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REVIEW

The Current Clinical Trial Landscape for Hidradenitis Suppurativa: A Narrative Review

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ABSTRACT

Hidradenitis suppurativa (HS) is a skin disease resulting from chronic, recurrent inflammation around hair follicles, characterized by proinflammatory cytokines such as IL-1, IL-17, IL-23, and TNF-α. While adalimumab, a TNF-α targeting human IgG monoclonal antibody, is the only approved treatment for HS, there are many other therapies being investigated now targeting other key players in inflammatory pathways such as the cytokines listed above, C5a in the complement pathway, and Janus kinase (JAK). This review discusses current clinical trials for biologics and small molecules, procedures, and wound dressings undergoing study in hidradenitis suppurativa.

Keywords: Hidradenitis suppurativa; Clinical trials; Treatment

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Key Summary Points

Elucidating the pathophysiology of hidradenitis suppurativa (HS) is revealing proinflammatory cytokines that present opportunities for therapy, such as IL-1, IL-17, IL-23, and TNF-α.

The clinical trial landscape for HS is robust, with 36 studies currently underway: 10 cytokine inhibitors, 14 non-biologic medications, 4 laser treatments, 4 procedures, and 4 wound dressings. These cover a total of 17 therapeutic targets.

Trials involving blockade of IL-17, JAK, and IL-1α are expanding upon prior clinical trials showing efficacy in HS, as measured by the Hidradenitis Suppurativa Clinical Response (HiSCR).

Pathways involving leukotriene A4 hydrolase, CD-40, IL-1β, IL-18, BTK, and others have been found to play a role in the pathogenesis of HS and are being studied as novel therapeutic targets.

Surgery and wound care play important roles in HS management. Trials investigating these modalities are underway and will provide high-quality evidence to guide therapy.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that causes painful, recurrent nodules, draining tunnels, and abscesses typically in the intertriginous regions of the body with a profound impact on quality of life [1]. The pathogenesis of HS is currently not well understood, however, genetic, environmental, and hormonal factors have been thought to be contributory. Various cytokines contribute to the inflammation that drives tissue damage in HS, including TNF-alpha, IL-1β, IL-1a, and IL-17 [2].

In recent years, research investigating HS has increased greatly, providing insights into potential pathways involved in the pathogenesis that may serve as therapeutic targets. Adalimumab is currently the only FDA-approved therapy for HS, but numerous other therapies are undergoing clinical trials, and multiple are drawing closer to approval. This brings hope to the treatment landscape for HS, which is advancing at an inspiring pace.

We have conducted this review of ongoing clinical trials studying new treatment options for HS to highlight the multitude of pathways and modalities under study, with the hope that many will prove beneficial and expand the armamentarium of treatments for this debilitating condition. A complete list of clinical trials referenced in this review is listed in Table 1. A summary of existing literature for medications used in the treatment of HS is included in Table 2. A summary of recently completed and active but not recruiting clinical trials for medications under investigation for HS treatment is included in Table 3.

METHODS

We conducted a search of current clinical trials being performed for HS on Clinicaltrials.gov. We included drug therapies, laser therapies, surgical procedures, and wound dressings, as they were all relevant to the outcome of HS. We noted the type of clinical study for each therapy including phase and blinding. We reviewed the available literature regarding the intervention for each trial. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Table 1 Summary of medications under investigation for HS currently recruiting or not yet recruiting

