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REVIEW ARTICLE

Targeted treatments for hidradenitis suppurativa: a review of the current literature and ongoing clinical trials

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ABSTRACT

Purpose: Targeted, immune-modulating drugs are at the forefront of therapy for HS, and a comprehensive clinical trial registry is needed to facilitate data pooling and clinical efficacy comparison.

Materials and methods: A systematic review of the ClinicalTrials.gov database was searched for planned, in-progress, completed, or terminated trials investigating the effect of targeted biologic therapies for hidradenitis suppurativa (HS). When results of RCTs were not available, case reports or series were included.

Results: Inflammatory mediators that are targeted by biologic agents include tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-17, IL-12, IL-23, phosphodiesterase 4 (PDE4), lymphocyte function-associated antigen 1 (LFA-1), and complement component 5a (C5a). Clinical efficacy was measured by reduction in Sartorius score, Hidradenitis Suppurativa Clinical Response (HiSCR), Dermatology Life Quality Index (DLQI), or pain Visual Analog Scale (VAS). TNF inhibitors (adalimumab, etanercept, and infliximab), IL-1 receptor antagonist (Anakinra), IL-17A inhibitor (secukinumab), IL-12/23 inhibitor (ustekinumab), and PDE4 inhibitor (apremilast) show promise due to statistically significant improvements in disease severity.

Conclusions: Currently, adalimumab is the only FDA-approved biologic available for the treatment of HS. However, results from trials of other biologic agents targeting downstream mediators are promising. Large-scale, randomized, placebo-controlled trials in patients with skin of color, as well as weight-based dosing trials, are needed.

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Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory-mediated disease of the apocrine glands that presents clinically as bilateral painful nodules, abscesses, sinus tracts, and scarring in the axillae and the inguinocrural and anogential regions. The estimated worldwide prevalence of HS is 1–4% (1). Females are three times more likely to be affected than males, though males tend to have more severe disease (2). HS significantly impacts quality of life and mental health (3). In addition to psychological deficits, HS is primarily a disease of low socioeconomic status (SES) (4), and is thus associated with other comorbidities that typically affect these populations, such as cardiovascular disease, inflammatory bowel disease (IBD), and inflammatory joint disorders (5).

The etiology of HS, though not completely understood, is multi-factorial and includes folliculopilosebaceous anatomical abnormalities, genetic mutations, immune dysregulation, endocrine influence, and an imbalance of surface and adnexal microbiota, in addition to modifiable factors, such as smoking and metabolic syndrome (1,2,5–7). In one cohort, the odds ratio of metabolic syndrome in HS patients was significantly higher than in matched controls (diabetes mellitus OR, 1.41; obesity OR, 1.71; hyperlipidemia OR, 1.14; hypertension OR, 1.19) (7).

Pathophysiologically, HS is characterized by occlusion by keratin plugging of the folliculopilosebaceous glands (1). As the follicle dilates, it eventually ruptures and affects adjacent apocrine ducts. Spillage of adnexal contents results in lympho-histiocytic inflammation, secondary bacterial infection, and biofilm formation, further amplifying the immune response. This, together with extension of suppurative material to adjacent tissue, causes ulceration, fibrosis, and sinus tract formation (2).

Genetic mutations

Autosomal dominant loss-of-function mutations in presenilin-1, presenilin enhancer-2, and nicastrin have been shown to play a role in the formation of HS. These genes encode γ-secretase, a transmembrane protease that regulates follicular differentiation and immune regulation via the Notch signaling pathway. Dysregulation of the Notch pathway causes aberrant follicular keratinization and epidermal hyperplasia, which are inciting events in HS formation. Hair follicles of Notch-deficient mice are replaced by epidermal cysts, which are precursors for HS lesions (8).

Immunologic dysregulation

Several inflammatory mediators have been implicated in HS pathogenesis (Table 1), but only some are targets of existing biologic agents (9). Biopsies of HS lesions have revealed an abundance of neutrophilic granulocytes, T helper 1 T cells (Th1),

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Table 1. Inflammatory mediators upregulated in the peripheral blood of HS patients (8,25,28).

