Hidradenitis suppurativa

Current and emerging treatments

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Learning objectives
After completing this learning activity, participants should be able to list the treatment options available for patients with hidradenitis suppurativa, discuss emerging therapeutic options, and compare the utility and effectiveness of these methods.

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The treatment of hidradenitis suppurativa (HS) has remained challenging because of the many knowledge gaps regarding etiology. However, recent studies into the pathogenesis of HS have enabled the investigation of newer therapies. The second article in this continuing medical education series reviews the evidence for established therapies for HS, including anti-inflammatories, antibiotics, and surgery. New and emerging therapies that specifically target cytokines involved in HS pathogenesis will be covered. The potential therapeutic roles of anticytokine therapies, including both the expanded application of existing molecules as well as the specific development of novel therapies for HS are discussed. With increased attention on HS and with numerous clinical trials currently underway, we hope that the variety of treatment options for HS will be expanded. (J Am Acad Dermatol 2020;82:1061-82.)

Key words: adalimumab; antibiotics; hidradenitis; secukinumab; ustekinumab.

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The treatment of hidradenitis suppurativa (HS) remains challenging. Early studies were limited by their small sample size and the lack of placebo groups. With greater awareness of disease prevalence and improved understanding of immunopathogenesis, however, newer therapies are emerging.

ESTABLISHED THERAPIES

Key points

- **Antibiotics are used to decrease inflammation and to treat secondary infection**
- **Systemic tetracyclines, alone or in combination with other agents, are frequently used as first-line treatments**
- **Prednisone does not have much benefit alone, but may increase the response to adalimumab**
- **Surgery remains an important treatment for HS; wide excision is the only known curative procedure**
- **Weight loss and smoking cessation counseling should be recommended for patients with HS**

Antibiotics/anti-inflammatories

HS lesions are frequently colonized with bacteria and antibiotics have anti-inflammatory properties, supporting the dual therapeutic rationale for these agents. Only commonly used antibiotics for HS are discussed here.

Antibiotic monotherapy is often used as first-line treatment.[1,2] A study of 46 patients with HS found that monotherapy with topical 1% clindamycin phosphate or systemic tetracycline (250 mg twice daily) both reduced the number of abscesses within 3 months and the number of nodules after 3 months.[3] Bacterial presence at treatment onset did not affect the outcome. There was also no difference in pain, HS severity score, or Physician's Global Assessment (PGA) between the 2 groups, but the difference in participant global self-assessment outcome favored oral tetracyclines.[1,3] There are no randomized, placebo-controlled trials of oral tetracyclines for patients with HS.

In moderate-to-severe disease, combination therapy is more common. Rifampin is a broad-spectrum antimicrobial that inhibits growth of most Gram-positive and some Gram-negative microorganisms.[4] It has immunomodulatory effects via suppression of antigen-induced transformation of sensitized lymphocytes and suppression of T cell function, altering cell-mediated hypersensitivity.[4,5] Clindamycin, a macrolide that inhibits protein synthesis, also modifies inflammation by suppressing complement-derived chemotaxis of polymorphonuclear leukocytes.[5]

The rifampin-clindamycin combination is effective for HS treatment.[6] A significant decrease in Sartorius score was found in most patients after 10 weeks. These results are consistent in the literature,[7-10] supporting this combination as a frequently selected treatment.[11] Although generally well tolerated, studies have found adverse digestive symptoms in 13% to 43% of patients.[6] Another combination consists of rifampin, moxifloxacin, and metronidazole.[6] This combination has similarly shown success,[9,11] particularly in patients with less severe disease,[8] but is associated with adverse effects, including gastrointestinal symptoms, vaginal candidiasis, and tendinitis.[6]