Clinical trial no.	Clinical trial phase	Agent	Target/mechanism	Route of administration
NCT05355805	2b	Izokibep	IL-17A inhibitor	Subcutaneous
NCT05322473	2	Sonelokimab	IL-17A and IL-17F inhibitor	Subcutaneous
NCT04179175	3	Secukinumab	IL-17A inhibitor	Subcutaneous
NCT04246372	2	Tofacitinib	JAK inhibitor	Oral
NCT05620823	3	Povorcitinib	JAK inhibitor	Oral
NCT05620836	3	Povorcitinib	JAK inhibitor	Oral
NCT04414514	2	Ruxolitinib	JAK inhibitor	Topical
NCT05635838	2	Ruxolitinib	JAK inhibitor	Topical
NCT05139602	2	Lutikizumab	IL-1 inhibitor	Subcutaneous
NCT03827798	2	Iscalimab	Anti-CD-40 monoclonal antibody	Subcutaneous
NCT03827798	2	LYS006	Leukotriene A4 inhibitor	Oral
NCT03827798	2	MAS825	IL-1β and IL-18 inhibitor	Subcutaneous
NCT03827798	2	Remibrutinib	BTK inhibitor	Oral
NCT04989517	1	AT193	AHR agonist	Topical
NCT05040698	2	Fostamatinib	Syk inhibitor	Oral
NCT05020730	2	PTM-001	Glycan-targeting antibody	Oral
NCT05348681	2a	RIST4721	CXCR2 inhibitor	Oral
NCT04982432	2	Orismilast	PDE4 inhibitor	Oral
NCT04649502	3	Metformin and doxycycline	Antiinflammatory effects	Oral
NCT05103423	1/2	BDB-001	TLR7/8 agonist	Intravenous
NCT05286567	1	RGRN-305	HSP90 inhibitor	Oral

IL interleukin, *JAK* Janus kinase, *PDE4* Phosphodiesterase-4, *BTK* Bruton's tyrosine kinase, *AHR* Aryl hydrocarbon receptor, *Syk* Spleen tyrosine kinase, *CXCR2* Chemokine receptor 2, *TLR7/8* Toll-like receptor 7/8, *HSP90* Heat shock protein 90

RESULTS

The search for "recruiting and not yet recruiting studies" for hidradenitis suppurativa on Clinicaltrials.gov on 22/12/2022 yielded a total of 48 results. After combing through the results, we eliminated repetitive or not pertinent studies, giving us a final 36 studies: 10 cytokine inhibitors, 14 other drugs, 4 lasers, 4 procedures, and 4 wound dressings. There were a total of 17 therapeutic targets.

Table 2 Summary of existing literature for medications under investigation for HS treatment

Agent (route of admission)	Target mechanism	Outcome (placebo)
Secukinumab (subcutaneous)	IL-17	Casseres et al.: HiSCR week 20: 67%
		SUNSHINE: HiSCR week 16: 45% (versus 34%)
		SUNRISE: HiSCR week 16: 42–46% (versus 31%)
Tofacitinib (oral)	JAK	"Improvement" in two patient case series
Povorcitinib (oral)	JAK	First phase 2 trial: HiSCR week 8: 43%
		Second phase 2 trial: HiSCR week 8: 88% (versus 57%)
Bermekimab (subcutaneous)	IL-1α	TNF-α failure: HiSCR week 12: 63%
		TNF-α naive: HiSCR week 12: 61%
IFX-1 (intravenous)	C5a	HiSCR week 16: non-superior to placebo (47%)
Apremilast (oral)	PDE4	HiSCR week 16: 53%
Metformin monotherapy (oral)	Antiinflammatory effects	Subjective clinical response 12 months: 68%
Risankizumab (subcutaneous)	IL-23α	HiSCR week 16: non-superior to placebo; 43–47% (versus 42%)

IL Interleukin, *JAK* Janus kinase, *PDE4* Phosphodiesterase-4, *C5a* Complement 5a, *HiSCR* Hidradenitis Suppurativa Clinical Response, *TNF* Tumor necrosis factor

PHARMACOLOGIC THERAPIES

IL-17 Inhibitors

Izokibep is a small molecule, anti-mimetic subcutaneous IL-17A inhibitor that is currently being evaluated in a randomized, double-blind phase 2 trial for HS [3, 4]. The study will evaluate for Hidradenitis Suppurativa Clinical Response (HiSCR) at week 16 compared with placebo.[4] While it has not been studied in HS previously, a randomized, double-blind, placebo-controlled phase 2 trial in 135 patients showed that izokibep may be efficacious in psoriatic arthritis [5]. Adverse events reported include injection site erythema and infection [5].

Sonelokimab is a nanobody that is administered subcutaneously and is an inhibitor of IL-17A and IL-17F [6]. It is currently undergoing a phase 2, double-blind, parallel-group trial for HS [6, 7]. Patients will be randomized to sonelokimab at one of two doses, placebo, or adalimumab [6]. The primary outcome of the study is HiSCR75 at week 12 [6]. In plaque psoriasis, a phase 2b trial showed rapid and significant clinical improvement with sonelokimab treatment [7]. Potential adverse effects include nasopharyngitis, upper respiratory tract infections, inflammatory bowel disease, and *candida* infections [7].

