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REVIEW ARTICLE

Biologic Treatment for Hidradenitis Suppurativa

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Abstract
Patients with hidradenitis suppurativa (HS) are often undertreated and there are limited efficacious therapies available for treating this population. Biologics are an emerging therapeutic modality used in the management of many inflammatory conditions including HS. Implementation of biologics is typically reserved for moderate-to-severe cases or in those cases that are refractory to treatment. Though many biologics have been trialed for use in HS, only one biologic, adalimumab, is currently US FDA (Food and Drug Administration) approved for the treatment of moderate-to-severe HS. Limitations in the use of biologics for HS include the many scoring systems utilized in research studies and the relatively few well-designed, adequately powered clinical trials.

Key Points

Adalimumab is currently the only FDA-approved treatment for moderate-to-severe hidradenitis suppurativa (HS).

Many biologics have been studied in HS, of which some show promise. However, robust evidence, such as data from well-designed clinical trials, to support their use is largely lacking.

The lack of a universal scoring system in HS is an important limiting factor to acknowledge in HS research.

1 Introduction

Patients with hidradenitis suppurativa (HS) have painful inflammatory nodules, abscesses, and fistula distributed classically in the axilla, groin, buttocks, and inframammary region. The pathophysiology of HS is complex; contributing factors include immune dysregulation, hormones, genetics, the microbiome, environmental and physical factors, among others. A variety of therapeutic regimens have been employed in the management of HS, including lifestyle interventions, surgery, topical antibiotics, systemic antibiotics, systemic hormonal therapies, topical steroids, intra-lesional steroids, systemic steroids, and biologics. The potential efficacy of biologics in HS was first realized in patients with inflammatory bowel disease (IBD) undergoing treatment with biologics who incidentally happened to demonstrate improvement in their HS [1].

Several studies have demonstrated an altered inflammatory milieu in HS, supporting a mechanism for the efficacy of biologics [2–4]. As our understanding of cytokines involved in HS pathophysiology expands, several biologics have been trialed in HS management including agents targeting tumor necrosis factor (TNF), interleukin-12 (IL-12) and interleukin-23 (IL-23), interleukin-17 (IL-17), and interleukin-1 (IL-1). This paper reviews existing research on use of biologics in HS. Commonly used dosing, expected time to response, duration of response, and safety concerns will also be reviewed. Of note, longitudinal data regarding the safety of biologics in HS is lacking, in part given the more recent adoption of biologics for HS. Experience obtained from use of biologics in other conditions, including psoriasis, rheumatologic diseases, and inflammatory bowel disease, is frequently extrapolated to the HS population and will therefore be reviewed in this article.

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2 Hidradenitis Suppurativa Scoring Systems

Prior to discussing the research supporting efficacy of biologics in HS, it is important to understand how HS severity is assessed and monitored in clinical trials. Various scoring systems have been used in HS clinical trials. Hurley staging was originally developed in 1989 with the intent of guiding treatment options [5]. Hurley staging is a three-stage system in which the different stages are defined by the presence or absence of draining tracts, scarring, and normal intervening skin [6, 7]. Critiques of the Hurley staging system include the fact that it does not account for inflammation nor does it incorporate the number of anatomical sites involved [6, 7]. While Hurley staging remains useful in clinical practice, its use in clinical trials is limited as it is a static scoring system. Impetus among researchers to develop an outcome measurement that accurately captured dynamic response to treatment for use in clinical trials therefore led to the development of several additional scoring systems.

The modified Sartorius score (mSS) is a weighted scoring system that accounts for the number of regions involved, types of lesion involved, distance between involved lesions, and presence or absence of intervening normal skin [8]. However, a limitation of mSS is that the score requires detailed counting of lesions and measuring in between lesions, which can be time consuming [9]. The Hidradenitis Suppurativa Severity Index (HSSI) is another early scoring system that is determined by the number of involved sites, percent body surface area affected by HS, number of lesions, number of dressing changes, and pain as measured by a visual analog scale (VAS) [10].

The Hidradenitis Suppurativa Physician's Global Assessment (HS PGA) was developed thereafter in anticipation of larger clinical trials in HS. HS PGA is an ordinal scale that categorizes patients into one of six categories, clear, minimal, mild, moderate, severe, or very severe. In a phase II clinical trial, clinical response, as measured by HS PGA, was defined as having a score of either clear, minimal, or mild and a concurrent 2-grade improvement in score compared with baseline score [11]. One critique of HS PGA is that it may be too rigid a scoring system [12]. Hidradenitis Suppurativa Clinical Response (HiSCR), which was developed after HS PGA using data from a clinical trial data set, is a binary scale defined as a reduction of at least 50% in the total abscess and inflammatory nodule count with no increase in both the abscess count and the draining fistula count relative to baseline [12]. It has been validated by both patient- and physician-reported outcomes [9]. A recent observational study demonstrated that HiSCR has acceptable inter- and intra-rater reliability, further supporting its use as a scoring tool in clinical trials [13].