Cytokines	Chemokines	Soluble cytokine receptors	Adhesion molecules	Enzymes and their inhibitors	Antibacterial proteins	microRNAs
TNF-α (10,19,20)	CXCL6 (9)	IL-22BP (9)	sE-selectin (9)	MMP2 (9)	BD2 (9)	miR-146a (9)
IL-10 (9–11)	CXCL9 (9)	sVEGF-R1 (9)	sP-selectin (9)	MMP8 (29)	Lipocalin 2 (9)	miR-126 (9)
IL-17A (9,21)	CXCL11 (9)			Cystatin C (9)		
IL-6 (22)	CCL18 (9)	–	–	–	–	–
IL-19 (9)	CX3CL1 (9)					
IL-22 (9,11)	CCL2 (9)	–	–	–	–	–
IL-1 (10,21)						
IL-12/23 p40 (9,12–17)	–	–	–	–	–	–
IFN-γ (8,11,19,21)						
PDE4	–	–	–	–	–	–
Complement C5a						
Uteroglobin (9)	–	–	–	–	–	–

TNF: tumor necrosis factor; IL: interleukin; IFN: interferon; PDE: phosphodiesterase; CXCL: chemokine (C-X-C motif) ligand; CCL: chemokine (C-C motif) ligand; sVEGF-R: soluble vascular endothelial growth factor receptor; MMP: matrix metalloproteinase; BD2: beta-defensin 2; miR: micro ribonucleic acid.

