly secreted by dendritic cells and activated macrophages in peripheral tissues such as the skin [60]. Several studies indicate that IL-23 is a central mediator in regulation of cellular inflammation. Interleukin-23 and IL-17 form an axis via Th17 cells with a strong association to activation and pathogenicity of the immune system. As IL-17 is considered a key cytokine in the inflammation of HS, IL-23 and IL-12 are regarded as promising targets in the future treatment of various auto-immune diseases including HS [61, 62].

4.1.1 Ustekinumab

Ustekinumab is a human IgG1 anti-p40 monoclonal antibody targeting IL-12 and IL-23. By interfering with binding to their cell surface, IL12Rβ1-receptor protein ustekinumab effectively neutralizes IL12- and IL23-mediated cellular responses. Additionally, it downregulates IFN-γ, IL-8, IFN-γ inducible protein-10, and Monocyte Chemoattractant Protein (MCP)-1 [63, 64].

One open-label trial was performed that treated 17 patients with either 45 mg or 90 mg ustekinumab on weeks 0, 4, 16 and 28. A > 50% change in the modified Sartorius Score (mSS) was used as the primary outcome measure. Five patients dropped out, three due to unresponsiveness, one for psychological reasons, and one because of adverse events (AEs). After 40 weeks, 35% achieved the 50% improvement on the mSS. Furthermore, 47% achieved HiSCR [65].

4.1.2 Guselkumab

Guselkumab is a fully human IgG1-λ monoclonal antibody that binds to the p19 subunit of IL-23 and inhibits the intracellular and downstream signaling of IL-23.

Its use for HS is only described retrospectively. Casseres et al presented a chart review of eight patients with moderate-to-severe HS, who were treated with guselkumab 100 mg subcutaneously. Guselkumab was administered according to the psoriasis regimen at weeks 0, 4 and every 8 weeks thereafter. After treatment with guselkumab, 63% of the patients noted an amelioration of their HS [66].

Another case series reported three patients treated with guselkumab following the psoriasis regimen. IHS4, DLQI and VAS for pain were measured at baseline, after 8 weeks and after 12 weeks. Significant improvement was seen for all three patients on all outcomes [67]. The potential benefit of guselkumab was acknowledged by pharma and investigators resulting in the recent finalization of both a multicenter,
double-blind RCT (NCT03628924) and a multicenter open-label mode of action study (NCT04061395).

### 4.1.3 Risankizumab

Risankizumab is a humanized IgG1 monoclonal antibody targeting the p19 subunit of IL-23 [68]. So far, only retrospective data on the efficacy of risankizumab within small groups have been reported. Marques et al described two patients with severe, therapy-resistant HS who were successfully treated with risankizumab. Both patients achieved HiSCR after three months of therapy without serious AEs in 16 months of therapy. After four months of treatment, significant improvement in clinical picture, laboratory parameters, and patient-reported outcomes were observed and have remained stable during the rest of therapy [69]. A Phase II RCT (NCT03926169) is planning to include 220 patients.

#### 4.2 Anti-interleukin-17

The IL-17 cytokine family consists of 6 cytokines (IL-17A to –F) with five different receptor subtypes (IL-17RA to –RE), which bear no resemblance to other known cytokine receptors [70]. Interleukin-17A and -F are secreted by a range of immune cells, whereas IL-17B, -C and –D are mostly of epithelial origin [71]. The IL-17 receptors are present on various cell types in multiple tissues. Upon ligation of ligand and receptor, tissue-specific transcription of genes for a host of different pro-inflammatory cytokines, chemokines and matrix metalloproteases (MMPs) is initiated. [72]. Besides this array of inflammatory effects, IL-17 exerts its greatest inflammatory potential through the capability for recruitment of immune cells and synergistic actions with pro-inflammatory cytokines such as TNF, IL-1β, IFNγ, granulocyte-macrophage...
colony-stimulating factor (GM-CSF) and IL-23 [73]. Analysis with reverse transcription polymerase chain reaction (RT-PCR) showed a 30-fold increase in gene expression of IL-17 in lesional HS skin compared with healthy skin. Furthermore, immune-histochemical analysis on serial tissue sections of lesional HS skin and healthy skin confirmed this increase with marked infiltration of lesional HS skin in both the papillary ($p < 0.0001$) and reticular dermis ($p < 0.0001$) [74]. Also IL-17C is found to be elevated in lesional HS tissue [75].