Secukinumab is a subcutaneous IL-17A inhibitor that may be effective for HS [8]. Previously, an open-label trial with 20 patients found that 70% of the participants reached HiSCR by 24 weeks [8]. Another open-label trial with 9 patients found that 67% of participants reached HiSCR by 20 weeks [9]. Two phase 3 trials (SUNRISE and SUNSHINE) evaluating two dosing regimens of secukinumab for HS have been completed [10–12]. These trials randomized 541 (SUNSHINE) and 543 (SUNRISE)

Table 3 Summary of medications under investigation for HS treatment recently completed and active but not recruiting clinical trials with primary completion date between 1 January 2021 and 22 April 2023

Clinical trial no.	Clinical trial phase	Agent	Target/mechanism	Outcome
NCT03926169 [58]	Phase 2	Risankizumab	IL-23A monoclonal antibody	HiSCR week 16: non-superior to placebo; 43–47% (versus 42%)
NCT04979520 [87]	Phase 1	Brodalumab	IL-17 inhibitor	Results not posted
NCT04901195 [88]	Phase 3	Bimekizumab	IL-17A/F inhibitor	Results not posted
NCT04430855 [89]	Phase 2	Upadacitinib	JAK inhibitor	HiSCR week 12: superior to placebo; 38% (versus 24%)
NCT04756336 [90]	Phase 2	LTX-109	Antimicrobial	Results not posted
NCT03713632, NCT03713619 [10–12]	Phase 3	Secukinumab	IL-17 inhibitor	SUNSHINE: HiSCR week 16: 45% (versus 34%) SUNRISE: HiSCR week 16: 42–46% (versus 31%)
NCT04762277 [91]	Phase 2	Spesolimab	IL-36R inhibitor	Results not posted
NCT04493502 [92]	Phase 2	LY3041658	CXCR1/CXCR2 inhibitor [93]	Results submitted, quality control review has not concluded
NCT04856930 [94]	Phase 2	Imsidolimab	IL-36 receptor inhibitor [95]	Results not posted
NCT05040698 [43]	Phase 2	Fostamatinib	Syk inhibitor	Results not posted
NCT05216224 [96]	Phase 2	ATI-450	Small molecule MK2 inhibitor	Results not posted
NCT04092452 [97]	Phase 2	PF-06650833	IRAK4 inhibitor	Results submitted, quality control review has not concluded
NCT04092452 [97]	Phase 2	PF-06700841	TYK2/JAK1 inhibitor	Results submitted, quality control review has not concluded
NCT04092452 [97]	Phase 2	PF-06826647	TYK2 inhibitor	Results submitted, quality control review has not concluded
NCT03972280 [98]	Phase 1	CSL324	Recombinant anti-G-CSF receptor monoclonal antibody	Results not posted
NCT05286567 [62]	Phase 1	RGRN-305	HSP90 inhibitor	Results not posted
NCT04772885 [99]	Phase 1	KT-474	IRAK4 degrader	Results not posted

IL Interleukin, *JAK* Janus Kinase, *PDE4* Phosphodiesterase-4, *C5a* Complement 5a, *HiSCR* Hidradenitis Suppurativa Clinical Response, *MK2* MAPK-activated protein kinase 2, *IRAK4* Interleukin-1 receptor-associated kinase 4, *TYK2* Tyrosine kinase 2, *G-CSF* Granulocyte-colony stimulating factor, *Syk* Spleen tyrosine kinase, *CXCR* Chemokine receptor, *HSP90* Heat shock protein 90

patients to secukinumab 300 mg every 2 weeks, every 4 weeks, or placebo [11, 12]. The SUNSHINE trial found that 45% of patients receiving the every 2-week dose achieved HiSCR at week 16, which was significant compared with placebo (34%) [11, 12]. For the patients receiving the every 4-week dose, 42% achieved HiSCR at week 16, but this was not significant compared with placebo [11, 12]. The SUNRISE trial found that 42% of patients receiving every 2 weeks dosing and 46% of patients receiving every 4 weeks dosing achieved HiSCR at week 16, both significant compared with placebo (31%) [11, 12]. For those receiving the every 2-week dose, 76% of patients in the SUNSHINE trial and 84% of patients in the SUNRISE trial maintained their response at week 52 [12]. For those receiving the every 4-week dose, 81% of patients in the SUNSHINE trial and 77% of patients in the SUNRISE trial maintained their response at week 52 [12]. A third phase 3 trial is recruiting to evaluate secukinumab for HS [13]. Adverse effects may include headache, nasopharyngitis, fungal infections, new-onset inflammatory bowel disease, and worsening of hidradenitis up to week 16 [12].