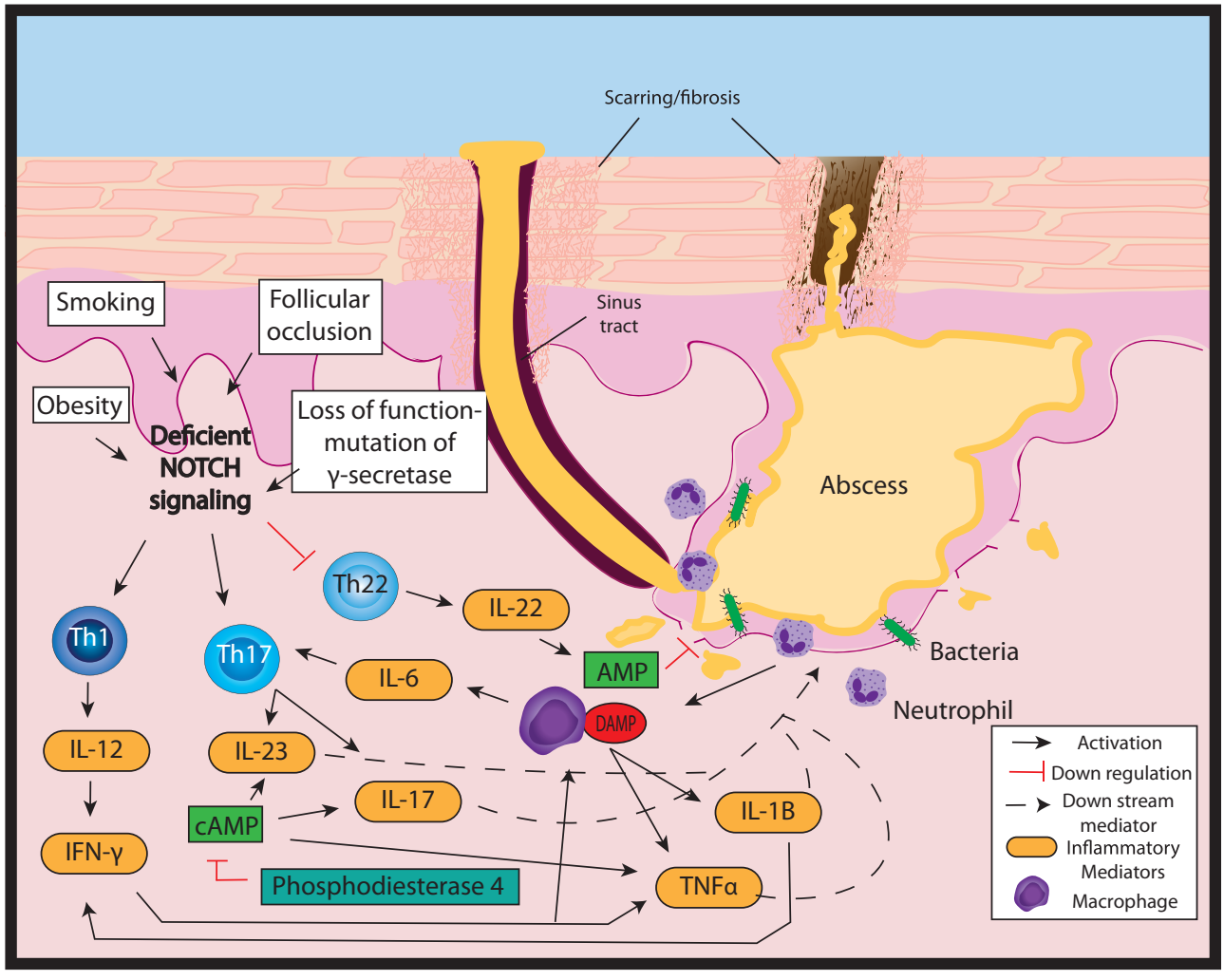

Figure 1. Inflammatory pathways in hidradenitis suppurativa.

T helper 17 T cells (Th17), macrophages, and dendritic cells. Cytokines involved include tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukins (IL-1β, IL-10, IL-17A, and IL-23) (Figure 1) (10,11). IL-12/Th1 and IL-23/Th17 pathways propagate phagocyte-dependent immune responses in HS (10,12). IL-12/Th1 is a crucial component of inflammatory conditions, as it induces IFN-γ and subsequent macrophage activation. However, Th17 appears to exert a more robust inflammatory effect than Th1 by producing IL-23 within HS lesions (13,14). IL-23 plays a role in neutrophil chemo-attraction, antimicrobial proteins (AMPs) production, and wound healing through scar formation (13). It is structurally related to IL-12 (a Th1 cytokine), but has distinct subunits, IL-12p35 and IL-23p19, the latter of which predisposes more strongly for auto-inflammatory conditions (15). In animal models, IL-23p19 deficient mice are resistant to developing autoimmune encephalomyelitis and collagen-induced arthritis, while IL-12p35 deficient mice did not manifest the same resistance (16,17). In humans, IL-23p19 has been found in clinical samples of

auto-inflammatory conditions closely related to HS, such as Crohn's disease. The variation in the IL-23 receptor gene leads to greater susceptibility to autoimmune diseases (15).

Rupture of keratin-filled epidermal cysts is followed by release of danger-associated motif patterns (DAMPs) that signal keratinocytes and local immune cells to exert an inflammasome-mediated innate immunity reaction (18). More specifically, DAMPs bind to macrophages to produce TNF-α and IL-1β. HS lesions have a five-fold increase in TNF-α levels compared to other inflammatory dermatologic conditions, specifically psoriasis (10). When compared to chronic wounds, effluent from HS lesions has higher levels of TNF-β (9.24 pg/ml vs. 1.65 pg/ml, $p = .03$) (19). Similarly, increases in soluble TNF-α receptor 1 and 2 have been documented, speculating prolonged or chronic TNF-α upregulation (20). IL-1 levels are also elevated in lesional and peri-lesional HS skin (10). Presence of IL-1β within keratinocytes of HS lesions is essential for further inducing IL-17 and IFN-γ-producing cells (21).

IFN-γ is crucial in both the innate and adaptive immunity response. Compared to healthy non-HS individuals, the skin of HS individuals has elevated IFN-γ mRNA and protein expression (7). Additionally, levels of IFN-γ within HS wound fluid are significantly elevated when compared to effluent from chronic wounds (1418 pg/ml vs. 102.5 pg/ml, $p = .027$), insinuating high levels of active, chronic inflammation (11,19). Of note, the etiologies of these chronic wounds were not reported.

Wild type Notch signaling activation signals CD4 + T cells to secrete IL-22. Thus, an impaired Notch pathway leads to IL-22 deficiency (8). HS lesion biopsies have reduced expression of membranous IL-22 receptors and increased expression of IL-22 binding protein, the natural IL-22 inhibitor. An increase in levels of the anti-inflammatory cytokine IL-10 is negatively correlated with levels of IL-22 as well as IL-20, its downstream mediator (11). Deficiency of IL-22 and IL-20 plays an important role in loss of antimicrobial defense and upregulation of AMP production (11). Low baseline levels of AMPs play a role in defense against commensal cutaneous bacteria (11). Wolk et al. saw a relative deficiency of AMPs in HS lesions, which correlates with the deficiency of its stimulator (11).

