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Review

Immune Dysregulation and Current Targeted Biologics in Hidradenitis Suppurativa

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Abstract: 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. A hallmark of HS pathophysiology is dysregulation of both the innate and adaptive immune system. The role of immune system dysregulation in HS development has motivated researchers to explore the utility of biologic immunomodulators. In 2015, adalimumab, a tumor necrosis factor-α inhibitor, was approved by the Food and Drug Administration (FDA) for treatment of moderate-to-severe HS in the US. In 2023, secukinumab, an interleukin-17A (IL-17A) inhibitor, was approved by the European Medicines Agency for treatment of moderate-to-severe HS in Europe. Ongoing clinical trials have shown promising clinical responses to targeted therapies against other pro-inflammatory cytokines including IL-17, IL-12, IL-1, IL-36, IL-6, IL-10, interferon γ, C5a, and Janus kinase (JAK). We provide an update on the efficacy and clinical usage of targeted biologics in HS treatment.

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

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1. Introduction

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 systems [1,2]. The prevalence of HS in the US is estimated to be around 0.1%; however, this is likely an underestimation due to delays in HS diagnosis [3]. HS typically presents during young to middle adulthood and disproportionately affects women, African Americans, and biracial individuals [1,3]. In its early stage, HS manifests as painful nodules and abscesses in intertriginous areas including the axillae, groin folds, gluteal cleft, and inframammary folds [4,5]. As the disease advances, these lesions progress to form sinus tracts and fistulas which heal as fibrotic scars [6]. Patients experience significant reduction in their quality of life due to the pruritus, purulent drainage, disfigurement, and movement restriction associated with these lesions [7,8]. Studies show that HS patients have an increased risk of developing chronic pain, depression, and suicidal ideation [9,10].

The etiology of HS is influenced by multiple factors including genetic predisposition, hormone imbalance, and patient comorbidities [11–13]. Approximately 30% of patients report family history of HS [14]. The most common mutations seen are γ-secretase mutations which impair Notch signaling. Impaired Notch signaling results in keratinocyte proliferation, increased pro-inflammatory cytokine release, and dysregulation of the complement system [15]. Current medical treatments target the pro-inflammatory cytokines and pathogens that perpetuate this cycle. Anti-androgen therapies, such as spironolactone and finasteride, are also often utilized [16,17]. Studies have shown that obesity, diabetes,

metabolic syndrome, and nicotine use all confer increased risk of developing HS [5,18,19]. Several autoimmune and endocrine disorders have been found to be associated with HS, including inflammatory bowel disease, psoriasis, arthritis, and polycystic ovary syndrome [20–23]. Additionally, viral infections such as human immunodeficiency virus (HIV) predispose patients to develop HS with the involvement of atypical sites, such as face or thighs [24]. However, no clear association was found between HS and COVID-19 infection [25].

Topical and systemic antibiotics remain first line treatments for HS. The most used antibiotics possess both anti-inflammatory and antibacterial properties such as tetracyclines, clindamycin, rifampin, and dapsone [26]. For mild to moderate HS, topical clindamycin is used first line due to its ability to inhibit biofilm formation and resorcinol is used second line due to its keratolytic and antiseptic properties [27,28]. Bleach baths and topical antiseptics are used concurrently to further decrease overall bacterial burden [29]. In more advanced HS, systemic clindamycin, rifampicin and tetracyclines are used for their anti-biofilm and anti-inflammatory properties [13,26]. A six-week IV infusion of ertapenem can be used for severe HS that has been unresponsive to oral antibiotics [6]. Intralesional Kenalog injections may also be administered to alleviate pain and inflammation and reduce the size of active lesions [30]. Other treatments that have been utilized include photodynamic therapy, laser hair removal, botulinum toxin, and retinoids [31–34]. Despite the wide variety of available therapies, they have variable efficacy in inducing disease remission. As a result, many patients still frequently undergo HS exacerbations and recurrences over the course of their lifetime [35,36]. Treatment of HS requires a multimodal approach that involves modification of patient lifestyle and diet, as well as adherence to multiple medical treatments and undergoing surgical procedures, placing a large burden on patients and their families.