JAK Inhibitors

Currently, one trial is evaluating the expression of the JAK/STAT pathway in HS by utilizing immunostaining of HS biopsy samples, as well as in pyoderma gangrenosum and psoriasis [14].

Tofacitinib is an oral small molecule JAK inhibitor that blocks IL-6 signalling [15]. One case series of two patients demonstrated that treatment with tofacitinib may lead to clinical improvement in treatment-resistant HS [15]. One of the patients initially had Hurley stage III disease and achieved remission with tofacitinib, and the other patient had significant improvements in pain level and healing of ulcerations [15]. However, a case of tofacitinib-induced HS was also reported in a patient receiving tofacitinib for rheumatoid arthritis [16]. There is currently an open label phase 2 trial evaluating the use of tofacitinib in a variety of autoimmune and/or autoinflammatory skin conditions in patients with Down syndrome, including HS [17]. Patients will be treated with 5 mg twice a day and the primary outcomes include safety (assessed by number of serious adverse events) and change in activation of the interferon pathway in white blood cells [17]. Previously reported adverse events include infection, varicella zoster reactivation, and immunosuppression [15].

Povorcitinib, also known as INCB054707, is an oral JAK1-specific inhibitor [18]. Two phase 2 clinical trials demonstrated that povorcitnib is well tolerated and may be efficacious for moderate-to-severe HS [18]. The first study included ten patients, in which 70% developed a treatment-associated adverse event, but none were deemed serious [18]. At week 8, 43% achieved HiSCR [18]. The second study included 35 patients, who were randomized to povorcitinib 30 mg, povorcitinib 60 mg, povorcitinib 90 mg, or placebo [18]. Overall, 81% developed a treatment-associated adverse event, but again, none were deemed serious [18]. At week 8, 88% achieved HiSCR [18]. Two phase 3 trials are currently in process [19, 20]. Both trials will randomize patients to povorcitnib at one of two doses or placebo, then evaluate HiSCR at week 12 [19, 20]. Reported adverse effects include fatigue, headache, folliculitis, nasopharyngitis, thrombocytopenia, diarrhea, and upper respiratory tract infections [18].

Ruxolitinib is a JAK1/2-specific inhibitor that may be used topically or orally [21]. There are currently two phase 2 trials to evaluate the efficacy of topical ruxolitinib for HS [22, 23]. One is an open-label trial that will assess HiSCR at week 16 [22]. The other is a double-blind trial comparing ruxolitinib 1.5% cream versus vehicle twice a day [23]. The primary outcome is change in abscess and inflammatory nodule (AN) count at week 16 [23]. To our knowledge, no prior studies have been published about the use of ruxolitinib in HS. Given the topical route of administration, there is lower risk of systemic side effects, but adverse events may include nasopharyngitis and headache [21].

IL-1 Inhibitors

Lutikizumab, also called ABT-981, is an immunoglobulin administered subcutaneously that inhibits IL-1α and IL-1β [24]. A phase 2, randomized, double-blind, placebo-controlled trial is currently underway in moderate-to-severe HS that has failed TNF-alpha inhibitor therapy [25].The primary outcome is HiSCR at week 16 [25]. To date, there are no other studies investigating the role of lutikizumab in HS. An open-label phase 2 clinical trial showed that bermekimab, another IL-1α inhibitor, may be effective in moderate-to-severe HS [26]. The study included 42 patients divided into two groups [26]. Group A included 24 patients who previously failed a TNF-alpha inhibitor, and group B included 18 patients who had not been previously treated with a TNF-alpha inhibitor [26]. The primary endpoint was safety, and while no serious adverse events were reported, 58 non-serious adverse events were reported [26]. One of the secondary outcomes was HiSCR, and 63% of patients in group A and 61% of patients in group B achieved HiSCR at week 12. Possible adverse events associated with IL-1 inhibitors include injection site reactions, nausea, gastrointestinal disorders, and infections [26].