The European Hidradenitis Suppurativa Foundation (EHSF) recently developed a dynamic scoring tool called the International Hidradenitis Suppurativa Severity Score System (IHS4), which is calculated by assigning weighted points to the number of nodules, abscesses, and draining tunnels. This scoring system has also been validated by patient- and physician-reported outcomes [14]. Another recently developed scoring tool is the Acne Inversa Severity Index (AISI). AISI is a scoring system where individual lesions are given weighted points that are then multiplied by the number of sites at which these lesions are found [10, 15]. However, to our knowledge AISI has not been implemented in any clinical trials to date. Lastly, some studies have assessed HS by the disease activity score, which is calculated by measuring the affected areas and multiplying that by the degree of inflammation at each site, and then summing the scores of all affected areas [16, 17].

There are many scoring systems in place; at present, none comprehensively capture all dimensions and presentations of HS. Importantly, no scoring system takes into effect duration of disease or the underlying etiology of the disease. For example, there is no accounting for whether a patient has an underlying genetic defect or more hormonally driven presentation. Further, as evidenced by the number of scoring systems in use, another challenge in studying the efficacy of biologic therapies in HS has been the development of a scoring system that is well validated and universally adopted. The multiple scoring systems invoked in clinical trials for HS are prohibitive to comparing results between clinical trials and also to the ability of researchers to perform meta-analyses.

3 Biologics Targeting Tumor Necrosis Factor

Most preclinical studies have reported an increase in TNF in HS skin lesions [3, 18]. Consistently, Emelianov et al. found TNFα to be elevated in the epidermis and dermis in HS skin compared with control skin with the exception of immunoreactivity of TNFα at the proximal outer root sheath, where it was decreased compared with control skin [19]. Moreover, TNF receptors (TNF-R), TNF-R1 and TNF-R2, are also increased in HS skin [2]. In addition to elevated levels in the skin, HS patients also have higher serum levels of TNFα compared with healthy controls [20]. In contrast to the multiple studies that indicate TNFα is increased in HS, one study found levels of TNF to be decreased in lesional and non-lesional skin compared with control skin [21]. In another study, there was no significant difference in TNFα mRNA expression between lesional and non-lesional HS skin [22].

3.1 Adalimumab

Adalimumab is a fully human IgG1 monoclonal antibody that neutralizes and prevents TNFα from binding to membrane bound and soluble receptors [23–25]. It is currently the only FDA-approved therapy for treatment of moderate-to-severe HS. Adalimumab in HS is dosed at 160 mg subcutaneously at day 0, 80 mg at day 15, and, starting at day 29, it is thereafter dosed at 40 mg weekly. There is no weight adjustment for adalimumab [25] (Table 1).

Less frequent dosing, as used in psoriasis, was previously studied and found not to be efficacious in HS. In a study examining use of adalimumab (160 mg at week 0, 80 mg at week 1, followed by 40 mg every other week [EOW] for 12 weeks), of the ten patients in the study and six who completed the study, no patients achieved the primary endpoint, defined as a 50% decrease in HSSI compared with baseline [26]. Additionally, in a double-blind, randomized clinical trial (RCT) in which 21 patients were randomized to adalimumab (80 mg as an initial dose, followed by 40 mg EOW for 12 weeks) or placebo, reduction seen in the Sartorius score was significant at 6 weeks but not at 12 weeks. Moreover, there was no significant difference in Hurley score, pain VAS, or Dermatology Life Quality Index (DLQI) [27].

Higher dosing of adalimumab was compared with EOW dosing in a phase II study in which 154 patients with moderate-to-severe HS were randomized to adalimumab 40 mg weekly, adalimumab 40 mg EOW, or placebo. After 16 weeks, patients in the weekly dosing cohort demonstrated greater response compared to the EOW dosing cohort. During the open-label component of this study, all patients were transitioned to 40 mg EOW but were later escalated to weekly dosing if their HS PGA was ≥ 3 at follow-up. Of note, 63% of patients had suboptimal response to EOW dosing and were increased to weekly dosing. The results of this study were important as they suggested that weekly dosing, compared with EOW dosing as in psoriasis, is important in the treatment of HS patients [11]. Post-hoc analyses of this study revealed that more patients receiving weekly as compared with EOW dosing and placebo had a positive HiSCR response [12, 25]. Moreover, a Cochrane review, which examined the evidence from Kimball et al. and Miller et al., found no statistically significant difference in adalimumab EOW versus placebo in terms of DLQI score, pain, severity score, physician global assessment, or work productivity impairment [11, 27, 28]. In regards to safety, a study that compared data from studies on adalimumab EOW dosing versus weekly dosing in patients with HS, psoriasis, Crohn's disease, ulcerative colitis, and rheumatoid arthritis (RA) reported that the safety profiles of the two dosing regimens were comparable [29].

The FDA approved adalimumab based on the results of two phase III, double-blind RCTs, PIONEER I and II, which included 307 and 326 patients, respectively. In PIONEER I, patients were required to stop treatment with oral antibiotics 28 days prior to the baseline visit, whereas in PIONEER II, patients were allowed to continue treatment with oral antibiotics. Patients receiving weekly adalimumab had a greater clinical response, quantified by the HiSCR measure, which was used as the primary endpoint for this study. In PIONEER I, 41.8% of those receiving adalimumab versus 26.0% of subjects receiving placebo and in PIONEER II 58.9% of subjects receiving adalimumab versus 27.6% of those subjects receiving placebo reached the primary end point [30]. In a secondary analysis of PIONEER I and II looking at Patient's Global Assessment of Skin Pain (PGA-SP), treatment with adalimumab also improved skin-related pain [31].