The management of HS lesions also includes surgical excision [37,38]. Depending on HS severity, a deroofing procedure, skin-tissue sparing excision or wide radical excision may be performed [39–41]. Surgeons utilize ultrasound to determine the extent and advancement of lesions within the dermis. For Hurley stage I and II patients, deroofing procedures are the preferred treatment [39]. Hurley stage II and III patients can also undergo skin-tissue sparing excision with electrosurgical peeling [40]. Hurley stage III patients sometimes undergo wide radical excision that includes removal of sinus tracts, nodules, and scar tissue with a 1–2 cm margin [41,42]. Unfortunately, this procedure carries increased risk of pain, wound dehiscence, infection, hematoma, graft necrosis, decreased joint mobility and hypertrophic scarring [43]. Therefore, further investigation on the underlying immune dysregulation and the role of immunomodulatory therapies in the treatment of HS is urgently needed.

2. Pathogenesis

The pathogenesis of HS has been heavily studied; however, much remains to be elucidated. The higher temperature, moisture level, and concentration of pilosebaceous-apocrine units within intertriginous areas increase susceptibility to microbial proliferation [44]. Early HS lesions demonstrate increased levels of skin commensal bacteria while advanced HS lesions are characterized by decreased skin commensals and increased pathogenic bacteria [45,46]. Within sinus tracts and fistulas, keratin debris and hair fragments facilitate the formation of biofilms by gram-negative anaerobes [47]. Biofilms play a significant role in antimicrobial resistance and are one reason HS lesions are so difficult to eradicate [47–49].

A hallmark of HS pathogenesis is dysregulation of both the innate and adaptive immune systems [50]. Friction and microscopic epidermal injury stimulate the innate immune response and facilitate pathogen invasion into the dermis and hair follicles of intertriginous areas, which initiates the formation of HS lesions [51]. Activation of the innate immune system stimulates hyperplasia of the follicular epithelium, which culminates in hair follicle rupture [5]. Recruitment of immune cells to the site of injury then initiates the formation of inflammatory nodules and abscesses [52]. Activation of toll-like receptors by pathogen-

and damage-associated molecular patterns prompts the release of pro-inflammatory cytokines (tumor necrosis factor-α/TNFα, interferon-α/IFNα, interleukin-1β/IL-1β, IL-6, IL-8) that activate dendritic cells [44]. Dendritic cells secrete IL-23 and IL-12, which trigger the adaptive immune response. IL-23 plays a key role in Th17 cell activation, facilitates keratinocyte proliferation, and stimulates release of IL-17, IL-22, IL-1β, and TNFα [53]. Th1 and Th17 cells release IL-17, IL-23, and TNFα, thus creating a positive feedback loop that perpetuates the cycle of chronic inflammation. Matushiak et al. found that higher serum levels of IL-17 in HS patients corresponded with more advanced disease [54]. IL-17 binds its receptor IL-17RA, which activates NF-kB, leading to increased pro-inflammatory gene expression. IL-17 also stimulates the release of chemokines chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL8, and CC motif chemokine ligand 20 (CCL20), which further attract neutrophils, macrophages, and lymphocytes to HS lesional areas [55].

Antimicrobial peptides (AMPs) produced by epithelial and immune cells constitute an important component of the skin's innate immune system due to their bactericidal activity [56]. Dysregulation of AMPs and the complement system contributes to the chronic inflammation and microbial dysbiosis seen in HS. Normally AMPs prevent overgrowth of commensal bacteria, inhibit pathogen invasion, and facilitate cutaneous wound healing [57]. AMPs that are dysregulated in HS include cathelicidin, defensins, dermcidin, S100 proteins, and RNase 7 [56,57]. Cathelicidin encodes the precursor protein to LL-37, which was found to be upregulated in HS patients [58]. LL-37 modulates leukocyte chemotaxis and facilitates T cell maturation [59]. These immune cells then release pro-inflammatory cytokines such as TNFα and IL-17, thus contributing to HS severity. Defensins stimulate keratinocyte proliferation and attract immune cells, which results in hair follicle plugging and prolongs inflammation [60]. Dermcidin-derived peptides further promote inflammation via production of TNFα, IL-8, CXCL10, and CCL20 [61]. S100 proteins are increased in HS lesional skin, where they facilitate leukocyte chemotaxis [62]. Finally, RNAse 7 promotes production of TNFα and IFNα, which perpetuate the inflammatory cycle [63,64].