OTHER DRUGS

CFZ533

CZF533, also known as iscalimab, is an anti-CD-40 monoclonal antibody [27]. CD-40 is present on B cells and plasma cells. When activated after binding its receptor, CD-40L on T cells, it promotes the formation of germinal centers, aids in immunoglobulin isotype switching, and, contributes overall to the adaptive inflammatory immune response [28]. Both B cells and plasma cells have been found to predominate the leukocyte population in the pathogenesis of HS, thus blocking this pathway is currently a proposed treatment mechanism [29]. Iscalimab was safe and effective in the treatment of rheumatoid arthritis in a randomized, double-blind, placebo-controlled trial with 76 patients and in Grave's disease in an open-label study. No adverse events were observed for patients on iscalimab [27, 30]. A phase 2 randomized, double-blind clinical trial is currently underway to evaluate iscalimab's use in HS. This trial will last 16 weeks and compare outcomes in patients treated with subcutaneous CFZ533 compared with placebo in moderate-to-severe HS. The primary outcome of the study is the proportion of patients who achieve HiSCR [31].

LYS006

LYS006 is an oral leukotriene A4 hydrolase small molecule inhibitor currently being evaluated in a randomized, double-blind phase 2 clinical trial for HS. The primary outcome of the study is the proportion of patients who achieve HiSCR [31, 32]. Leukotriene A4 hydrolase is the rate-limiting enzyme for the synthesis of leukotriene B4, a potent proinflammatory molecule. Along with blocking leukotriene B4, LYS006 has been shown to aid in the synthesis of lipoxin A4, an antiinflammatory molecule [33]. The antiinflammatory effects of LYS006 could be beneficial in treating HS.

MAS825

MAS825 is a subcutaneous IL-1β and IL-18 monoclonal antibody under investigation in a double-blind, randomized trial with a primary outcome of HiSCR response at week 16 [31, 34]. A previous trial focused on systemic juvenile idiopathic arthritis associated with interstitial lung disease with MAS825 found an overall increase in oxygen saturation and reduced pulmonary inflammatory infiltrates reduced with no reported side effects [34]. There are no prior studies evaluating MAS825 for the treatment of HS.

LOU064

LOU064, also known as remibrutinib, is a small molecule inhibitor of Bruton's tyrosine kinase [35]. Plasma cells have been shown to dominate the leukocyte population in HS lesions, and Bruton's tyrosine kinase (BTK) decreases the

proliferation of these plasma cells [29]. A random, double-blind, clinical trial of 311 patients with chronic spontaneous urticaria treated with remibrutinib showed rapid improvement and minimal adverse events. These possible adverse events include headache, nasopharyngitis, nausea, upper respiratory tract infections, diarrhea, renal abscess, aggravation of chronic spontaneous urticaria, and pyrexia [36].A current double-blind, randomized, phase 2 clinical trial is investigating moderate-to-severe HS treated orally with a high or low dose of LOU064. The study will run for 16 weeks and the primary outcome is the proportion of patients that achieve HiSCR [31].

Complement 5a Receptor Inhibitors

Complement 5a receptors play a role in the complement system, leading to neutrophil infiltration and contributing to inflammation. A case-controlled trial is currently investigating complement 5a receptors' antiinflammatory properties in the treatment of HS. Lesional and perilesional skin biopsies as well as plasma samples will be taken from 40 patients with HS or healthy volunteers. These samples will be directly analyzed or treated with complement 5a receptor inhibitors and examined for expression of a neutrophil adhesion molecule, CD11b, as well as complement 5a receptor expression on neutrophils. Measurement of cytokines and immune cell population profiling will also occur [37]. InflaRx conducted a double-blind, randomized, placebo clinical trial in 179 patients with HS being treated with IFX-1, a complement 5a receptor inhibitor, for 16 weeks. Complement 5a receptors were shown to have a favorable safety profile and low anti-drug antibody rates [38]. At the end of the trial, there was a failure to demonstrate dose-dependent HiSCR. HiSCR requires that inflammatory nodules must decrease by 50% and the number of fistula and abscesses cannot exceed baseline. HiSCR does not account for a reduction in tunnels, however, high dose IFX-1 was shown to reduce the number of draining fistulas from baseline. Therefore, InflaRx is planning to resubmit their study to the FDA with a different outcome to better showcase the efficacy of IFX-1 relative to the reduction in tunnels [38].