In regards to efficacy, approximately half of all patients treated with adalimumab can expect to have approximately a 50% reduction in inflammatory abscesses and nodules (HiSCR) as seen in the PIONEER studies [30]. Further, while many patients may experience some symptom improvement after the initial loading dose of adalimumab, the full efficacy of treatment may not be appreciated until after 1 year of treatment. Evidence in regard to long-term efficacy of adalimumab was demonstrated in an open-label extension (OLE) of PIONEER I and PIONEER II in which 151 patients were followed longitudinally for at least 96 weeks. Disease response, measured by HiSCR, was achieved by 52.3% of patients at week 168 [32]. It is not well understood why certain patients do not respond to adalimumab but it is likely in part related to the complex pathophysiology of HS.

3.2 Infliximab

Infliximab is a chimeric monoclonal antibody directed against TNFα that binds both soluble and transmembrane TNFα [33] (Table 1). Infliximab, unlike adalimumab, allows for weight-based dosing. Commonly used dosing of infliximab in HS patients is 5 mg/kg at weeks 0, 2, and 6 [34, 35], although some authors report using a fourth dose at week 10 [36]. This is typically followed by maintenance dosing every 8 weeks [34]. Shorter time intervals, such as every 4–6 weeks, and higher doses may be needed in some patients, especially after the loading period. Some authors advocate for treating with methotrexate and infliximab concurrently to prevent adverse events related to immunogenicity [37, 38].

In a double-blind, crossover RCT of 38 patients, those randomized to receive infliximab (5 mg/kg at weeks 0, 2, and 6, followed by a maintenance regimen every 8 weeks through week 22) demonstrated statistically significant improvement in VAS, DLQI, erythrocyte sedimentation rate (ESR), and PGA. More patients treated with infliximab compared with placebo reached the primary end point,

Table 1 Biologics for which evidence has either proven or suggested efficacy in hidradenitis suppurativa

Biologic	Commonly used dosing	Target	Expected time to response	Duration of response	Strength of studies	Safety concerns per FDA label	FDA-approved conditions
Adalimumab (FDA approved for moderate-to-severe HS)	160 mg SC at day 0, 80 mg at day 15, starting from day 29, adalimumab is dosed at 40 mg weekly [24]	TNFα	Clinical trial endpoints show improvement at 12 weeks [30], although patients who demonstrate partial response at this time point may show additional improvement over time with continued treatment [32]	Sustained response can be seen on continuous treatment	High (several double-blind RCTs with large number of subjects: PIONEER I—307 subjects, PIONEER II—326 subjects) [30]	Infection, including fungal infections Malignancy Allergic reactions including anaphylaxis Hepatitis B reactivation Demyelinating disease Cytopenias Heart failure Lupus-like syndrome [24]	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (adult and pediatric), plaque psoriasis, ulcerative colitis, HS, uveitis [24]
Infliximab (not FDA approved)	5 mg/kg at weeks 0, 2, and 6 followed by maintenance dosing every 8 weeks	TNFα	Variable	Variable	Moderate (one RCT with 38 subjects) [34]	Infection, including fungal infections Malignancy Hepatitis B reactivation Hepatotoxicity Heart failure Cytopenias Hypersensitivity Cardiovascular and cerebrovascular reactions Demyelinating disease Lupus-like syndrome Do not administer live vaccines or therapeutic infectious agents in patients treated with infliximab [33]	Crohn's disease (adults and children), ulcerative colitis (adults and children), rheumatoid arthritis (in combination with methotrexate), ankylosing spondylitis, psoriatic arthritis, plaque psoriasis [33]
Ustekinumab (not FDA approved)	Either 45 mg or 90 mg (if subject weighs > 100 kg) dosed at weeks 0, 4, 16, and 28	IL-12 and IL-23	Not adequately studied	Not adequately studied	Low (one open-label phase II study with 17 patients) [77]	Infection, including theoretical concern for infections with salmonella, mycobacteria or from BCG vaccination Tuberculosis Malignancy Hypersensitivity reaction Reversible posterior leukoencephalopathy syndrome [76] Noninfectious pneumonia	Plaque psoriasis (adults and adolescents), psoriatic arthritis, Crohn's disease [76]

Table 1 (continued)

Biologic	Commonly used dosing	Target	Expected time to response	Duration of response	Strength of studies	Safety concerns per FDA label	FDA-approved conditions
Anakinra (not FDA approved)	Dosed at either 100 mg or 200 mg SC daily	IL-1α	Not adequately studied	Not adequately studied	Low (one double-blind RCT of 20 patients [17], one open-label clinical trial with 6 patients [115])	Infection Do not use concurrently with TNF inhibitors Hypersensitivity reactions including anaphylaxis Risk of malignancy is unknown; effect on infections (both active and chronic) is unknown Live vaccines should not be administered in patients using anakinra Monitor neutrophil counts [113]	Rheumatoid arthritis, cryopyrin-associated periodic syndromes [113]
Bermekimab (MABp1) (not FDA approved)	Dosed at 7.5 mg/kg every 14 days up to 7 infusions	IL-1α	Not adequately studied	Not adequately studied	Low (one double-blind RCT of 20 patients) [117]	Not applicable	Not FDA approved for any conditions

BCG Bacillus Calmette-Guerin, *FDA* US Food and Drug Administration, *HS* hidradenitis suppurativa, *IL* interleukin, *RCT* randomized clinical trial, *SC* subcutaneous, *TNF* tumor necrosis factor

defined as ≥ 50% improvement in HSSI from baseline. These results were not statistically significant in the initial analysis ($p = 0.092$), although they were statistically significant in a post hoc HSSI composite response analysis ($p < 0.001$) [34].