Ertapenem is a broad-spectrum antibiotic that has demonstrated efficacy in treating HS.[9] In 1 retrospective study of 36 patients with HS treated with 1 g of intravenous ertapenem for an average of 59 days (in addition to medications they were already taking), 35 patients showed improvement. However, 17 patients had serious complications including diarrhea, peripherally inserted central catheter line thrombosis and vaginitis.[12] Moreover, 30 patients relapsed in an average of 5.8 weeks. Another study of Hurley stage II/III patients receiving intravenous ertapenem found an improved Hurley stage by 1 point in 17 of 30 patients.[7] Ertapenem might be used to achieve rapid improvement before surgery or other maintenance therapies, but should otherwise be considered for patients who are refractory to or contraindicated for other treatments.[12]

Although the intent of these therapies is to capitalize on both antiinflammatory and antibiotic properties, the antibiotic aspect of these medications always warrants consideration of antibiotic resistance. One study found patients using clindamycin were more likely to grow clindamycin-resistant *Staphylococcus aureus*.[10] A study of 69 patients with HS demonstrated high resistance to monobactams (75%), tetracyclines (64%), and lincosamides (51%).[13] Consequently, broad-spectrum combination treatment is considered the best option to limit resistance.[6]

Prednisone has also been tested as a therapeutic option for HS. In 1 study, 13 patients with recalcitrant HS were treated with 10 mg prednisone in addition to treatment they were currently receiving. Five patients showed remission after 4 to 12 weeks, and 3 maintained remission 6 months after prednisone discontinuation. Six patients showed improvement without complete remission and 2 patients had no response. Interestingly, 5 patients had no response

to adalimumab until prednisone was added, possibly because of the suppression of neutralizing antibodies.[14,15] The effect of higher doses of prednisone has not been thoroughly investigated.

Intralesional corticosteroid therapy can be effective for isolated HS lesions.[15] A case series with 33 patients with acute HS nodules or abscesses found a significant reduction in erythema, edema, suppuration, size, and patient-reported pain after intralesional triamcinolone treatment. This therapy presumably activates glucocorticoid receptors within lesions, resulting in the blockage of leukotriene synthesis and reduction of proinflammatory cytokines.[16] However, the efficacy of intralesional corticosteroid therapy is refuted by a randomized, double-blind, placebo-controlled 3-arm trial evaluating the efficacy of intralesional triamcinolone injection. This study divided all lesions among 32 patients into 1 of 3 groups: triamcinolone 10 mg/mL, 40 mg/mL, or normal saline (placebo). There was no statistically or clinically significant difference in the number of days to lesion resolution in either treatment arm compared with the placebo arm.[17]

Table I provides a comprehensive review of medical therapies for HS.

Surgery

Surgery is an option in HS management. For mild disease, deroofing or laser treatment may alleviate symptoms. Incision and drainage may be used in the acute setting for patients presenting with painful fluctuant abscesses.[18] For severe disease, wide excision is the only potentially curative treatment. Commonly used procedures are summarized in Table II.

Counseling

Lifestyle modification is paramount in HS management. Because obesity and increasing body mass index are associated with more severe disease, weight loss is strongly advised.[19,20] Of 383 patients with HS who completed a survey before and after bariatric surgery, 35% fewer patients reported symptoms and the mean number of involved sites decreased from 1.93 to 1.22.[19] Bariatric surgery has been debated, however, because of reports of worsening symptoms after surgery. One study described experiences of patients with HS posted on online forums and Facebook groups. About a third of patients discussing bariatric surgery noted worsening symptoms after surgery, seemingly because of the increase in skin folds.[21]

Smokers have a worse prognosis and poorer treatment outcomes; smoking cessation is thus advised for all patients with HS.[13,22] In a retrospective cohort study of 437 patients with HS, the frequency of ever being a smoker was 65%.[23] Tobacco was associated with treatment escalation (from topical to immunologic therapy or surgery).[23] Nonsmoking patients with HS have shown 2.8 times the odds of self-reported remission compared with smokers.[22] In addition, former smokers or nonsmokers have a 3-fold higher rate of achieving a response to medical therapy compared with smokers.[22] HS is also associated with an increased risk of adverse cardiovascular outcomes and all-cause mortality, further supporting the importance of smoking cessation.[24]