AT193

AT193 is a topical aryl hydrocarbon receptor (AHR) agonist currently being studied in a double-blind, randomized, placebo-controlled, phase 1 trial of 44 patients for the treatment of HS. The primary outcome is the safety of AT193 at 8 weeks [39, 40]. AHR is a nuclear receptor known for its antimicrobial properties, however, it has recently been proposed for the treatment of chronic inflammatory diseases such as inflammatory bowel disease and rheumatoid arthritis. AHR ligands have possible toxic, teratogenic, and carcinogenic effects, therefore, long-term adverse events need to be further studied [40]. Currently, there have not been studies published on AT193 in patients with HS.

Fostamatinib

Fostamatinib is a spleen tyrosine kinase inhibitor (Syk) that the FDA has approved for the treatment of immune thrombocytopenic purpura. Reported side effects of Syk inhibitors included diarrhea, hypertension, nausea, dizziness, and alanine aminotransferase increase [41]. Syk is a key player in the downstream signaling of B cells, therefore, inhibition of Syk may be a pharmacological target for HS [29]. A double-blind, placebo-controlled clinical trial consisting of 457 patients with rheumatoid arthritis treated with a Syk inhibitor showed clinically significant disease reduction with mild side effects of diarrhea, neutropenia, and hypertension [42]. Currently, there is an exploratory open-label 12-week clinical trial investigating the use of fostamatibnib for the treatment of HS, comparing gene expression profiling at baseline, 4 weeks, and 12 weeks. Specifically, cell counts of $CD3^+$, $CD11c^+$, neutrophil $elastase^+$, $CD20^+$, and $CD138^+$, cellular markers for various leukocytes, will be examined [43].

PTM-001

PTM-001 is a glycan-targeting antibody being investigated for HS through a double-blind, placebo-controlled, randomized clinical trial consisting of 50 patients. Protein levels of IL-1β in skin lesion biopsies will be examined at the end of 12 weeks [44]. Post-translational modifications (PTMs) are changes to proteins after translation, which can include glycosylation, phosphorylation, and acetylation. These modifications allow the protein to achieve its full function. It has been found that PTMs can contribute to inflammatory diseases, such as atopic dermatitis and psoriasis [45]. Thus, PTMs are a possible novel therapeutic target for HS.

RIST4721

A randomized, placebo-controlled, double-blind clinical trial is currently investigating RIST4721 in 33 patients with HS [46]. RIST4721 works as a CXCR2 inhibitor. CXCR2 is a neutrophil attractant and its inhibition has been investigated in the treatment of hepatocellular carcinoma [47]. Due to anti-neutrophilic properties, RIST4721 may be useful in treating HS inflammation. The primary outcome will measure the Treatment-emergent adverse effects and serious adverse events after 12 weeks [46].

Orismilast

Orismilast is an oral phosphodiesterase 4 (PDE4) inhibitor undergoing an open-label trial of 24 participants with HS, with a primary outcome of total count of abscesses and inflammatory nodules at 16 weeks [48]. PDE4 inhibitors decrease inflammatory cytokines and increase antiinflammatory cytokines in T cells, natural killer cells, dendritic cells, and neutrophils, which play a role in the pathogenesis of HS [49].

A previous randomized controlled trial showed that out of 15 patients with HS treated with apremilast, another PDE4 inhibitor, 53% had reduced clinical symptoms after 16 weeks. The most commonly reported adverse events included headache and gastrointestinal symptoms [49].

Metformin and Doxycycline

Metformin and doxycycline are studied in a 24-week double-blind controlled clinical trial utilizing the International Hidradentitis Suppurtiva Severity Score System (IHS4) [50]. Doxycycline is an antibiotic with immunomodulatory effects through inhibition of T-cell proliferation and cytokine production, inhibition of MMPS, and inhibition of other inflammatory molecules [51]. Metformin can increase intracellular levels of doxycycline while also contributing antiinflammatory mechanisms [52]. In a retrospective study examining 53 patients with HS treated with metformin, 68% showed a subjective clinical response and 19% showed quiescent disease on metformin monotherapy. Metformin was well tolerated, showing mild adverse events such as gastrointestinal side effects in some patients [53]. The drug combination of metformin and doxycycline has been studied for enhancement against multidrug resistant bacteria, however, no studies have been published on its use for HS treatment [51].