Studies have demonstrated various results regarding the long-term efficacy of infliximab in HS. In a study of ten patients treated with infliximab, seven patients experienced disease recurrence, in whom the average time to recurrence was 8.5 months [35]. Another study that followed ten patients demonstrated that relapse was common and occurred in half of patients with a median time to relapse of 37 weeks [37]. Other authors have suggested an even shorter duration of response. In a study of seven patients with severe HS, five out seven demonstrated improvement at week 6, but at week 10 only two of five patients receiving treatment demonstrated continued response to infliximab [36]. In a systematic review of 95 patients treated with infliximab, 85.3% demonstrated moderate or marked improvement during treatment. However, of the 48 patients who were followed longitudinally (mean follow-up of 53.8 weeks), only seven were stable after stopping infliximab whereas 15 recurred after stopping infliximab. Of those patients still being treated with infliximab, four were stable and eight demonstrated decreased response on continuous infliximab [38].

3.3 Etanercept

Etanercept, a soluble form of the TNF receptor, prevents the binding of TNF to its native receptor [39]. Some smaller studies have suggested potential efficacy of etanercept in HS, but data obtained from studies of higher quality with larger sample sizes argue against this [40–43] (Table 2). Results from a double-blind study of 20 patients randomized to either etanercept (50 mg twice weekly) or placebo revealed no significant difference in DLQI, patient global assessment, or physician global assessment [44]. Additionally, an open-label prospective clinical trial of 15 HS patients treated with etanercept (50 mg weekly over 12 weeks) did not demonstrate efficacy. PGA scores, lesion counts, and patient pain scores did not significantly improve after treatment. Though DLQI scores improved somewhat (19 vs 15, $p = 0.02$), the authors reported that this was of minimal clinical significance. Of interest, the patients who did demonstrate a response to etanercept treatment tended to have a lower body mass index (BMI) (27.5) compared to non-responders (36), although this difference was not significant ($p = 0.31$) [45]. As such, underdosing could have been a limitation in these studies.

Studies that did suggest efficacy for etanercept were of smaller sample sizes and less rigorous study design. In an open-label, phase II study of ten patients, etanercept (dosed at 50 mg weekly for 12 weeks) led to a > 50% decrease in

disease activity in six and seven subjects at 12 and 24 weeks, respectively [16]. Many of these patients (7 of 10), however, later experienced a recurrence 14–68 weeks after stopping treatment. Those who experienced a recurrence underwent a second course of etanercept; two patients failed the second course of treatment and five had a positive response [46]. Treatment with etanercept for six patients with treatment-resistant HS also suggested some efficacy. After etanercept treatment (25 mg twice weekly), improvement was demonstrated in DLQI scores (mean reduction of 64%) and patient-reported disease activity (mean reduction of 61%) at 24 weeks [47] (Table 2).

3.4 Golimumab

Golimumab is an antibody that binds both soluble and transmembrane TNFα [48]. No clinical trials have been performed to assess its efficacy in HS; however, a few case reports have been reported on use of golimumab in HS. A 42-year-old patient with a history of ulcerative colitis developed HS and pyostomatitis vegetans in the absence of any colonic symptoms. Subsequently, a colonoscopy was performed and revealed moderate ulcerative pancolitis. She was therefore initiated on golimumab (dosed at 200 mg subcutaneously initially then 100 mg subcutaneously monthly) and a 2-week course of amoxicillin-clauvanate. This led to resolution of her HS in 2 months, which at time of writing had not recurred on continued golimumab treatment [49]. In a different case report, a patient treated with golimumab 50 mg subcutaneously monthly over 8 months failed to respond to therapy and her HS actually worsened during treatment [50].

3.5 Certolizumab Pegol

Certolizumab is a TNF inhibitor that does not cross the placenta [51, 52]. One report describes management of a pregnant patient with HS and psoriasis who had previously been managed with adalimumab. She was switched to certolizumab during the third trimester [52]. Additionally, a retrospective review of off-label TNF inhibitor use for dermatologic indications reported use of certolizumab in two HS patients who did not respond to certolizumab or other TNF inhibitors [53].