BIOLOGIC THERAPIES

Key points

- **Advances in the understanding of HS pathogenesis has guided studies to investigate the therapeutic role of biologics for this disease**
- **Tumor necrosis factor−α inhibitors are effective and safe for the treatment of HS; adalimumab is the only therapy for HS approved by the US Food and Drug Administration**
- **There are several ongoing clinical trials for newer biologic therapies targeting multiple cytokines**
- **It is likely that multiple immunologic pathways are implicated in HS progression, so complete treatment may need to target >1 pathway**

Tumor necrosis factor−α inhibitors

Adalimumab (ADA) is the only drug for moderate-to-severe HS that has been approved by the US Food and Drug Administration.[25] ADA binds soluble and transmembrane TNF-α[15] and significantly reduces mammalian target of rapamycin (mTOR) activity in patients with HS.[26] Initial trials found a reduction in Sartorius score after 6 weeks.[27] In a larger trial of patients treated with ADA (40 mg weekly), 17.6% achieved a PGA score of 0 to 2 with at least a 2-grade improvement compared with baseline.[27,28] Improvements in secondary outcomes, including increased quality of life and decreased pain, also occurred.[27] Two separate phase III multicenter, double-blind, placebo-controlled studies (PIONEER I and PIONEER II) with 633 combined patients with moderate-to-severe HS showed that 50.6% of patients receiving ADA 160 mg at week 0, 80 mg at week 2, and 40 mg weekly starting at week 4 achieved Hidradenitis Suppurativa Clinical Response (HiSCR) compared with only 26.8% of placebo at week 12.[25,29] Two groups were defined: "responders" who achieved HiSCR, and "partial

Table I. Medical treatments for hidradenitis suppurativa, excluding biologics and surgery

Treatment	MOA	Severity (Hurley stage)*	Advantages†	Disadvantages†	Grade, ‖,‡	Evidence level, strength of recommendation¶,§,**,#
Anti-inflammatories/antibiotics						
Topical clindamycin	Binds 50s bacterial subunit	I or II[3]	• Common for localized HS without deep abscesses • Few AEs • Inexpensive	• Requires constant application • Ineffective in stage III disease or for multiple affected areas	B	IIb, B
Clindamycin/ rifampin	Binds 50s bacterial subunit; inhibits DNA-dependent RNA polymerase	II or III[71]	• Standard treatment • Large study of Hurley stage I patients experienced remission • Inexpensive • Well tolerated in most	• In women yeast infections, RB • GI intolerance in some, possible hepatic issues • Rifampin has many drug interactions; decreases the effectiveness of many medications	B	III, C
Oral tetracycline	Binds the 30s ribosomal subunit	I or II	• Can be effective in more widespread lesions with frequent exacerbations	• Not available in all countries • Has not shown significantly better effects than topical clindamycin[72]	B	II, B
Ertapenem	Beta-lactam antibiotic	I, II, or III	• Limited reports show dramatic effect	• Expensive, little data • Need IV access • Long term use could select out for RB	C	IV, C
Oral dapsone	Competitive inhibition of bacterial dihydropteroate synthase	I or II	• May work where antibiotics fail	• Many potential AEs (neuropathy, hemolytic anemia, and methemoglobinemia) • Response not durable; rapid relapse after use • Consider giving with cimetidine	C	IV, C