Absolute levels of inflammatory cytokines may correlate with the clinical inflammatory picture. Significant linear correlations have been demonstrated between moderate-to-severe HS and levels of IL-6 ($r = 0.53$), C-reactive protein (CRP; $r = 0.54$), and erythrocyte sedimentation rate (ESR; $r = 0.60$) (22). Macrophages and neutrophils secrete IL-6, which helps to polarize Th17 lymphocytes and CRP expression (22). Intense neutrophilic activation, which occurs in the later stages of HS pathogenesis (23), causes terminal production of IL-6 and CRP, which may explain why IL-6 is only present in the most severe cases of HS (22).

PDE4 is an enzyme that reduces levels of intracellular cyclic adenosine monophosphate (cAMP), a pro-inflammatory molecule that stimulates production of cytokines elevated in the serum and/or lesions of patients with HS, including TNF-α, IL-17, IL-23, and IL-10 (10,11,13,19,20,24). C5a, a complement-activated product, is a strong chemoattractant of neutrophils, eosinophils, T-lymphocytes, and phagocytic cells. Inhibition of the activated complement system decreases recruitment of downstream mediators that closely contribute to HS (25). Additionally, C5a has been shown to upregulate TNF-α and IL-1 expression in fresh human peripheral blood mononuclear cells (25). LFA-1 is found on T-cells, B-cells, macrophages, neutrophils, and natural killer (NK) cells. Binding of LFA-1 to intercellular adhesion molecule 1 (ICAM-1), an adhesion receptor on keratinocytes and endothelial cells, signals increased leukocyte adhesion and migration of leukocytes, increasing inflammatory response (26).

Metabolic dysregulation

Dysregulation of the mammalian target of rapamycin (mTOR) pathway is closely associated with metabolic and inflammatory conditions, including HS. Insulin is a stimulator of the mTOR pathway. In patients with the metabolic syndrome with associated insulin resistance, hyperinsulinemia increases expression of mTOR (27). Increased expression of mTOR has been reported in lesional and non-lesional skin of HS patients, and has been directly correlated with disease severity (27). Increased mTOR activation stimulates steroidogenic secretion, which stimulates sebaceous gland proliferation and promotes follicular adhesion and subsequent follicular plugging (7). Insulin-like growth factor 1 (IGF-1), a downstream product of the mTOR pathway (27), promotes hyperkeratinization of follicles and sebaceous gland lipogenesis, contributing to perifollicular fibroblast proliferation and plugging (28).

Matrix metalloproteinase 8 (MMP8), which is released from granulocytes following TNF-α stimulation, degrades extracellular matrix components and apolipoprotein A-1 of high-density lipoprotein (HDL). Levels of MMP8 in the lesional skin and serum of HS patients have been positively correlated with disease severity (29). Interestingly, blood MMP8 levels negatively correlate with HDL-cholesterol levels, which may explain the association between metabolic syndrome and HS (29). Additionally, macrophages within adipose tissues of obese patients secrete TNF-α and IL-1 β, further augmenting the inflammatory cascade (8).

The multitude of factors that lead to development of HS challenges clinicians to determine the best treatment modality. The utility of topical and systemic antibiotics, surgical excision, phototherapy, immunosuppressive drugs, and immunomodulatory drugs truly depends on the severity of the disease, as well as the patient's lifestyle preferences (30). Disease severity is classified by the Hurley staging system or the modified Sartorius score (mSS); both assessment tools classify the severity and extent of HS based on the number of involved regions, nodules, and sinus tracts (31). The Hidradenitis Suppurativa Clinical Response (HiSCR) score is an objective tool to measure the acute response to treatment, which is defined as a $>50\%$ reduction in abscess and inflammatory lesion count, without increase in the number of abscesses or draining fistulas when compared with baseline (32). Fifty percent reduction in HiSCR is typically chosen as a threshold as it equates with clinical improvement in quality of life and pain level, though the HiSCR does not aim to directly measure these values (32).

Currently, the only FDA-approved targeted treatment for HS is adalimumab (Humira®), a monoclonal antibody against TNF-α. The efficacy of adalimumab was initially observed in patients with Crohn's disease and comorbid HS who had significant resolution of HS lesions in addition to diminished IBD symptoms (22). Since this incidental discovery, numerous studies have shown an increased level of TNF-α in the lesional and peri-lesional skin of patients with HS (10,19,20), which has formed the basis of deciphering pathways that drive HS formation. A comprehensive registry that includes all previous, current, and future trials for targeted treatment for HS is lacking. Herein, we provide a comprehensive review of biologic agents targeted against the inflammatory mediators that contribute to the morbidity of HS, including those approved for HS, those currently or recently under investigation in clinical trials, and those that have shown promise for decreasing HS severity.