Abnormal activation of the complement system also plays a role in the immune system dysregulation seen in HS [65,66]. Rupture of hair follicles releases microbes and keratin, which initiate the production of complement proteins. C3a and C5a stimulate production of TNFα and IL-1β, which further promote pro-inflammatory cytokine release and immune cell activation [65].

3. Current Biologics

The central role of immune system dysregulation in HS development has motivated researchers to explore the utility of biologic immunomodulators. Similar to many inflammatory dermatoses, the treatment of HS historically relied on nonspecific anti-inflammatory and immunosuppressive therapies for maintenance treatment, including NSAIDS, topical and oral corticosteroids, and anti-metabolites like methotrexate. Biologics offer a more targeted approach to immunotherapy, offering an enhanced efficacy and safety profile compared to nonspecific immunosuppressives and an alternative to maintenance antibiotic therapy, especially in refractory Hurley Stage II and III disease. Current biologics being researched for HS treatment will be reviewed here to guide clinical treatment (Table 1). Only agents with published case studies and clinical trials available on PubMed will be included in this discussion. Molecular targets of therapies are illustrated in Figure 1.

Table 1. Summary of biologic therapies in HS.

Drug	Study	Study Details	Study Results
		TNF-α inhibitors	
Adalimumab	Kimball et al., 2016 [67]	PIONEER I (n = 307) Adalimumab 40 mg weekly SC (n = 153) Placebo (n = 154) PIONEER II (n = 326) Adalimumab 40 mg weekly SC (n = 163) Placebo (n = 163)	41.8% achieved HiSCR at week 12 26.0% achieved HiSCR at week 12 58.9% achieved HiSCR at week 12 27.6% achieved HiSCR at week 12
	Zouboulis et al., 2019 [68]	Open-label extension (OLE) (n = 151) Adalimumab 40 mg weekly	52.3% met HiSCR at week 168
Infliximab	Grant et al., 2010 [69]	Phase II RCT (n = 38) Infliximab 5 mg/kg IV at weeks 0, 2, 4, 6, 14, and 22 (n = 15) Placebo (n = 18)	27% met ≥50% reduction in HSSI 5% met ≥50% reduction in HSSI
	Ghias et al., 2020 [70]	Prospective open-label study (n = 42) Infliximab 7.5 mg/kg every 4 weeks Infliximab 10 mg/kg every 4 weeks	47.6% achieved clinical response at week 4 and 70.8% at week 12 37.5% achieved clinical response at week 4 and 50% at week 12
Etanercept	Lee et al., 2009 [71]	Phase II open-label trial (n = 15) Etanercept 50 mg weekly	29% reported moderate improvement at 12 weeks
	Adams et al., 2010 [72]	Randomized, double-blind trial (n = 20) Etanercept 50 mg twice weekly (n = 10) Placebo (n = 10)	No significant difference in PGA, patient global assessment, or DLQI between etanercept and placebo groups at 12 or 24 weeks
Golimumab	Ramos et al., 2022 [73]	Case report (n = 2)	Successful response to golimumab
	Melendez-Gonzalez et al., 2021 [74]	Retrospective cohort study (n = 13) Golimumab 2 mg/kg or 200 mg every 4 weeks	6/9 patients with available data for HiSCR calculation achieved HiSCR. IHS4 significantly improved, but other assessments did not show significant improvement
Certolizumab	Esme et al., 2022 [75]	Retrospective cohort study (n = 11) Certilizumab 400 mg every 2 weeks	54.5% achieved HiSCR at week 12 with significant decreases in DLQI and IHS4 at weeks 12 and 24
		IL-17 inhibitors	
Secukinumab	Prussick et al., 2019 [76]	Open-label trial (n = 9) Secukinumab 300 mg weekly for 5 weeks then every 4 weeks	67% achieved HiSCR at 24 weeks
	Casseres et al., 2020 [77]	Open-label trial (n = 20) Secukinumab 300 mg weekly for 5 weeks then every 2 weeks (n = 11) or every 4 weeks (n = 9)	70% achieved HiSCR by week 24, including 5/6 patients with prior exposure to TNF-α inhibitors
	Kimball et al., 2023 [78]	SUNSHINE trial (n = 541) Secukinumab 300 mg every 2 weeks (n = 141) Secukinumab every 4 weeks (n = 180) Placebo (n = 180) SUNRISE trial (n = 543) Secukinumab 300 mg every 2 weeks (n = 180) Secukinumab every 4 weeks (n = 180)	45% met HiSCR at 16 weeks 42% met HiSCR at 16 weeks 34% met HiSCR at 16 weeks Secukinumab every 4 weeks vs. placebo not statistically significant. Responses were sustained through week 52 42% met HiSCR at 16 weeks 46% met HiSCR at 16 weeks