### 4.2.1 Secukinumab

Secukinumab is a fully human IgG1 kappa monoclonal antibody with a high selectivity for IL-17A, which it selectively binds and neutralizes [76]. The potential as a therapeutic agent in HS has thus far only been described in case reports and one ex vivo study. The case reports all noted a significant improvement in patient-reported pain after administration of 300 mg secukinumab according to the psoriasis regimen for several months [77, 78], with one case study also showing a reduction in inflammatory lesions [79]. One study reported a paradoxical anti-IL17–induced HS after the aforementioned regimen [80]. Vossen et al were able to demonstrate a significant downregulation of relative mRNA expression of inflammatory cytokines and antimicrobial peptides (AMPs) in an ex vivo assay of HS lesional skin, but protein production of pro-inflammatory cytokines was not significantly inhibited by secukinumab [26]. Two Phase III trials with 541 patients each are currently recruiting (NCT03713632–NCT03713619).

### 4.2.2 Bimekizumab

Bimekizumab is a humanized monoclonal antibody of the IgG1 isotype, binding to both IL-17A and -F, thus conveying inhibition of both isoforms [81]. A Phase II multicenter, double-blinded RCT with 90 patients has been completed and two Phase III RCTs with 490 patients are currently being conducted (BeHeard 1 and 2). (NCT04242498–NCT04242446).

### 4.2.3 CJM112

CJM112 is an IgG kappa monoclonal antibody binding to both IL-17A and the heterodimer IL-17AF. A randomized, double-blind, parallel-design Phase II study (NCT02421172) has been completed, but at present results have yet to be published [82].

### 4.2.4 Brodalumab

Brodalumab is a human monoclonal antibody binding to IL-17RA and thereby enables blockade of IL-17A, IL-17C and IL-17F. Two open-label cohort studies have been published, one administering brodalumab EOW and one administering brodalumab once weekly. In the open-label cohort study with brodalumab EOW, 10 patients received 210 mg of brodalumab subcutaneously at weeks 0, 1, 2 and every 2 weeks thereafter until week 24. The primary outcome measure was the HiSCR, but also the Sartorius score as the IHS4 were measured to assess clinical efficacy. At week 12 100% patients achieved HiSCR and 80% achieved an IHS4 category change. The clinical efficacy was maintained until week 24 [83].

The other open-label cohort study also included 10 patients but brodalumab 210 mg was administered every week until week 24. HiSCR was used to evaluate clinical efficacy and was met by all patients on week 4 and maintained until week 24 [84].

### 4.3 Anti-CD-40

CD40 is a cell surface receptor belonging to the TNF-R family. It is expressed on a wide range of mainly B cells and other antigen-presenting cells in various tissues. Additionally, CD-40 and its ligand CD-40L, have emerged as an immune-potentiating combination, which regulates the host immune response. The signaling pathway has effect via activation and proliferation of B cells, Ig class switching and generation of B cell memory, but also the production of a variety of cytokines, chemokines and cell adhesion molecules [85]. B cells were identified as a potential therapeutic target in HS, after a significant increase in B cells was found sequencing B cell receptor from RNA-sequencing data from HS skin and blood [86].

### 4.3.1 CFZ533 (Iscalimab)

CFZ533 (iscalimab) is a fully human, non-depleting monoclonal antibody that blocks the CD40 pathway [87]. A Phase II clinical study to assess the efficacy and safety in patients with moderate-to-severe HS is currently being conducted (NCT03827798). Publicly available data from the Novartis website reports CFZ533 to be an anti-CD40 monoclonal antibody.

### 4.4 Leukotriene A4 Inhibitor

Leukotriene A4 hydrolase (LTA4H) is an intracellular enzyme released by epithelial cells that classically functions as an epoxide hydrolase to generate leukotriene B4.
(LTB4) from leukotriene A4 (LTA4) [88]. LTB4 is a pro-inflammatory mediator capable of recruiting and activating a wide range of immune cells, including neutrophils [89].

4.4.1 LYS006

LYS006 is a small molecule-selective leukotriene A4 hydrolase inhibitor [90]. A Phase II clinical study to assess the efficacy and safety in patients with moderate-to-severe HS is currently being conducted (NCT03827798). Publicly available data from the Novartis website reports LYS006 to be an LTA4H inhibitor.

4.5 Anti-interleukin-36

The IL-36 cytokines consist of IL-36α, IL-36β, IL-36γ and IL-36Ra. They belong to the IL-1 superfamily and have a pro-inflammatory effect by promoting immune-cell infiltration and secretion of inflammatory and chemotactic molecules [91]. They influence numerous target cells such as T-cells, dendritic cells and keratinocytes. Evidence from past years has suggested a role of IL-36 in autoimmunity and inflammatory disease [92]. Additionally, RNA sequencing on HS lesional skin showed an increased expression of IL-36A, IL-36B, and IL-36G. These elevations were also observed in HS lesional skin using immunohistochemistry. All three genes were found primarily in the keratinocytes [93].