Materials and methods

The ClinicalTrials.gov database was searched for completed, planned, in-progress, or terminated clinical trials that investigate

the effect of targeted systemic therapies for HS. We searched the terms 'hidradenitis suppurativa,' 'acne inversa,' 'apocrine acne,' 'apocrinitis,' 'Fox-den disease,' 'hidradenitis axillaris,' 'pyoderma sinifica fistulans,' 'Velpeau's disease,' and 'Verneuil's disease,' which yielded a total of 48 studies. Of these, 27 were related to biologic treatment modalities. To access the results of these trials, PubMed was searched using terms ('hidradenitis suppurativa' OR 'acne inversa') and the medication name. Title and abstract review were performed. Due to the limited number of clinical trials open for HS, all phase levels of trials were reviewed. When trial results were not available in PubMed, results posted on ClinicalTrials.gov were used. When results were not available on ClinicalTrials.gov or PubMed, a World Wide Web search was used to find study results reported by pharmaceutical companies. Case reports and case series were included when larger trials were pending or unavailable. We excluded case reports when at least one randomized controlled study was completed for the biologic drug. In a few cases, studies were listed as 'completed' on ClinicalTrials.gov, but no study results were posted, and no published articles were found for these studies on PubMed or through a World Wide Web search. We included these studies but have noted that results are unavailable. Studies were included if they demonstrated that the drug in question worsened or did not improve the clinical status in patients with HS.

Results

TNF-α inhibitors

Adalimumab

Adalimumab (Humira®) is a fully human monoclonal antibody against soluble and membrane-bound TNF-α, and is FDA-approved for rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile idiopathic arthritis, Crohn's disease, and plaque psoriasis (PsO) (33). In 2015, adalimumab became the first and only FDA-approved medication for moderate-to-severe HS. In two separate, phase-III trials, multicenter double-blind, placebo-controlled study involving 633 patients with moderate-to-severe HS (PIONEER I, $n = 307$ and PIONEER II, $n = 326$), patients who received adalimumab 40 mg subcutaneously (SQ) weekly for 12 weeks had significantly lower HiSCR compared to those who received placebo (41.8% vs. 26.0% in PIONEER I, $p = .003$ (34); 58.9% vs. 27.6% in PIONEER II, $p < .001$ (35)). There was no significant difference in the number of adverse events when compared to placebo (Table 2) (34–36). In a phase III, open label extension (OLE) of the PIONEER I/II studies involving 88 patients with moderate-to-severe HS, 56.8% of patients receiving adalimumab 40 mg weekly for 120 weeks achieved HiSCR, with a mean change of −37.8% from baseline in abscess and inflammatory nodule count, and a mean change of −29.4% in draining fistulas (Table 2) (37,38). A phase III, multicenter, open-label, single-arm study involving 15 Japanese patients is currently recruiting participates to investigate the efficacy, safety, and pharmacokinetics of adalimumab (39). A phase IV trial aimed to determine the safety and efficacy of adalimumab prior to surgical interventions is currently recruiting approximately 200 HS patients (Table 2) (40). Several prospective post-marketing cohort studies are currently recruiting to assess adverse events (41), HiSCR (42), quality of life, skin pain, work productivity/activity, and health related problems (43,44).

Etanercept

Etanercept (Enbrel®), a dimeric fusion protein that binds to the soluble and leukocyte membrane-bound TNF-α receptor, is FDA-approved for moderate-to-severe RA, moderate-to-severe polyarticular juvenile RA, PsA, AS, and PsO (45). As a fusion protein, etanercept has 5-times greater half-life and 50-fold greater affinity for TNF-α, compared to a monomeric TNF-receptor (46). Trials of etanercept in HS have reported conflicting results. In a

Table 2. Completed, ongoing, and planned clinical trials of biologic agents in HS.