Table 1. *Cont.*

Drug	Study	Study Details	Study Results
Secukinumab	Kimball et al., 2023 [78]	Placebo (n = 183)	31% met HiSCR at 16 weeks Both comparator group results were significantly higher than placebo. Responses were sustained through week 52.
Ixekizumab	Odorici et al., 2020 [79,80] Megna et al., 2020 [79,80]	Case reports (n = 2)	Successful response to ixekizumab
	Esme et al., 2022 [81].	Case series (n = 5) Ixekizumab 160 mg once, then 80 mg every two weeks through week 12	4/5 patients achieved HiSCR
Bimekizumab	Glatt et al., 2021 [82]	Phase II RCT (n = 90) Bimekizumab 640 mg at week 0 then 320 mg every 2 weeks (n = 46) Placebo (n = 21) Adalimumab 160 mg at week 0, 80 mg at week 2, then 40 mg every week (n = 21)	57% achieved HiSCR at week 12 26% achieved HiSCR at week 12 60% achieved HiSCR at week 12
	NCT04242446, NCT04242498, NCT04901195 [83]	Phase III RCTs	Ongoing
Brodalumab	Yoshida et al., 2021 [84,85] Vagnozzi et al., 2023 [84,85]	Case reports (n = 2)	Successful response to brodalumab
	Frew et al., 2020 [86]	Open-label cohort study (n = 10) Brodalumab 210 mg at weeks 0, 1, and 2, then 210 mg every 2 weeks	100% achieved HiSCR at week 12
	Frew et al., 2021 [86,87]	Open-label cohort study (n = 10) Brodalumab 210 mg weekly	100% achieved HiSCR at week 4
CMJ112	Kimball et al., 2022 [88].	Phase II RCT CMJ112 300 mg weekly for first five doses, then every 2 weeks until week 16 (n = 33) Placebo (n = 33)	32.3% HS-PGA responders at week 16 12.5% HS-PGA responders at week 16
Izokibep	NCT05905783 [83]	Phase III RCT	Ongoing
Sonelokimab	NCT05322473 [83]	Phase II RCT	Ongoing
		IL-23 inhibitors	
Ustekinumab	Hollywood et al., 2022 [89,90] Valenzuela-Ubiña et al., 2022 [89,90].	Retrospective cohort study (n = 16) and case series (n = 10)	Successful response to ustekinumab
	Blok et al., 2016 [91]	Open-label cohort study (n = 17) Ustekinumab 45 mg or 90 mg (psoriasis dosing regimen; patients >100 kg received 90 mg)	35% experienced $\geq$ 50% reduction in mSS and 47% achieved HiSCR at week 40.
	Scholl et al., 2019 [92] Jiang et al., 2022 [93]	Case series Ustekinumab 90 mg every 8 to 12 weeks Ustekinumab 90 mg every 4 weeks	Successful response to high-dose ustekinumab
Guselkumab	Kearney et al., 2020 [94–96] Berman et al., 2021 [94–96] Casseres et al., 2019 [94–96]	Case reports (n = 2) and retrospective cohort study (n = 8)	Successful response to guselkumab