Table 2 Biologics that have been studied but are not used for treatment in hidradenitis suppurativa

Biologic	Target	Reason(s) for not using in HS
MEDI8968	IL-1R1	Lack of efficacy
Efalizumab	Lymphocyte function-associated antigen 1 (LFA-1)	Lack of efficacy; safety concerns
Etanercept	TNFα	Lack of efficacy

HS hidradenitis suppurativa, *IL* interleukin, *LFA-1* lymphocyte function-associated antigen 1, *TNF* tumor necrosis factor

3.6 Safety Concerns

A common safety concern in treatment with biologics is increased risk of infections. In psoriasis, the incidence rate of serious infections was higher in patients treated with infliximab (47.8 per 1000 person-years) compared with those patients treated with non-biologic systemic medications (14.2 per 1000 person-years) [54]. In data obtained from the Psoriasis Longitudinal Assessment and Registry (PSOLAR), increased risk of serious infections was observed in patients treated with adalimumab and infliximab as compared with non-biologic and non-methotrexate medications [55]. The incidence of cellulitis, a common occurrence in patients with HS, however, was not elevated in the registration studies for adalimumab. Combination therapy, including the use of steroids, appears to increase risk of infection in treated patients. The underlying diagnosis also appears to matter, with lower rates seen, for example, in the psoriasis population than in the rheumatologic populations [56].

Reactivation of latent tuberculosis is of special concern with use of biologics, especially TNF inhibitors, as TNFα is a key cytokine in the immune response to tuberculosis infection [57]. Among the TNFα inhibitors, risk of active tuberculosis is higher in infliximab and adalimumab compared with etanercept. In a review of phase III clinical trials, post-marketing surveillance, and national registries, ten tuberculosis cases were reported in 4590 patients (0.21%) treated with infliximab, nine cases in 7009 (0.12%) patients treated with adalimumab, and four cases in 7441 patients (0.05%) treated with etanercept [58]. Systemic fungal infections may also be rarely observed with anti-TNF therapy, including histoplasmosis [59] and coccidioidomycosis [60].

Increased risk of malignancy is another important concern to consider when prescribing biologics. Patients with HS are inherently at an increased risk of non-melanoma skin cancer (NMSC), especially squamous cell carcinoma (SCC). The etiology of this elevated risk is not fully understood but different theories have been proposed. One theory is that longstanding inflammation contributes to this risk [61, 62]. For example, diseased skin may facilitate local immune dysregulation in the skin that may promote tumor or infection development; this concept is referred to as the 'immunocompromised cutaneous district' [63]. There is also evidence to suggest that human papilloma virus (HPV) infection may contribute to the development of SCC in HS patients [62, 64]. In one study of eight anogenital tumor samples from HS patients, polymerase chain reaction (PCR) revealed the presence of HPV in all samples and, further, HPV-16, a high-risk type, was found in seven of the eight samples [64]. Other evidence

suggests that impaired Notch signaling may be involved in both HS and SCC; impaired Notch signaling may explain increased risk of SCC in the HS population [62]. Treatment with anti-TNF therapy appears to additionally impart elevated risk of NMSC. Reports have detailed cases of HS patients treated with adalimumab [65] and infliximab [66] developing metastatic SCC. Therefore, risk stratification for NMSC is important when considering initiating anti-TNF therapy in an HS patient, especially for the HS patient with substantive and long-standing disease burden.

In a meta-analysis of 74 RCTs of TNF inhibitor use in psoriasis, psoriatic arthritis, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, among other diseases (including 23 studies on adalimumab, 28 on etanercept, and 23 on infliximab), the relative risk of NMSC was 2.02 (95% confidence interval [CI] 1.11–3.95) and for other cancers excluding NMSC was 0.99 (95% CI 0.61–1.68) [67]. Similarly, in a meta-analysis of rheumatoid arthritis patients receiving treatment with tumor necrosis factor inhibitors, all malignancy risk was not increased (0.95, 95% CI 0.85–1.05) but was increased for NMSC (1.45, 95% CI 1.15–1.76) and melanoma (1.79, 95% CI 0.92–2.67), although the confidence interval for melanoma included the null value [68]. A study by Kamangar et al. also demonstrated increased rates of detection of NMSC among patients treated with biologics [69].

In contrast to infections and malignancy, more frequently encountered safety concerns include injection site reactions and infusion reactions. In the IBD and rheumatology literature, patients who develop antibodies against a biologic are more likely to develop an infusion reaction [70, 71]. Anti-drug antibodies may also limit the efficacy of the biologic. In a meta-analysis of studies assessing use of TNF inhibitors in autoimmune diseases, rates of anti-drug antibodies were highest in infliximab, followed by adalimumab, certolizumab, golimumab, and lastly etanercept [72]. Adalimumab tends to be less immunogenic as it is a human antibody [25]. Certain human leukocyte antigen (HLA) alleles may be protective against formation of anti-drug antibodies whereas others may increase risk of their formation [23]. Concomitant methotrexate treatment with infliximab is suggested to possibly prevent adverse events related to immunogenicity [37, 38]. Indeed, it has been reported that infliximab monotherapy, compared with combined infliximab/immunomodulator therapy, primarily being methotrexate, has higher rates of severe adverse events [38].

Other adverse events, including menstrual disorders, have been reported in association with adalimumab; adverse effects per FDA labeling associated with the discussed TNF-inhibitors can be found in Table 1 [24, 73, 74].

4 Biologics Targeting IL-12 and IL-23

Expression of IL-12 and IL-23 mRNA is elevated in lesional HS skin [18, 75]. In contrast, one study reported no significant difference in IL-12 levels in HS compared with healthy control skin [2].