Agent	Trade name	Manufacturer	Target/mechanism	Route of administration	Clinical trial phase	Clinical trial #	Reference
Adalimumab	Humira®	AbbVie	TNF-α inhibitor	SQ	II, III, IV	NCT00918255 NCT01468207 NCT01468233 NCT01635764 NCT02904902 NCT02808975 NCT03001115 NCT01387815 NCT02739828 NCT02786576 NCT00827996	(34,35,37,39–44,82,83)
Etanercept	Enbrel®	Amgen	TNF-α inhibitor	SQ	II	NCT00107991 NCT00949546 NCT00329823	(47,48,51)
Infliximab	Remicade®	Janssen Biotech	TNF-α inhibitor	IV	II	NCT00795574	(54)
Anakinra	Kineret®	Swedish Orphan Biovitrum AB	IL-1 receptor antagonist	SQ	II	NCT 01516749 NCT01558375	(57,59)
MEDI8968	–	Amgen	IL-1 Receptor I inhibitor	SQ	II	NCT01838499	(60)
MABp1	Xilonix®	XBiotech	IL-1α inhibitor	IV or SQ	II	NCT02643654	(62)
CJM112	–	Novartis	IL-17A inhibitor	SQ	II	NCT02421172	(63)
Secukinumab	Cosentyx®	Novartis Pharma AG	IL-17A inhibitor	SQ	I	NCT03099980	(66)
Bimekizumab	–	UCB Biopharma	IL-17A/IL-17F inhibitor	IV or SQ	II	NCT03248531	(67)
Ustekinumab	Stelara®	Janssen Biotech	IL-12 and IL-23 inhibitor	SQ	II	NCT01704534	(71)
Apremilast	Otezla®	Celgene Corporation	PDE4 inhibitor	PO	II	NCT02695212 NCT03049267	(73,74)
Efalizumab	Raptiva®	Genentech	LFA-1 inhibitor	SQ	I	NCT00134134	(76)
IFX-1	–	InflaRx GmbH	Complement C5a inhibitor	IV	II	NCT03001622	(79)

phase II, open-label trial involving 15 patients with moderate-to-severe HS, etanercept 50 mg SQ weekly for 12 weeks failed to show significant clinical response measured by PGA score (response rate, 20%; 95% CI: 4.3–48.1) (47). In a double-blind, randomized controlled trial involving 20 patients with HS, etanercept 50 mg SQ twice weekly for 12 weeks also failed to show statistically significant differences in physician or patient global assessment (PGA) and dermatology life quality index (DLQI) between treatment and placebo groups ($p > .05$ for all comparisons) (48) (Table 2) (47–50). In a phase II, non-randomized, interventional, open-label trial involving six patients with severe, recalcitrant HS, treatment with etanercept 25 mg SQ weekly for 24 weeks lead to reductions in patient-reported disease activity (−61%), DLQI (−64%), and relapse rates. This study was completed in 2006, prior to the FDA's approval of adalimumab, and patients reported that etanercept was the most effective treatment they had received for their condition (other treatments included combinations of high-dose oral antibiotics, dapsone, isotretinoin, antiandrogenic OCP, and/or surgery) (Table 2) (51,52). The general consensus from these high quality, phase II clinical trials is that etanercept is not effective for treating moderate-to-severe HS.

Infliximab

Infliximab (Remicade®) is a chimeric mouse/human monoclonal antibody against TNF-α that is FDA-approved for the treatment of Crohn's disease, ulcerative colitis, psoriasis, PsA, AS, and RA (53). In a phase II, randomized, double-blind, crossover assignment study involving 38 patients with moderate-to-severe HS, 60% of patients receiving infliximab (intravenous [IV] 5 mgs/kg on weeks 0, 2, 6, 14, and 22) had a 25% to <50% decrease in the HS Severity Index score (HSSI) compared to the placebo group (5.6%) at week 8, which was the end of the double-blind phase of the trial (54,55). Additionally, 88.9% of patients in the placebo group had a <25% decrease in HSSI from baseline, compared to 13.3% of patients in the infliximab group ($p < .001$). Compared to those who received placebo, patients who received infliximab had significant improvements in the mean change in DLQI (10.0 vs. 1.6, $p = .003$), visual analog score (VAS) (39.8 vs. 0.6, $p < .001$), PGA (1.8 vs. 4.7, $p < .001$), and reductions in serum ESR (11.7 vs. −5.9, $p = .01$) at week 8 (Table 2) (54,55). To our knowledge, no phase III studies are planned or in progress.