BDB-001

BDB-001 is being investigated in a multicenter, double-blind, randomized clinical trial of 49 patients with HS [54]. Treatment adverse events, development of anti-BDB-001 antibodies, and peak plasma concentration of BDB-001 will be examined at 8 weeks. BDB-001 is a toll-like receptor (TLR) 7 and TLR 8 agonist with known anti-tumor and anti-viral effects. Reported adverse events were fever, fatigue, chills, and rash [55]. Activation of TLRs leads to acute inflammation, however, the prolonged use of TLR agonists can cause tolerance leading to hyporesponsiveness and antiinflammatory effects [56]. There are no prior studies in HS.

Risankizumab

Risankizumab is an IL-23A monoclonal antibody approved for the treatment of psoriasis and psoriatic arthritis. Early cases demonstrated success in individual patients. Possible adverse

events with treatment include headache, fatigue, upper respiratory infections, tinea infections, and injection site reactions [57]. It was investigated in a multicenter, double-blind, randomized clinical trial for HS treatment with low and high dosing regimens. At 16 weeks, the HiSCR ranged from 43% to 47%, but there was no significant difference with the placebo (42%) [58]. Other IL-23 monoclonal antibodies have reported efficacy in case reports, but less promising outcomes in larger trials. Guselkumab showed positive outcomes in six case reports, however, a case series reported high doses of guselkumab showed adverse treatment outcomes [59, 60]. A case series of five patients treated with tildrakizumab showed improvement in quality of life scores after 8 weeks of treatment [59].

RGRN-305

RGRN-305 is a human shock protein 90 (HSP90) small molecule inhibitor. HSP90 is involved in downstream signaling of IL-17 and TNF alpha [61]. In a randomized, placebo-controlled, double-blind trial, oral RGRN-305 is being investigated after 16 weeks of treatment. The primary outcome is the proportion of patients achieving HiSCR-50 [62]. IL-17 and TNF alpha contribute to the pathogenesis of HS.

LASERS

While drugs, creams, and injections serve to control or mitigate the symptoms of HS, once tunnels have formed, surgical intervention becomes necessary.

Flexible diode lasers are now being used as a tissue-sparing treatment of tunnels from within [63]. These lasers have previously been tested in perianal tunnels and HS tunnels with promising results [64]. This treatment has the potential to diminish side effects, such as scarring, to shorten surgical recovery periods and to improve control of inflammation. Potential adverse effects included postoperative pain, erythema, and mild swelling [65]. A randomized, contralaterally controlled, blinded clinical trial is underway to determine the efficacy of a 1470 nm intralesional diode laser in terms of pain scores, ultrasound evaluation, clinical photos, clinical measures of disease activity, quality-of-life scores, and skin biopsies [63].

A single center, open-label, baseline-controlled clinical trial is being performed to evaluate the utility of an Erbium:YAG 2940 nm fractionated ablative laser in treating axillary scarring due to HS [66, 67]. Case reports have demonstrated benefits of fractionated lasers in the treatment of HS and HS scarring [68, 69].

Fractional ablative CO2 lasers used to facilitate steroid (triamcinolone) delivery are also being evaluated for efficacy in a single group assignment clinical trial for Hurley Stage I or II [70]. Fractional ablative CO2 laser therapy will be performed on non-inflammatory and inflammatory nodules, sinus tracts, abscesses, and scars, followed by an immediate topical application of triamcinolone acetonide.

Another clinical trial is assessing the effectiveness of deroofing in combination with a long-pulsed 1064 nm Nd:YAG laser. Deroofing consists of removing larger HS nodules and tunnels to heal by secondary intention [71]. Studies have shown that 83% of deroofed lesions do not recur within 34 months, and although post-surgical complications may include bleeding, there was no infection or decreased range of movement [72]. When compared with other surgical methods such as incision and drainage, wide excision, and limited excision, deroofing showed a significantly lower rate of lesion recurrence [72]. In one previous study, deroofing with a CO2 laser was performed after multiple sessions using a long pulse Nd:YAG laser to destroy hair follicles. The combination of these therapies also resulted in decreased rates of recurrence, and healing was complete after 15 days [73].

