Current Targeted Biologics in Hidradenitis Suppurativa

Subjects: Dermatology

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Hidradenitis Suppurativa (HS) is a debilitating cutaneous disease characterized by a vicious cycle of chronic inflammation and tissue destruction that stems from disruption of the skin microbiome and abnormal activation of both the innate and adaptive immune system.

Keywords: immune dysregulation ; biologics ; hidradenitis suppurativa ; adalimumab ; infliximab ; secukinumab

1. TNF-α Inhibitors

TNF-α is a proinflammatory cytokine secreted by both innate and adaptive immune cells as well as non-immune cells, including fibroblasts, neurons, smooth muscle cells, and keratinocytes [1]. TNF-α was first implicated in the treatment of Hidradenitis Suppurativa (HS) in the early 2000s based on several small case reports and series showing efficacy in treating HS with anti-TNF-α agents that were approved for other conditions, such as infliximab, etanercept, and adalimumab [2][3][4]. TNF-α agents have shown efficacy in reducing the amount and size of inflammatory HS lesions and have been proven especially beneficial when combined with surgical therapy [5]. In the past 20 years, numerous emerging trials further supported the clinical efficacy of TNF-α in the treatment of moderate-to-severe HS.

1.1. Adalimumab

Adalimumab, a fully humanized monoclonal antibody against soluble and transmembrane TNF-α, is the first FDA-approved biologic for the treatment of moderate-to-severe HS in adults and adolescents [6]. Adalimumab works by binding to soluble and transmembrane TNF-α and significantly reducing mammalian target of rapamycin (mTOR) activity in patients with HS [7]. Approval was based upon two phase III, double-blind, placebo-controlled studies (PIONEER I and PIONEER II), which enrolled a total of 633 patients [8]. In each study, a significantly higher proportion of patients in the adalimumab group than in the placebo group met a Hidradenitis Suppurativa Clinical Response (HiSCR), defined as at least a 50% reduction from baseline in the total abscess and inflammatory-nodule count, with no increase in the abscess or draining-fistula count, at week 12 (PIONEER I: 41.8% vs. 26.0%, $p = 0.003$; PIONEER II: 58.9% vs. 27.6%, $p < 0.001$). The proportions of patients who experienced adverse events, including infectious events, were generally similar between treatment groups in each period [8]. The long-term efficacy of adalimumab was tested in an open-label extension (OLE) of these trials that followed patients longitudinally for at least 96 weeks. Achievement of HiSCR was maintained through the end of the OLE in 52.3% of patients who received adalimumab weekly. Sustained improvement in lesion counts, skin pain, and Dermatology Quality of Life (DLQI) score were also observed, and the safety profile throughout the OLE was similar to that observed in the PIONEER studies [9]. Biologic therapies are recommended for patients who did not achieve satisfactory, sustained disease control with lifestyle and dietary modification, antibiotics, and hormonal agents such as metformin and antiandrogenic agents [10]. Adalimumab and secukinumab are the only FDA-approved biologics for HS, with more real-world data supporting adalimumab due to its longer availability on the market [11].

1.2. Infliximab

Infliximab is a chimeric monoclonal antibody that inhibits TNF-α by binding soluble and bound TNF-α, thus reducing circulating TNF-α levels to exert anti-inflammatory effects [12]. Infliximab was first proposed as an efficacious treatment for HS in a case report describing improvement in HS in a patient being treated with infliximab for Crohn's Disease [2]. Clinical trials evaluating infliximab have been conducted, but they involved far fewer patients than trials for adalimumab. In a single-center, randomized double-blind, placebo-controlled trial of 38 patients with moderate-to-severe HS, 4/15 (27%) of the infliximab patients vs. 1/18 (5%) of the placebo patients achieved the primary endpoint of a ≥50% decrease in the Hidradenitis Suppurativa Severity Index (HSSI) score. The infliximab group also showed reduced inflammatory markers at week 8 and significant improvements in mean Dermatology Life Quality Index (DLQI) compared with the placebo group [13]. However, "wearing off effects" occurred during the maintenance period 4 weeks after each infusion [13], suggesting higher doses and/or shorter interval infusions may be more efficacious. Ghias et al. evaluated the efficacy of infliximab 7.5

to 10 mg/kg with a maintenance frequency every 4 weeks in a prospective trial of 42 patients. They found that 47.6% of the patients receiving infliximab 7.5 mg/kg achieve clinical response at week 4 and 70.8% at week 12. A higher dosage of infliximab at 10 mg/kg had a similar but not superior response [14].