4.1 Ustekinumab

Ustekinumab is a monoclonal antibody with activity against P40, a subunit of both IL-12 and IL-23 [76]. Commonly used dosing of ustekinumab in HS patients is similar to the psoriasis regimen (45 mg of ustekinumab or 90 mg if the subject weighs > 100 kg, with induction phase dosing at weeks 0 and 4 followed by a maintenance phase with additional dosing at weeks 16 and 28 [77] (Table 1).

Few studies exist that examine the efficacy of ustekinumab in HS. An open-label, prospective study of 17 patients (of whom 12 completed the protocol) found that 47% of patients achieved HiSCR-50 and 82% of patients obtained either a moderate or marked improvement of the mSS score after treatment with ustekinumab [77]. In a review of three patients with moderate-to-severe HS treated with ustekinumab (45 mg subcutaneously at 0, 1, and 4 months), one patient demonstrated complete remission whereas another patient developed new HS lesions in addition to several adverse effects during treatment. The third patient initially demonstrated improvement, which was followed by a recrudescence in his HS. This later responded to antibiotics and increased dosing of ustekinumab to 90 mg [78]. Case reports in the literature have reported durable efficacy. In one case report, a 50-year-old female treated with ustekinumab was, at the time of writing, without active lesions after 1.5 years of treatment. Her course on ustekinumab was complicated by two exacerbations managed with antibiotics and steroids [79]. In another case of a patient with concurrent psoriasis, Bechet's disease, and HS who underwent treatment with ustekinumab for her psoriasis, treatment led to gradual improvement and later remission of her HS for 3 years [80].

4.2 Other Agents Targeting IL-23

Guselkumab is a monoclonal antibody with activity against IL-23 that is currently used in psoriasis [81, 82]. A phase II clinical trial to assess the use of guselkumab in HS, in different dosing regimens including both intravenous and subcutaneous guselkumab, is currently recruiting [83] (Table 3). Risankizumab is another IL-23 antagonist approved for psoriasis [84]. A phase II study studying risankizumab in moderate-to-severe hidradenitis suppurativa is planned but not yet recruiting [85].

4.3 Safety Concerns

In a recent study from PSOLAR, incidence rates of various adverse events were studied in patients with psoriasis treated with ustekinumab. The authors reported the following incidence rates: malignancy 0.68/100 patient-years (PY), major adverse cardiac events 0.33/100 PY, serious infection 1.60/100 PY, and mortality 0.46/100 PY [86]. In a meta-analysis of six randomized controlled trials assessing use of ustekinumab for plaque psoriasis, no statistically significant difference was seen in adverse effects when comparing those patients treated with placebo, ustekinumab 45 mg, and ustekinumab 90 mg, except in regard to infection. Patients treated with ustekinumab 45 mg had a higher rate of infection compared with placebo [87]. Other adverse events associated with ustekinumab use can be found in Table 1. As it is more targeted in its immunologic inhibition, it appears that ustekinumab may have fewer safety concerns than TNF inhibitors. However, further data is needed before formal conclusions can be made.

5 Biologics Targeting IL-17

IL-17 and IL-17A levels, as well as mRNA expression of IL-17, are elevated in HS skin compared with healthy control skin [2, 18, 75]. Serum IL-17 levels are also higher in patients with HS compared with healthy controls and, further, serum IL-17 levels correlate to HS severity [4].

5.1 Secukinumab

Secukinumab is an anti-IL-17A human monoclonal antibody that inhibits binding of IL-17A to its receptor [88]. Only case reports describing efficacy of secukinumab in HS are published in the literature [89–92]. Secukinumab in these reports is typically dosed according to the psoriasis dosing (300 mg subcutaneously weekly during weeks 0–4, then administered every 4 weeks) [89–91]. Three clinical trials studying use of secukinumab in HS are currently ongoing (Table 3). One is an investigator-initiated exploratory phase I clinical trial of secukinumab dosed at 300 mg weekly for the first 5 weeks followed by every 4 weeks over 24 weeks [93]. The results have not been formally published. However, they were reported at the European Academy of Dermatology and Venereology congress and are available online; the online report details that 14 of the 18 patients achieved HiSCR [94]. Two additional studies, SUNSHINE and SUNRISE, are looking at two different dosing regimens of secukinumab, 300 mg every 2 weeks and 300 mg every 4 weeks, compared with placebo over 16 weeks, with a long-term efficacy period up to 1 year [95, 96].

5.2 Other Agents Targeting IL-17

Studies assessing the efficacy of other IL-17 agents, such as bimekizumab and CJM112, have been completed but the results are not published (Table 3). Additionally, a clinical trial studying brodalumab is underway. A phase II clinical trial has been completed on the efficacy, safety, and pharmacokinetics of bimekizumab use in HS. This trial studied bimekizumab at two different dosing regimens and included an active comparator to adalimumab as well as comparison with placebo. The results have not been published yet [97]. Bimekizumab is a human monoclonal antibody that targets two isoforms of IL-17, IL-17A and Il-17F, and has been studied in psoriasis previously [98]. CJM112 is another anti-IL-17 biologic that has been studied in HS [40, 41]. A phase II, double-blind RCT to study the efficacy and safety of CJM112 is complete but the results are not yet publicly available [40, 41, 99]. Brodalumab is an antagonist against IL-17 receptor A [100]. A phase II clinical trial studying the use of brodalumab in HS is planned but not yet recruiting [101].