Table 1. *Cont.*

Drug	Study	Study Details	Study Results
Guselkumab	Dudink et al., 2023 [97]	Phase II open-label study (n = 20) Guselkumab 200 mg every 4 weeks	65% achieved HiSCR at 16 weeks
	Kimball et al., 2023 [98]	Phase II RCT (n = 184) Guselkumab 200 mg SC every 4 weeks (n = 59)	50.8% achieved HiSCR at week 16
		Guselkumab 1200 mg IV every 4 weeks for 12 weeks then 200 mg SC every 4 weeks (n = 60)	45.0% achieved HiSCR at week 16
		Placebo (n = 62)	38.7% achieved HiSCR at week 16 Results of treatment groups to placebo were not statistically significant.
Risankizumab	Repetto et al., 2022 [99]	Case series (n = 6) Risankizumab 150 mg at week 0 and 4, then every 12 weeks thereafter (psoriasis dosing)	3/6 achieved HiSCR at month 3, and all achieved HiSCR at month 6
	Kimball et al., 2023 [100]	Phase II RCT (n = 243) Risankizumab 180 mg at weeks 0, 1, 2, 4, and 12 (n = 80)	46.8% achieved HiSCR at week 16
		Risankizumab 360 mg at weeks 0, 1, 2, 4, and 12 (n = 81)	43.4% achieved HiSCR at week 16
		Placebo (n = 82)	41.5% achieved HiSCR at week 16 The study was prematurely terminated due to poor efficacy results.
		IL-1 inhibitors	
Anakinra	Zarchi et al., 2013 [101,102]	Case report (n = 1)	Successful response to anakinra
	Russo and Alikhan, 2016 [101,102]	Case report (n = 1)	Unsuccessful response to anakinra
	Tzanetakou et al., 2016 [103]	Phase II RCT (n = 20) Anakinra 100 mg daily (n = 10)	78% achieved HiSCR at 12 weeks
		Placebo (n = 10)	30% achieved HiSCR at 12 weeks
	Leslie et al., 2014 [104]	Case series (n = 6) Anakinra 100 mg daily	Successful response to anakinra
Bermekimab (MABp1)	Kanni et al., 2018 [105]	Phase II RCT (n = 20) Bermekimab 7.5 mg/kg IV every 2 weeks (n = 10)	60% achieved HiSCR at week 12
		Placebo (n = 10)	10% achieved HiSCR at week 12
	Kanni et al., 2021 [106]	Phase II OLE (n = 8)	75% achieved HiSCR at week 12
	Gottlieb et al., 2020 [107]	Phase II open-label study (n = 42) Bermekimab 400 mg weekly (n = 24) (participants who previously failed anti-TNF therapy)	63% achieved HiSCR at 12 weeks
		Bermekimab 400 mg weekly (n = 18) (anti-TNF naïve participants)	61% achieved HiSCR at 12 weeks
	NCT04988308 [83]	Phase II RCT (n = 151)	Prematurely terminated due to meeting futility criteria
Lutikizumab	NCT05139602 [83]	Phase II RCT	Ongoing
		IL-36 inhibitors	
Spesolimab	NCT04762277 [83]	Phase II RCT	Ongoing
Imsidolimab	NCT04856930 [83]	Phase II RCT	Ongoing