1.3. Etanercept

Etanercept is a recombinant human TNF inhibitor that acts as a soluble TNF receptor and binds TNF-α and TNF-β. In a phase II open-label trial of 15 patients receiving etanercept 50 mg weekly for 12 weeks, 29% of patients reported moderate improvement in their disease. However, results showed no clinically significant decrease in DLQI after treatment and no participants had complete remission at 12 weeks [15]. In another single-center, randomized, prospective, double-blind, placebo-controlled study, etanercept administered twice weekly for 12 weeks was evaluated in 20 patients with HS. Results showed no statistically significant difference among physician global assessment, patient global assessment, and DLQI at 12 or 24 weeks between treatment and placebo groups [16].

1.4. Golimumab

Golimumab is a human anti-TNFα monoclonal antibody that binds to soluble and membrane-bound TNF-α. However, strong evidence supporting the use of golimumab in HS is currently lacking. Smaller studies have reported varying degrees of success in using golimumab. Ramos et al. reported success in using golimumab in two patients with HS and arthritis after treatment failure with adalimumab [17]. In another retrospective cohort study evaluating golimumab use in thirteen patients with severe and recalcitrant HS previously failing adalimumab and infliximab, six out of nine patients who have available data for HiSCR calculation achieved this. Additionally, IHS4 significantly improved; however, most other clinical and laboratory assessments did not show significant improvement [18].

1.5. Certolizumab

Certolizumab pegol is a pegylated, Fab-only humanized antigen-binding fragment of a monoclonal antibody that binds to TNF-α that is only approved for plaque psoriasis in dermatology [19]. Though only a few cases have presented the role of certolizumab in HS, especially in the pregnant population due to the low risk of placental transfer [20][21], more evidence is emerging regarding its use in severe HS resistant to adalimumab and other biologic agents. Esme et al. conducted a retrospective cohort study involving the use of certolizumab dosed at 400 mg every 2 weeks in 11 severe, recalcitrant HS patients who have previously failed adalimumab. Out of 11 patients, 54.5% achieved HiSCR at week 12. There was a significant decrease in the DLQI and IHS4 scores of the patients at weeks 12 and 24 compared to baseline [22].

2. IL-17 Inhibitors

IL-17 is a pro-inflammatory cytokine that is released by both Th1 and Th17 cells, but it is associated primarily with the latter. It binds the IL-17 receptor, which is expressed on endothelial cells, fibroblasts, osteoblasts, keratinocytes, monocytes, and macrophages. IL-17 stimulates the release of several chemokines that mediate the recruitment of neutrophils, macrophages, and lymphocytes, further sustaining tissue inflammation through both the innate and adaptive immune systems [23]. Studies have found a Th17 cell-skewed cytokine profile in HS lesional skin, with elevated levels of Il-1, IL-23, and IL-17. Biopsy samples were found to be enriched with both Th17 cells and regulatory T cells; however, the ratio of the two cells was highly dysregulated and favored Th17 cells over regulatory T cells [24]. Furthermore, Matushiak et al. found that higher serum levels of IL-17 in HS patients corresponded with more advanced disease, while TNF-α did not show a correlation with severity [25]. Observations from these studies and others provide rationale to investigate IL-17 as a potential target in the development of new biologic therapies for HS treatment.