5.3 Safety Concerns

Increased risk of infections, as in other biologics, is of concern in IL-17 inhibitors such as secukinumab [88]. In a meta-analysis of seven phase III clinical trials on use of secukinumab, the most common adverse event reported was respiratory infections [102]. Of interest, IL-17 plays a role in protection against candida infections, and a small increased risk of candida infections in patients treated with IL-17 inhibitors has been observed in clinical trials [103]. Neutropenia and leukopenia are also observed in treatment with secukinumab, given the role of IL-17 in neutrophil trafficking [104]. Some concern exists that IL-17 inhibition via biologic therapy may increase the risk of IBD; however, this association has been difficult to elucidate [105]. This type of risk would potentially limit use of IL-17 antagonists in the HS population, as IBD is frequently comorbid in HS [106]. Additionally, reports have described cases of oral ulcers associated with IL-17 initiation such as ulcerative lichenoid mucositis [107], oral lichen planus [108], and oral lichenoid reaction [109]. Some authors suggest that increased risk of candidiasis infection with use of anti-IL-17 biologics may promote the development of oral lichen planus [108].

Interestingly, exacerbation of HS has been reported as an adverse event of anti-IL-17 therapy. Ixekizumab, an anti-IL17A monoclonal antibody, has been studied in psoriasis but not in HS. In a study of ixekizumab for chronic plaque psoriasis, exacerbation of HS was reported as three separate adverse events in one patient [110].

6 Biologics Targeting IL-1

In a study of HS skin, IL-1β levels were increased 54-fold compared with healthy control skin. Further, in this study treatment with adalimumab was shown to decrease the levels of IL-1β [2]. Bechara et al. also reported that IL-1 mRNA levels were elevated in lesional as compared with non-lesional skin [22]. Another study demonstrated that keratinocytes from the hair follicles of patients with HS secreted higher levels of IL-1β compared with healthy donors [111]. Recently, IL-1α was also reported to be elevated in lesional HS skin as compared with control skin [18].

6.1 Anakinra

Anakinra is an IL-1α receptor antagonist. Via competitive inhibition, anakinra binds to the IL-1 receptor, thereby preventing both IL-1α and IL-1β from binding [17, 112, 113]. Anakinra dosing starts at 1–2 mg/kg and can be up-titrated to 8 mg/kg [114].Two clinical trials utilized a dosing regimen of anakinra 100 mg subcutaneously daily in HS [17, 115]. Other authors have reported using up to 200 mg daily [112] (Table 1).

In an open-label clinical trial, treatment with anakinra for 8 weeks led to a significant improvement in Sartorius score, physician and patient global assessment, and DLQI in six patients, of whom five completed the study. These patients were subsequently followed for eight additional weeks after finishing treatment, during which time disease activity increased to levels similar to those seen prior to treatment [115]. In a later study, 20 patients (of whom 19 completed the study) were treated with anakinra in a double-blind RCT. A significantly greater improvement in disease activity score was seen in those patients treated with anakinra at the end of 12 weeks. In this study, patients treated with anakinra were also more likely to achieve HiSCR at week 12 but the change in HiSCR was not statistically significant at 24 weeks. Moreover, there was no significant difference in VAS score, DLQI, or Sartorius score between the placebo and treatment groups. Disease activity scores increased after stopping treatment; however, time until HS exacerbation was significantly longer in patients treated with anakinra [17]. Other literature describing use of anakinra in HS has been largely limited to case reports in both HS exclusively [112] and in PASH (pyoderma gangrenosum, acne and HS) syndrome [114]. Case reports have reported that efficacy may be seen as early as 1 month [112]. Alternatively, some case reports have reported a lack of efficacy and even worsening of HS with anakinra [50, 116].

6.2 Other Agents Targeting IL-1

Bermekimab (also known as MABp1) is another biologic with activity against IL-1α [117–119]. In a double-blind RCT of 20 patients with moderate-to-severe HS randomized to treatment with MABp1 versus placebo, 60% of subjects treated with MABp1 reached the primary endpoint (positive HiSCR) compared with 10% of subjects receiving placebo (odds ratio 13.5, 95% CI 1.19–152.51; $p=0.035$). MABp1 was dosed at 7.5 mg/kg every 14 days; patients were treated with up to a maximum of seven infusions [117] (Table 1). Additionally, a phase II clinical trial studying MABp1, dosed at 400 mg subcutaneously weekly in two cohorts (one cohort with prior anti-TNF exposure and the other consisting of TNF-naïve subjects) to assess its safety and efficacy in HS, is currently recruiting [120]. A clinical trial studying use of MEDI8968, a subcutaneous biologic that binds to IL-1R1, thereby inhibiting the activity of IL-1α and IL-1β,

Table 3 Biologics that are either being studied for hidradenitis suppurativa or have been studied but the results are not published