Table 1. *Cont.*

Drug	Study	Study Details	Study Results
		CXCR1/2 inhibitors	
Eltrekibart	NCT06046729 [83]	Phase II RCT	Ongoing
		TNF-OX40L inhibitors	
SAR442970	NCT05849922 [83]	Phase II RCT	Ongoing
		JAK inhibitors	
INCB054707 (povorcitinib)	Alavi et al., 2022 [108]	Study 1: open-label RCT (n = 10) INCB054707 15 mg once daily Study 2: phase II RCT INCB054707 30 mg once daily (n = 9) INCB054707 60 mg once daily (n = 9) INCB054707 90 mg once daily (n = 8) Placebo (n = 9)	43% achieved HiSCR at week 8 56% achieved HiSCR at week 8 56% achieved HiSCR at week 8 88% achieved HiSCR at week 8 57% achieved HiSCR at week 8
Upadacitinib	Kozera et al., 2022 [109]	Retrospective cohort study (n = 20) Upadacitinib 15 mg daily for 4 weeks. Dose increased to 30 mg daily if clinical response was not sufficient after 4 weeks	75% achieved HiSCR at week 4 and 100% achieved HiSCR at week 12
	NCT04430855 [83]	Phase II RCT	Results not yet published
	NCT05889182 [83]	Phase III RCT	Ongoing

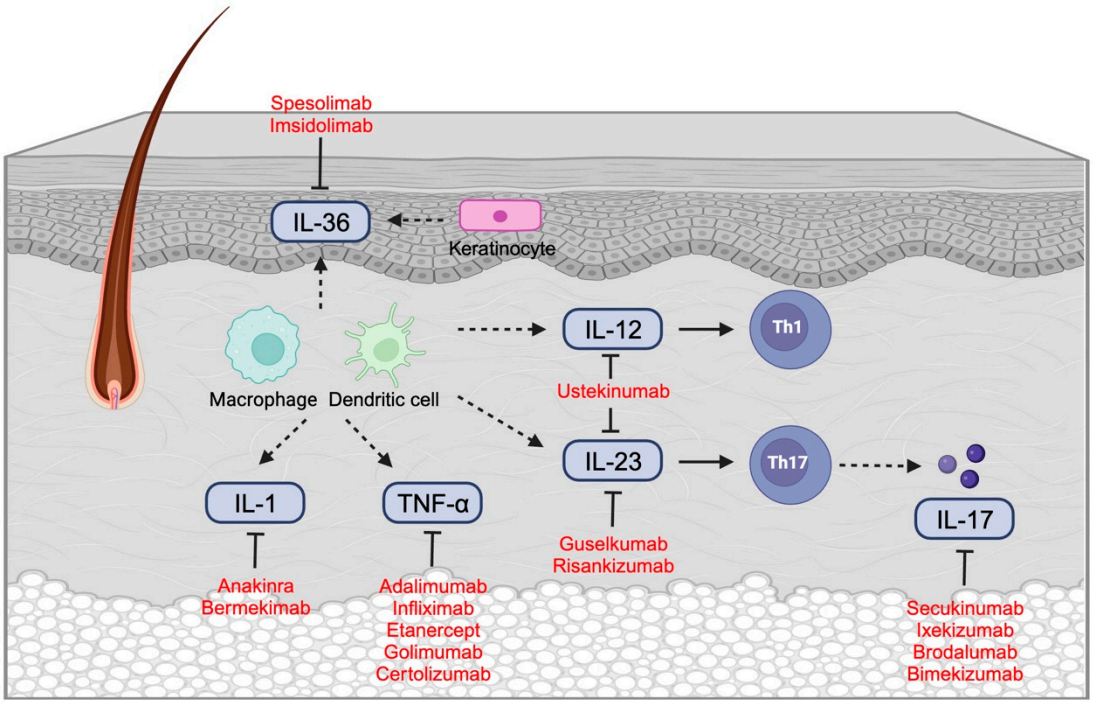

Figure 1. Molecular targets and current biologics. IL-36: Interleukin 36; IL-1: Interleukin 1; IL-23: Interleukin 23; IL-12: Interleukin 12; IL-17: Interleukin 17; TNFα: Tumor Necrosis Factor α. (Created by BioRender.com on 2 January 2024).

4. 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 [110]. TNF-α was first implicated in the treatment of 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 [111–113]. 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 [114]. In the past 20 years, numerous emerging trials further supported the clinical efficacy of TNF-α in the treatment of moderate-to-severe HS.