2.1. Secukinumab

Secukinumab is a human monoclonal antibody that inhibits IL-17A. Previous smaller studies have supported the use of secukimumab in HS but until recently larger trials have been lacking. Prussick and colleagues treated nine moderate-to-severe HS patients with secukinumab 300 mg administered subcutaneously weekly for 5 weeks, then every 4 weeks for 24 weeks. They found that 67% of participants achieved HiSCR without serious adverse events such as new-onset inflammatory bowel disease [26]. Casseres et al. conducted an open-label trial in 20 patients with moderate-to-severe HS (Hurley stages II and III) dosed with two secukinumab levels—after five weekly injections of 300 mg secukinumab subcutaneously, maintenance doses were administered every 2 weeks or 4 weeks. Amongst all the patients, 70% achieved HiSCR by week 24, including five out of six patients with prior TNF-α inhibitors exposure. The drug was also well tolerated with no serious adverse events noted [27]. In 2023, secukinumab was approved in Europe and US for the treatment of moderate-to-severe HS in adults with an inadequate response to conventional therapies. Approval was based

upon results from two large, multinational trials. In the two identical trials (SUNSHINE trial [*n* = 541] and SUNRISE trial [*n* = 543]), adults with moderate-to-severe HS were randomized to receive secukinumab 300 mg every two weeks (Q2W), secukinumab 300 mg every four weeks (Q4W), or a placebo. In the SUNSHINE trial, the 45% secukinumab Q2W group achieved HiSCR at 16 weeks, compared to 34% in the placebo group (p = 0.0070). The difference between the secukinumab Q4W group (42%) and placebo group was not statistically significant (42% and 34%, respectively, p = 0.042). In the SUNRISE trial, both the secukinumab Q2W (42%, p = 0.015) and Q4W (46%, p = 0.0022) groups had significantly higher rates of HiSCR achievement compared to placebo (31%). Disease responses were sustained through the end of the trials at week 52. Secukinumab was generally well tolerated across all groups, and the safety profile in the trials was consistent with that previously reported [28]. Due to convincing efficacy data from larger trials as well as the subcutaneous route of administration, secukinumab is now considered the most well-supported second line treatment after failing adalimumab.

2.2. Ixekizumab

Ixekizumab is a humanized IgG4 monoclonal antibody that binds to soluble IL-17A and IL17A/F. Though not FDA-approved for HS in dermatology, there have been few studies that demonstrated its potential efficacy in treating HS. Two case reports showed that ixekizumab can be used for patients with concomitant HS and psoriasis [29][30]. Most recently, Esme and colleagues reported a small case series of five Hurley stage III patients with refractory HS disease to conventional treatments and adalimumab. With a primary end point of HiSCR, four out of five patients achieved HiSCR. No adverse event was recorded [31].

2.3. Bimekizumab

Bimekizumab is a humanized monoclonal antibody that targets IL-17A and IL-17F. The efficacy of bimekizumab was evaluated against a placebo and adalimumab in a phase II, double-blind, placebo-controlled clinical trial with 90 patients with moderate-to-severe HS. At week 12, 57% of patients achieved HiSCR compared to 26% of placebo patients. Furthermore, 46% of bimekizumab patients achieved $HiSCR_{75}$ and 32% achieved $HiSCR_{90}$ at week 12, defined as at least 75% and 90% reductions in total abscess and inflammatory-nodule count, respectively, with no increase in the abscess or draining-fistula count from baseline. A total of 10% of placebo-treated patients achieved $HiSCR_{75}$ and none achieved $HiSCR_{90}$; in adalimumab-treated patients, 35% achieved $HiSCR_{75}$ and 15% achieved $HiSCR_{90}$. The rates of adverse events were similar between the bimekizumab, placebo, and adalimumab groups [32]. Bimekizumab is currently being evaluated for HS in three phase III clinical trials (NCT04242446, NCT04242498, NCT04901195) [33].

2.4. Brodalumab

Brodalumab is a human monoclonal antibody that binds to the IL-17 receptor and interferes with signaling of various isoforms of IL-17. Several case reports have demonstrated HS improvement in patients using brodalumab to manage comorbid psoriasis, demonstrating concurrent improvement in both diseases [34][35]. An open-label study evaluated brodalumab every 2 weeks in a cohort of 10 patients with moderate-to-severe HS. All patients achieved HiSCR at week 12, with some achievement occurring as early as week 2 [36]. A subsequent open-label cohort study evaluated brodalumab weekly in 10 patients with moderate-to-severe HS, some of whom participated in the Q2W study. A 100% HiSCR response was observed at week 4 with weekly dosing, and in contrast to dosing every 2 weeks, no cyclical disease suppression or recurrence was observed over 24 weeks [37]. The status of further clinical trial evaluation of brodalumab is currently unclear.