SURGICAL AND PROCEDURAL TREATMENTS

A number of surgical procedures are currently employed in the treatment of HS, including deroofing (discussed above), skin-sparing excision with electrosurgical peeling, and complete

excision of sinus tracts [74]. Additional surgical approaches are being investigated.

Botulinum toxin may be effective for HS, but the exact mechanism for this remains unknown [75]. One randomized, double-blind, placebo-controlled study in 20 patients demonstrated improvements in quality of life and symptoms with intradermal injection of botulinum toxin without any reported adverse effects [76]. The primary outcome of this study was DLQI at 3 months, which improved from a median of 17 to 8 in the treatment group compared with a median of 13.5 to 11 in the placebo group [76]. An observational study is underway to investigate if botulinum toxin reduces intralesional IL-17 levels in HS lesions, as well as if it has impacts on quality of life and pain levels [77].

Capsule fecal microbiota transplantation (cFMT) is also a prospective treatment option for chronic inflammatory illnesses such as HS, as there are alterations in both skin and gut microbiomes in patients with HS [78]. A randomized, quadruple-blind clinical trial is currently in phase 2 and compares the efficacy of cFMT with placebo in treating various inflammatory diseases including HS [79].

Other novel treatments for HS include clinical trials for battlefield acupuncture and radiofrequency-based treatment. Battlefield acupuncture is being tested against sham acupuncture for the assessment of pain relief in patients with HS in a randomized, single-blind clinical trial [80]. Radiofrequency-based selective electrothermolysis treatment is currently used for acne vulgaris, epilation, and skin rejuvenation due to its high specificity and minimal destruction of surrounding tissue. In a single group assignment clinical trial, it is now being assessed for safety, tolerance, and histometric changes in the axillae of patients with HS [81].

DRESSINGS AND ANTISEPTICS

Dressings play a large role in the care of HS lesions, both for drainage and after surgery. Currently, there is a clinical trial comparing the efficacy of human cadaveric allografts with a biodegradable polyurethane porous matrix adhered to a transparent sealing membrane for post-surgical care. The trial will assess graft adherence and presence of shear, friction, or infection after an aggressive wide excision with thorough debridement and cleansing [82].

There are a number of post-surgical dressings that are being tested with minor procedures. Gentian violet is used as a topical antiseptic for cutaneous yeast infections and may play a role in healing active ulcerations. Single group assignment clinical trials are now being performed to assess gentian violet's efficacy in improving lesional healing of draining wounds in HS [83]. Another trial also combines gentian violet with methylene blue and ovine forestomach dressings for non-healing wounds or draining abscesses/nodules due to HS. The combination of methylene blue with gentian violet serves as an antibacterial foam dressing that can be worn for a week without inhibiting growth factors. The foam wicks away bacteria from the wound surface by using natural negative pressure via capillary flow. The ovine forestomach serves a similar purpose to the allografts mentioned above in stabilizing, building, and organizing tissue in wounds [84].

Another randomized, parallel assignment clinical trial compares a bioelectric dressing with a standard gauze dressing for post-debridement healing. The bioelectric dressing is a single layer, broad-spectrum antimicrobial dressing that contains microcell batteries of silver and zinc arranged in a dot-matrix pattern and is applied to the surgical site with a hydrogel [85].

While the wet-to-dry dressing technique is commonly employed after surgery, including HS surgery, there is no evidence to support its use. A randomized, triple-blind clinical trial is underway comparing wet-to-dry dressings with an alternate option of petrolatum with non-stick gauze to measure changes in wound healing, pain, and quality of life [86].

CONCLUSIONS

Hidradenitis suppurativa is a debilitating disease with limited treatment options available, making disease control a challenge for many patients. Fortunately, efforts to expand

therapeutic options are underway, as demonstrated by the robust clinical trial landscape, with 36 active trials investigating a range of pharmaceutical therapies, surgical treatments, medical devices, and wound care strategies. It is a promising time for the treatment of HS, and the future holds promise for people affected by HS and the providers helping them.

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