4.1. 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 [115]. Adalimumab works by binding to soluble and transmembrane TNF-α and significantly reducing mammalian target of rapamycin (mTOR) activity in patients with HS [116]. Approval was based upon two phase III, double-blind, placebo-controlled studies (PIONEER I and PIONEER II), which enrolled a total of 633 patients [67]. 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 [67]. 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 [68]. 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 [117]. 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 [118].

4.2. 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 [119]. 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 [111]. 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 $\geq$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 [69]. However, "wearing off effects" occurred during the maintenance period 4 weeks after each infusion [69], 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 [70].

4.3. 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 [71]. 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 [72].

4.4. 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 [73]. 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 [74].

4.5. 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 [120]. 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 [121,122], 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 [75].

5. 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 [123]. 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 [124]. 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 [54]. 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.

5.1. 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 [76]. 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 [77]. 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 [78]. 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.

5.2. 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 [79,80]. 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 [81].

5.3. 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 [82]. Bimekizumab is currently being evaluated for HS in three phase III clinical trials (NCT04242446, NCT04242498, NCT04901195) [83].

5.4. 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 [84,85]. 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 [86]. 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 [87]. The status of further clinical trial evaluation of brodalumab is currently unclear.

5.5. 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) [125]. At 16 weeks, the proportion of HS-PGA responders was significantly higher than placebo (32.3% vs. 12.5%, $p = 0.03$) [88].

6. 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 [126]. 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.

6.1. 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 [89,90]. 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 [91].

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 [92]. Another study from the HS clinic at our own institution demonstrated improvement with ustekinumab at maintenance doses of 90 mg every 4 weeks [93].

6.2. Guselkumab

Guselkumab is a monoclonal antibody specifically directed against IL-23. Several case reports and series have reported success in using guselkumab in HS [94–96]. 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 [97]. 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 [98].

6.3. 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 [127]. 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 [99]. 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 [100].

7. 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 [128]. 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 [129].

7.1. 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 [101,102]. 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 [103]. Similar results were observed in a small case series of six patients treated with the same protocol [104].

7.2. 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 [105]. 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%) [106]. 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 [107].

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) [83].

8. 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 [130]. 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 [131]. Thomi et al. confirmed that all three IL-36 isomers were upregulated in HS lesional skin but IL-36RA was not significantly expressed [132].

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 [83].

9. Other Biologic Agents

Several other biologic therapies are currently being investigated in phase II/III clinical trials; however, results from case studies or trials have not yet been published at the time of this review and were not discussed. These agents include CXCR1/2 inhibitor eltrekibart (NCT06046729), IL-17 inhibitor izokibep (NCT05905783), IL-1α/β inhibitor lutikizumab (NCT05139602), TNF-OX40L inhibitor SAR442970 (NCT05849922), and IL17A/F inhibitor Sonelokimab (NCT05322473) [83].

10. JAK Inhibitors

Alongside biologic therapies, small molecule therapies inhibiting the JAK-STAT signaling pathway are also being investigated for the treatment of multiple dermatologic conditions, including HS. JAK inhibitors have received FDA approval for the treatment of dermatoses such as atopic dermatitis and alopecia areata as well as other inflammatory conditions such as rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease [133]. One major advantage of JAK inhibitors over monoclonal antibodies is their oral route-of-administration. In addition to invasive routes-of-administration and high therapy cost, biologic therapies require additional resources devoted to refrigerated transportation and storage, safe needle disposal, and patient/caregiver training, which can often lead to patient frustration, non-adherence, or discontinuation altogether. Development of effective oral therapies can decrease therapy cost and increase convenience and compliance [134]. However, others have raised the potential increased risk of major adverse cardiovascular events (MACEs), including malignancy and thrombosis, and all-cause mortality associated with JAK inhibitors, especially in patients with inflammatory conditions such as HS. A recent report by Joseph Bailey et al. indicated that HS is associated with increased risks of MACE [135]. Though no large-scale data that specifically evaluated the risks of MACE associated JAK inhibitors in HS patients exist in the literature, a recent systematic review and network meta-analysis for the use of JAK inhibitors in rheumatoid arthritis (RA) patients revealed no notable disparity in the rate of MACEs between JAK and placebo. However, it did show higher rates of all-cause mortality in comparison to adalimumab [136]. Overall, there is no clear contraindication that exists for the use of JAK inhibitors in HS patients with cardiovascular risk factors, but clinicians must carefully weigh the risks vs. benefits and monitor patients longitudinally for potential adverse events.