IL-1 antagonist

Anakinra

Anakinra (Kineret®) is a recombinant IL-1 receptor A (IL-1Ra) antagonist that contains an additional methionine residue at the amino terminus, differentiating it from native human IL-1Ra. Anakinra is approved for moderate-to-severe RA and neonatal-onset multisystem inflammatory disease (NOMID) (56). In an open-label, non-randomized study involving six patients with moderate-to-severe HS, treatment with anakinra SQ (100 mg/0.67 ml) daily for 8 weeks lead to a significant reduction in the Sartorius score (−34.8 units from baseline, $p = .024$) (Table 2) (57). In a double-blind, randomized, placebo-controlled trial involving 20 patients with Hurley stage II or III HS, treatment with anakinra (100 mg/0.67 ml SQ) daily for 12 weeks led to a significant decrease in the disease activity score (defined by Tzanetakou et al. as the sum of scores, two largest diameters in each affected area in millimeters multiplied by the degree of inflammation at each lesion of all affected areas) compared a placebo (78% vs. 20%, $p = .02$) (58,59). HiSCR was seen in 78% of patients in the anakinra arm compared to 30% in the placebo arm at 12 weeks ($p = .04$). The change in HiSCR at 24 weeks trended toward non-significance (10% vs. 33%, $p = .28$). Changes in other endpoints included a significant decrease in serum levels of interferon-γ in the anakinra arm at 12 weeks ($p = .04$), with a concomitant increase in IL-22 in the anakinra arm at 24 weeks ($p = .02$) (Table 2). Exact values were not presented (58,59).

MEDI8968

MEDI8968 is a fully human monoclonal antibody that binds selectively to IL-1RI to inhibit IL-1α and IL-1β from exerting their pro-inflammatory effects (60). A phase IIa, randomized, double-blind, placebo-controlled, multicenter study involving 109 patients with moderate-to-severe HS, was designed to assess the safety, tolerability, and preliminary efficacy of the drug in within a 12-week time course; however, the trial was terminated early due to a lack of efficacy in reducing HS severity or pain compared to placebo (Table 2) (60).

MABp1

MABp1 (Xilonix®), a fully human monoclonal antibody that targets IL-1α (61), is currently being studied in patients with colorectal cancer, infectious and inflammatory disease, and dermatological conditions such as pyoderma gangrenosum, PsA, and acne vulgaris. A phase II, randomized, parallel-design, quadruple-blinded trial involving 20 patients with moderate-to-severe HS treated with MABp1 for 12 weeks has been completed, but results have not been published (Table 2) (62). The primary outcome measure was a positive difference in HiSCR score between the study and placebo group.

IL-17 inhibitor

CJM-112

CJM-112 is a fully human monoclonal antibody that targets IL-17 (63). A phase II, randomized, double-blind, parallel-design (high dose CJM-112, low dose CJM-112, and placebo), multicenter study in 66 patients with moderate-to-severe chronic HS has been completed, but results have not been published. The primary endpoint was clinical reduction in HS-PGA score over a 16-week treatment (Table 2) (63).

Secukinumab

Secukinumab (Cosentyx®) is a fully human monoclonal antibody that inhibits interleukin-17A and is approved for the treatment of moderate-to-severe PsA, PsO, and AS (64). In a case report of a patient with treatment-resistant (recalcitrant to adalimumab, infliximab, anakinra, cyclosporine, and rifampicin/clindamycin) Hurley Stage III HS encompassing the neck, axillae, breasts, genital skin, and buttocks, secukinumab 300 mg SQ weekly for 4 weeks, followed by 300 mg SQ every fourth week for an additional 8 weeks, led to patient-reported improvements of 16 abscesses and inflammatory nodules during the last 4 weeks prior to assessment (65). Additionally, the patient's pain VAS improved from 5 to 3 and pain/utility/handicap VAS improved from 7 to 4. The patient-reported improvement was not paralleled by physician-graded clinical scores. The reported reduction in 16 lesions could have been due to the natural waxing and waning history of HS rather than success from treatment. A single-arm, open-label, interventional, pilot study of secukinumab (300 mg SQ weekly for five weeks, then every four weeks thereafter) for patients with HS is currently recruiting. The primary endpoint will evaluate clinical HS symptoms over the course of 24 weeks (Table 2) (66).

Bimekizumab

Bimekizumab (UCB4940) is a highly selective humanized monoclonal antibody that inhibits IL-17A and IL-17F (67). A phase II, multicenter, double-blind, placebo-controlled, non-inferiority trial comparing bimekizumab, adalimumab, and placebo is currently recruiting HS patients (Table 2) (67).