Biologic	Target	Status
Bimekizumab	IL-17A and IL-17F	A phase II study has been completed but the results are not available (NCT03248531) [97]
CJM112	IL-17	A phase II study has been completed but the results have not been published (NCT02421172) [99]
Secukinumab	IL-17	A phase I clinical trial is listed as currently recruiting on clinicaltrials.gov (NCT03099980) [93]
		Two phase III clinical trials are listed as currently recruiting (NCT03713632, NCT03713619) [95, 96]
Brodalumab	IL-17 receptor A	A phase II clinical trial is planned but not yet recruiting [135]
IFX-1	C5a	A phase II clinical trial has been completed but results have not been published in a peer reviewed journal [130, 131]
		A phase II clinical trial is currently active but not recruiting (NCT03487276) [129]
Guselkumab	IL-23	A phase II clinical trial is listed on clinicaltrials.gov is currently recruiting (NCT03628924) [83]
Risankizumab	IL-23	A phase II study in moderate-to-severe hidradenitis suppurativa is planned but not yet recruiting [133]
CFZ533	CD40	A phase II clinical trial is currently recruiting (NC03827798) [135]

HS hidradenitis suppurativa, *IL* interleukin

in HS was stopped prematurely as, compared with placebo, MEDI8968 was found to not be efficacious in reducing pain or HS severity at an interim analysis [41, 121].

6.3 Safety Concerns

Information regarding the long-term safety of IL-1 antagonists is less readily available compared to other biologics. The FDA labeling for anakinra states that the impact of the drug on rate of malignancy and infections is unknown [113]. In part, the limited safety data regarding anakinra may be secondary to its limited use by rheumatologists for RA as it is less effective than other biologics [122]. Common adverse reactions include injection site reactions, infections, and immunogenicity [122]. In a retrospective study of 475 patients treated with IL-1 inhibitors, anakinra (421 treatment courses) and canakinumab (105 treatment courses), four infections, four anaphylactic reactions, and one neoplasm were observed [123]. In a meta-analysis of ten studies on use of anakinra in rheumatoid arthritis, the pooled relative risk of infections in patients treated with anakinra was not statistically significant (1.06, 95% CI 0.94–1.20) [124]. Additional information on adverse events included on the FDA labeling of anakinra can be found in Table 1. Further investigation on the long-term safety of IL-1 antagonists is warranted.

7 Other Biologics

7.1 Efalizumab

Efalizumab, a biologic that inhibits lymphocyte function-associated antigen 1 (LFA-1), was studied in a small cohort of five patients, in which clinical benefit was not observed in any patients and two patients had worsening of their disease [125, 126]. After four cases of progressive multifocal leukoencephalopathy (PML) associated with efalizumab were reported, this drug was voluntary withdrawn from the market in 2009 [41, 43, 127] (Table 2).

7.2 IFX-1

Some authors hypothesize that complement may be involved in recruiting neutrophils to active sites of HS. C5a and components of the membrane attack complex (C5b-9) are elevated in plasma samples from patients with HS as compared with healthy controls. Levels of complement were low in pus sampled from HS patients. Interestingly, plasma complement concentration was higher in Hurley stage I patients compared with patients who were stages II and III, suggesting complement activation may be an early event in HS pathogenesis [128]. IFX-1 is a monoclonal antibody that binds C5a, a component of the complement cascade [128, 129]. One phase II clinical trial on IFX-1 has been completed [130]. The results have not been published in an academic journal. The company's website reports the results of a study completed in 12 patients who received nine doses of intravenous IFX-1. On day 134, 83% of patients had achieved HiSCR [131]. A phase II trial, studying four intravenous doses of IFX-1 compared with placebo, is currently ongoing but not recruiting [129] (Table 3).

7.3 CFZ533

CFZ533 is a monoclonal antibody with activity against CD40 [132]. CD40 is found on antigen presenting cells and B cells, among other cell types. The binding of CD40 to its ligand, CD40L, can activate multiple immune processes [132, 133]. Interestingly, patients with PASH have increased expression of CD40 and CD40 ligand (CD40L) in skin biopsies of pyoderma gangrenosum compared with controls. However, the authors did not specifically biopsy sites of HS. This observation led the authors to conclude that the CD40/CD40L system may contribute to the inflammation observed in PASH [134]. CFZ533 is currently being studied in a phase II platform clinical trial [135] (Table 3).

8 Laboratory Monitoring with Biologics

There are no specific guidelines dictating management of the HS patient on biologics. Prior to initiating a patient on a biologic, we perform screening labs for hepatitis B, hepatitis C, and tuberculosis infections. Tuberculosis screening should be repeated annually. Routine drug monitoring for the HS patient managed with a biologic includes a chemistry panel and complete blood count with differential and liver function tests obtained at baseline and repeated every 6 months.

9 Conclusion

Several biologics have been studied in HS, however, adalimumab remains the only FDA-approved treatment for management of moderate-to-severe HS. Other biologics suggest therapeutic promise, but implementation of these biologics is limited by the lack of well-designed, adequately powered clinical trials to study their efficacy. In order to expand upon the therapeutic options available to HS patients, further research using validated HS scoring systems is important. Further, longitudinal studies assessing efficacy and safety over time are also of paramount importance.

Compliance with Ethical Standards

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