4.5.1 Spesolimab

Spesolimab is a monoclonal antibody against the IL-36 receptor and is currently under investigation as a therapeutic agent in Phase II trials in moderate-to-severe palmoplantar pustulosis [91]. A trial (NCT04762277) for the efficacy in HS is under way.

4.6 Inhibitors of the Janus Kinase Family

Kinases in the Janus Kinase (JAK) family include JAK1, JAK2, JAK3 and non-receptor tyrosine-protein kinase TYK2 [94]. Signals from cytokines IL-2R, IL-4R, IL-5R, IL-6R, IL-13R and type I interferons activate JAKs, which subsequently activate signal transducers and activators of transcription proteins (STATs). After activation STATs enter the nucleus to bind to transcriptional regulatory sites of target genes and induce inflammation. Signals from cytokines IL-23, IL-12 and type I interferons activate tyrosine kinase (TYK)2. Furthermore, IL-1 receptor-associated kinase (IRAK)4 functions downstream of multiple innate immune cell receptors, such as toll-like receptors (TLR) and IL-1Rs [95].

4.6.1 INCB054707

Several studies are conducted to assess the efficacy of kinase inhibitors in HS. INCB054707 is a JAK1 inhibitor and has been tested in two Phase II trials (NCT03569371 – NCT03607487) to assess the safety in patients with moderate-to-severe HS. These trials have been completed but have not yet been published. Another Phase II RCT (NCT04476043) with 200 patients is currently recruiting. Upadacitinib is a JAK1 inhibitor, a Phase II trial (NCT04430855) with 68 patients is active, but not recruiting. Three kinase inhibitors are tested in a Phase II RCT (NCT04092452) with 192 patients. PF-06650833 is an Irak4 inhibitor, brecopitinib is a Tyk2/JAK1 inhibitor and rupsacitinib is a Tyk2 inhibitor. There is also one Phase I trial (NCT04772885) with 124 healthy participants testing KT-474, which is an Irak4 inhibitor.

4.7 Complement C5a Inhibitors

Besides the adaptive immune system, upregulation of the innate immune system was also described in lesional HS skin [11]. The complement system appears to play an important role in cutaneous health. Activation of the immune system via anaphylatoxins, opsonization, and bacterial lysis are primary functions of complement, which are all potential early and/or amplifying events in HS [96]. Complement pathway activation was described in HS plasma with elevated levels of C5a and C5b-9 [97]. Furthermore a deposition of complement components C1q, C3b, and C4d in the deeper layers of HS lesions was observed [86]. C5a exerts strong chemotaxis and activation of neutrophils at the inflammatory areas. Thereby complement C5a inhibition is thought to be a profitable target in HS.

4.7.1 Vilobelimab (IFX-1)

Vilobelimab (IFX-1) is a monoclonal IgG4 kappa antibody that selectively binds to C5a, blocking its biological activity. The first trial conducted was an open-label single-arm trial including 12 patients. After 50 days, 75% achieved HiSCR and after 134 days this increased to 83.3% [98]. However, data from the following Phase II RCT (NCT03487276), are yet to be published.

4.7.2 Avacopan

Avacopan is a small molecule oral C5aR antagonist. An RCT (NCT03852472) randomized 398 patients in three groups 1:1:1, respectively, in the placebo, avacopan 10 mg twice daily and avacopan 30 mg twice daily group. The results of this RCT are yet to be published.
4.8 CXCR-1 and CXCR-2

CXCR-1 and CXCR-2 are two surface receptors expressed by several leukocytes such as neutrophils, when activated they mediate neutrophil recruitment and trigger cytotoxic effects at sites of infection [99]. HS is considered a neutrophil-driven dermatosis. Therefore, this pathway could be promising.

4.8.1 LY3041658

LY3041658 is a monoclonal antibody that neutralizes chemokines that bind to the CXCR-1 and CXCR-2. One Phase II trial (NCT04493502) with 52 patients is recruiting.

5 Conclusion

In the last 10 years, interest in HS has risen substantially resulting in the first EMA- and FDA-approved anti-TNF-α biologic—adalimumab. However, all biologics (adalimumab, infliximab, etanercept, anakinra, beremikab) for which high-level evidence exists, struggle to achieve adequate disease control. Therefore, treatment usually consists of a combination of anti-inflammatory treatment with surgery. Fortunately, many more biologics with new immunological targets (IL-12, IL-17, IL-23, IL-36, CD-40, Janus kinase family members, complement, LTA4 and CXCR1/2) are currently being investigated for HS [100].

Declarations

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Author contributions HHZ was invited author for this article, PA and KD performed the literature search and data analysis. PA, KD, ARJVV, KrvS, CBA, EPP and HHvdZ wrote the text and critically revised the work.

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