2.5. CMJ112

CMJ112 is a human monoclonal IgG1/κ antibody that targets IL-17A. A phase II, exploratory, randomized, double-blind, placebo-controlled study was performed to evaluate CMJ112 in 66 patients with moderate-to-severe HS. The primary efficacy endpoint was measured by the HS-Physician Global Assessment (HS-PGA) responder rate, defined as a ≥2-point reduction in HS-PGA score. The HS-PGA score classifies patients into six categories of severity, with one point meaning clear of disease and six indicating very severe disease (>5 abscesses + draining fistulas) [38]. At 16 weeks, the proportion of HS-PGA responders was significantly higher than placebo (32.3% vs. 12.5%, p = 0.03) [39].

3. IL-23 Inhibitors

Like IL-17, IL-23 is another pro-inflammatory cytokine associated with the Th17 cell lineage. IL-23 promotes survival and proliferation of Th17 cells and stimulates release of other cytokines like IL-17 and TNF-α. IL-23 is structurally similar to IL-12, sharing a p40 protein chain, but IL-23 differs from IL-12 in its ability to induce the production of IL-17 and the

differentiation of Th17 cells [40]. The IL-23/Th17 axis has been shown to be important in the pathogenesis of various autoinflammatory diseases like psoriasis and inflammatory bowel disease, leading to exploration of IL-23 blockade as a potential treatment option in HS.

3.1. Ustekinumab

Ustekinumab is a monoclonal antibody that binds to the p40 subunit common to both IL-12 and IL-23. Several case series and studies supported the efficacy of ustekinumab for HS [41][42]. One prospective, year-long, open-label study investigated the efficacy of ustekinumab 45 mg or 90 mg (the psoriasis dosing regimen; patients > 100 kg received 90 mg) in 17 patients with moderate-to-severe HS. The primary endpoint was measured by a ≥50% reduction in the modified Sartorius scale (mSS) score at week 40. A total of 35% of patients experienced a ≥50% reduction in mSS, while $HiSCR_{50}$ was achieved in 47% of patients [43].

Several case series particularly supported the use of high-dose, high-frequency ustekinumab for the treatment of HS based on evidence for the improvement of Crohn's disease treatment with escalated doses. One case series demonstrated improvement in patients receiving maintenance 90 mg ustekinumab every 8 to 12 weeks [44]. Another study from the HS clinic at researchers' own institution demonstrated improvement with ustekinumab at maintenance doses of 90 mg every 4 weeks [45].

3.2. Guselkumab

Guselkumab is a monoclonal antibody specifically directed against IL-23. Several case reports and series have reported success in using guselkumab in HS [46][47][48]. Prospective studies have been conducted to evaluate guselkumab for HS with less encouraging results. In a phase II, open-label study, 20 patients with moderate-to-severe HS were given guselkumab 200 mg subcutaneously every 4 weeks for 16 weeks. A total of 65% of patients achieved HiSCR with statistically significant decreases in median abscess and inflammatory nodule count and median International Hidradenitis Suppurativa Severity Score System (IHS4). However, overall patient-reported outcomes did not show a similar trend [49]. A larger phase II, randomized, double-blind, placebo-controlled study investigated guselkumab in 184 adults with moderate-to-severe HS for 36 weeks. Patients were randomized to receive guselkumab 200 mg subcutaneous (SQ) every 4 weeks, guselkumab 1200 mg intravenous every 4 weeks for 12 weeks then 200 mg subcutaneous every 4 weeks from weeks 16–36, or a placebo. While both the guselkumab SQ and guselkumab IV groups achieved numerically higher HiSCR results at week 16 compared to the placebo (50.8%, 45.0%, 38.7%, respectively), the results were not statistically significant [50].

3.3. Risankizumab

Risankizumab is a fully humanized IgG1κ monoclonal antibody targeting IL-23 that has shown excellent efficacy for the treatment of psoriasis in its phase III trial data as well as many comparison trials versus adalimumab, ustekinumab, and secukinumab [51]. However, data supporting risankizumab as a treatment for HS are more limited. Repetto et al. presented a case series of six patients with HS treated with risankizumab, with three patients reaching HiSCR at month 3 and all patients reaching HiSCR at month 6 [52]. A phase II, double-blind, placebo-controlled trial was performed with 243 patients who were randomized to receive risankizumab SC 180 mg, risankizumab SC 360 mg, or a placebo at weeks 0, 1, 2, 4, and 12. HiSCR was achieved by 46.8% of patients with risankizumab 180 mg, 43.4% with risankizumab 360 mg, and 41.5% with the placebo at week 16. The study was terminated early due to poor efficacy results [53].