Several trials are currently ongoing to evaluate this class of therapy for HS. Currently, the results of two open-label phase II studies have been published evaluating INCB054707 (now named povorcitinib) in adult patients with moderate-to-severe HS. In Study 1, 10 patients received 15 mg INCB054707 daily for 8 weeks. In Study 2, 35 patients were randomized to receive 30, 60, or 90 mg, or a placebo daily for 8 weeks. Overall, 3 patients (43%) in Study 1 and 17 patients (65% overall: 30 mg, 56%; 60 mg, 56%; 90 mg, 88%) receiving INCB054707 vs. 4 patients (57%) receiving the placebo in Study 2 achieved HiSCR at week 8. Safety results showed that 70% of patients in Study 1 experienced at least one treatment-emergent adverse event (TEAE), while 81% of patients in Study 2 experienced at least one TEAE, though no serious TEAEs were observed in either study. The most common TEAEs were upper respiratory infections, fatigue, headache, and asymptomatic thrombocytopenia [108].

Upadacitinib is a selective JAK-1 inhibitor that was recently FDA-approved for the treatment of atopic dermatitis [133]. A phase II trial evaluating upadacitinib for HS treatment has been completed (NCT04430855), and a phase III trial is currently in recruitment (NCT05889182) [83]. The results of the phase II study have not yet been published in the literature, but Kozera et al. published a real-life, retrospective cohort study evaluating upadacitinib monotherapy in 20 patients. All patients received upadacitinib 15 mg daily up to week 4. If the clinical response was not sufficient after 4 weeks, treatment doses were increased to 30 mg daily. In total, 15 patients (75%) achieved HiSCR at week 4, with 100% achieving HiSCR at week 12. $HiSCR_{75}$ was achieved in six patients (30%) at week 4 and 19 patients (95%) at week 12, while $HiSCR_{90}$ was achieved in four patients (20%) at week 4 and increased to six patients (30%) at week 12. All results were maintained up to week 24 [109]. Overall, JAK inhibitors remain a promising treatment for HS, especially considering oral route-of-administration and lower cost, and we await further clinical trial data.

11. Conclusions and Perspective

Hidradenitis Suppurativa is a debilitating dermatologic disease characterized by a vicious cycle of chronic inflammation and tissue destruction. While much work remains to elucidate the mechanisms contributing to HS pathophysiology, it is clear that both the innate and adaptive immune systems play a role in HS severity and offer opportunities for targeted treatment development. Studies have shown that the dysregulation of AMPs, activation of the complement system, and stimulation of Th1 and Th17 cells all contribute to the production of pro-inflammatory cytokines which perpetuate the cycle of chronic inflammation seen in HS. While the TNFa, IL-17, and IL-23 inhibitors have received the most attention recently, researchers are also assessing the efficacy of biologics targeting IL-12, IL-1, IL-36, IL-6, IL-10, IFNγ, C5a, and JAK.

Early recognition and prompt treatment of HS are crucial for improving disease prognosis and preserving patient quality of life. We are excited that biologics are broadening the treatment landscape, especially because HS commonly proves to be recalcitrant to conventional treatments, but it is crucial for clinicians to utilize a multimodal approach for successful management of HS. These strategies include combining nutrition and lifestyle modifications, medical therapies, and concomitant surgical management for moderate-to-severe disease. The toll HS takes on the psychosocial well-being of patients must also be recognized and can impact adherence to treatment; sensitivity and care is paramount to establishing a successful therapeutic relationship. Furthermore, HS commonly presents during adolescence, and data regarding the safety and efficacy for novel therapies in this population are limited. While much progress has been made in increasing the treatment options available to patients, further studies are much needed to better characterize HS pathophysiology and develop effective long-term therapies that minimize HS recurrence.

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