IL-12 and -23 inhibitor

Ustekinumab (Stelara®) is a fully human monoclonal antibody that inhibits both Th1 and Th17 pathways by binding to the common p40 subunit on both IL-12 (Th1) and IL-23 (Th17) (68). It is approved for moderate-to-severe Crohn's disease, moderate-to-severe PsO, and PsA (68). Following positive results from case series of patients with moderate-to-severe HS treated with ustekinumab (69), Blok et al. completed a phase II, open-label, prospective study involving 17 patients with moderate-to-severe HS who received either 45 or 90 mg of ustekinumab SQ at weeks 0, 4, 16, and 28 (70). Of the 12 patients who completed the study, 82% had a significantly improved mean mSS at week 40 compared to baseline (60.18 vs. 112.12; $p < .01$). Subjects also had significant reductions in mean HSSI (19.59 vs. 26.28, $p = .01$), DLQI (59% vs. 71%; clinically meaningful improvement in 41% of patients), and pain VAS (4.6/10 vs. 5.8/10) compared to baseline. Serum LTA4 levels were also decreased following treatment compared to baseline (Table 2) (70,71).

PDE4 inhibitor

Apremilast (Otezla®) is an orally administered phosphodiesterase four inhibitor approved for adults with active PsA and moderate-to-severe PsO (72). In a case series of nine patients with moderate-to-severe HS who failed other HS therapies (including a combination of canakinumab, infliximab, isotretinoin, doxycycline, clindamycin/rifampicin, adalimumab, riclosan lotion, triamcinolone injections, and/or surgery), apremilast (30 mg twice daily for 2–3 months) led to significant improvements in Sartorius score compared to baseline (56.11 vs. 68.11, $p = .028$). Subjects also reported significant decreases in pain VAS (7.17–2.00, $p = .026$), which positively correlated with a reduction in DLQI score (21.33–9.33, $p = .027$) ($r = .655$, $p = .021$) (24). Although this case series reported positive results, it was limited by a small sample size ($n = 9$). Two additional trials are currently recruiting patients with HS. The first, a double-blind, randomized, placebo-controlled trial involving 20 patients, will assess the cytokine profile over the course of 16 weeks of treatment with apremilast (Table 2) (73). The second, an open-label, single center study, will recruit approximately 20 subjects over the course of 28 weeks. (Table 2) (74).

LFA1 inhibitor

Efalizumab (Raptiva®), a recombinant, humanized, monoclonal antibody that inhibits CD11a, a subunit on LFA-1, was approved for moderate-to-severe PsA in 2003 (75). A phase I, open-label trial involving five patients with severe, refractory HS was conducted in 2006 (76,77). Patients received 0.7 mg/kg weekly of SQ efalizumab for the first two doses, and 1.0 mg/kg weekly for 10 subsequent doses. Only 2 of the 5 participants completed the 12-week study, and neither patient experienced clinical improvement of HS following efalizumab (Table 2) (76,77). In 2009, efalizumab was found to be associated with bacterial sepsis, viral meningitis, invasive fungal disease, and progressive multifocal leukoencephalopathy (PML). The drug was subsequently withdrawn from the U.S., Canadian, and European marketplaces (78).

Complement C5A inhibitor

IFX-1 is a chimeric monoclonal antibody directed against complement C5a (79). Currently, there is an ongoing, open-label, phase II trial of IFX-1 in 12 patients with severe HS over an 8 week course. Clinical endpoints include HiSCR, DLQI, VAS for disease and pain, PGA, mSS, and formation of serum anti-drug antibodies (Table 2) (79).

Discussion

The multifactorial pathogenesis of HS presents a variety of options for treatment. As we enter the dawn of targeted therapies for HS, the use of biologic treatments has the potential to dampen disease severity at multiple inflammatory points (Figure 1). Although the only FDA-approved medication for HS is adalimumab, several other biologics have demonstrated potential in targeting inflammatory cytokines involved in HS, including TNF-α (etanercept, infliximab), IL-1 (anakinra), IL-17A (secukinumab), IL-12/23 (ustekinumab), and PDE4 (apremilast) (Table 2). Agents that block other inflammatory mediators detected in HS patients may lead to the development of new targeted therapies (Table 1).

Additional studies are needed to assess various dosing regimens for targeted therapies, including weight-based dosing for overweight and obese HS patients. Importantly, the majority of subjects enrolled in HS clinical trials are Caucasian; this may not accurately reflect the true demographics of the disease since non-Caucasians represent a large portion of patients with HS (80,81). Future studies are also needed to examine the benefit of combination therapeutic regimens that include biologics, antibiotics, androgen modulating treatments, and lifestyle modifications.

Disclosure statement

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