4. IL-1 Inhibitors

The IL-1 family is composed of several cytokines. In particular, IL-1α, IL-1β, and IL-36 are proinflammatory cytokines that have been investigated for the treatment of HS. The IL-1 family is considered a key cytokine in the innate immune system that activates the adaptive immune system, serving as an important link between the two [54]. IL-1β has been noted to be particularly high in HS lesional skin, surpassing levels seen in lesional psoriatic skin. IL-1α was noted to be only minimally increased in HS lesions compared to healthy and psoriatic skin [55].

4.1. Anakinra

Anakinra is a recombinant human IL-1 receptor antagonist that blocks both IL-1α and IL-1β and is FDA-approved for rheumatoid arthritis and neonatal-onset multisystem inflammatory disease. Data supporting the use of anakinra in HS have been mixed. Case reports have been published documenting both success and failure of anakinra in the treatment of severe HS [56][57]. Only one small trial evaluating anakinra for the treatment of HS has been published. The study was a double-blind, randomized, placebo-controlled trial with 20 patients with Hurley stage II or III HS. The treatment phase

spanned 12 weeks with an additional 12-week observational period after cessation of treatment. A total of 78% of patients in the anakinra arm achieved HiSCR after 12 weeks compared to 30% in the placebo arm (p = 0.04). Results were not sustained after cessation of treatment after week 12, with 33% of placebo patients achieving HiSCR at week 24 compared to only 10% of anakinra patients [58]. Similar results were observed in a small case series of six patients treated with the same protocol [59].

4.2. Bermekimab

Bermekimab is a fully human recombinant monoclonal antibody that inhibits IL-1α. A randomized trial of 20 HS patients not eligible for adalimumab assessed bermekimab (then named MABp1) treatment for 12 weeks. A total of 60% of patients receiving bermekimab achieved HiSCR at week 12 compared to 10% of patients receiving a placebo (p = 0.035). After 12 weeks of observation following the last dose, 40% of patients treated with bermekimab achieved HiSCR compared to none of the patients treated with the placebo [60]. A subsequent open-label extension study was conducted with eight of the patients who received a placebo in the blinded study. After 12 weeks of bermekimab treatment, HiSCR was achieved by six of the eight patients (75%) [61]. Another phase II, open-label study stratified patients into two groups based on whether they had previously failed an anti-TNF therapy or whether they were anti-TNF naïve (n = 24 and n = 18, respectively). Each group received 400 mg bermekimab SC weekly. A total of 63% of patients who had previously failed an anti-TNF therapy and 61% of patients who were anti-TNF naïve achieved HiSCR after 12 weeks [62].

A phase II, placebo and active comparator-controlled, double-blind, dose-ranging study investigating bermekimab with 151 patients with moderate-to-severe HS was initiated. However, it was prematurely terminated due to meeting futility criteria related to the primary endpoint (NCT04988308) [33].

5. IL-36 Inhibitors

The IL-36 family is a critical regulator of the innate immune system and is constitutively expressed in epithelial and immune cells. It is composed of three proinflammatory agonists—IL-36α, IL-36β, and IL-36γ—and three antagonists—IL-36Ra, IL-37, and IL-38 [63]. Hessam et al. showed that the proinflammatory members and IL-36RA were upregulated in HS lesions compared to healthy skin. IL-37 and IL-38 were significantly upregulated in perilesional HS skin compared to healthy skin but decreased in lesional skin [64]. Thomi et al. confirmed that all three IL-36 isomers were upregulated in HS lesional skin but IL-36RA was not significantly expressed [65].

No published clinical trial data are available for any anti-IL-36 agents; however, two phase II trials are ongoing for anti-IL-36 receptor monoclonal antibodies spesolimab (NCT04762277) and imsidolimab (NCT04856930) in the treatment of HS [33].

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