Minocycline/rifampin	Inhibits 30s subunit; Inhibits DNA-dependent RNA polymerase	I or II[73]	• May be more effective than clindamycin/rifampin • Generics inexpensive	• In women yeast infections, RB • Extended release minocycline is expensive • GI intolerance, possible hepatic issues • Minocycline can cause headaches and rare side effects (including HSS) • Rifampin has many drug interactions; decreases the effectiveness of many medications	C	NR
Fluoroquinolones/metronidazole/rifampin (triple therapy)	Inhibits ligase activity of type II topoisomerases, gyrase and topoisomerase IV; Produces intermediate compounds and free radicals that are cytotoxic to facultative anaerobic bacteria; Inhibits DNA-dependent RNA polymerase	II or III	• Might work when clindamycin/rifampin and minocycline/rifampin fail • Inexpensive	• Tendon rupture • CNS issues, particularly in the elderly • Yeast infections, RB • GI upset • Metronidazole can cause sacral neuropathy • Must avoid alcohol	NR	IV, C
Topical dapsone	Inhibits myeloperoxidase and eosinophil-peroxidase within neutrophils and eosinophils, respectively	I or II	• Few AEs • Soothing vehicle	• Expensive • Not effective for majority of patients	NR	NR

Continued

Table I. Cont'd

Treatment	MOA	Severity (Hurley stage)*	Advantages†	Disadvantages†	Grade, ‖,‡	Evidence level, strength of recommendation¶,§,**,#
Immunosuppressives						
Prednisone	Glucocorticoid receptor agonist; Inhibits proinflammatory cytokine production, decreases number of circulating lymphocytes, induces cell differentiation, and stimulates T cell apoptosis	II or III	• May augment adalimumab therapy[14]	• Sexual AE • Gynecomastia • Sparse evidence	C	IV, D
Intralesional corticosteroids	Glucocorticoid receptor agonist; Inhibits release of phospholipase A2; causes vasoconstriction; has direct inhibitory effect on DNA and inflammatory transcription factors	NED	• Quick acting • Can have cumulative effect abating or burning out HS	• Rare adrenal suppression • Limited duration of effectiveness of 2-4 weeks • Does not always expedite lesion resolution • Painful	C	IV, D
Cyclosporine	Calcineurin inhibitor; binds cyclophilin; blocks T-cell activation by preventing IL-2 transcription	II or III	• Few reports show tremendous anti-inflammatory effectiveness • Safer to use for months over oral corticosteroids	• Requires laboratory and vital sign monitoring • Can promote SCC • Renal AEs • Hypertension	E[74]	IV, D
Dimethyl fumarate	Activates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, involved in the cellular response to oxidative stress; Impairs IL-12 and IL-23 production by dendritic cells and macrophages	II or III[74]	• Has been effective in decreasing inflammation in psoriasis vulgaris patients[75]	• Unproven for HS	E[74]	NR

Hydroxychloroquine	May impair complement-dependent antigen-antibody reactions; inhibits locomotion of neutrophils and chemotaxis of eosinophils; increases pH, which interferes with lysosomal degradation of hemoglobin	NED	• Pilot study in progress	• No published data[76]	NR	NR
Hormonal therapy						
Spironolactone	Competitive aldosterone receptor antagonist in cortical collecting tubule of nephron	I or II	• Inexpensive • May reduce menstrual flares • Low doses may be as effective as higher doses (helpful for patients with tolerability issues)[77]	• Diuretic • Increases K^+ • May require laboratory monitoring • May affect menses • Rare neural and muscular AEs	C	IV, D
OCP (as a class)	Progestogen negatively feeds back on hypothalamus, decreases pulse frequency of GnRH, decreases secretion of FSH and LH; estrogen stabilizes uterus endometrium and negatively feeds back to the anterior pituitary to decrease FSH secretion	I or II	• Inexpensive, except branded products with drospirenone which may be best type of OCP for females with HS	• Increased risk of blood clots in particular if drospirenone is part of OCP	D[78]	IV, D

Continued

Table I. Cont'd

Treatment	MOA	Severity (Hurley stage)*	Advantages†	Disadvantages†	Grade, ‖,‡	Evidence level, strength of recommendation¶,§,**,#
Cyproterone acetate and ethinyloestradiol	Cyproterone acetate is antiandrogenic and progestogenic, with weak partial glucocorticoid activity, weak inhibition of steroidogenesis, and an agonist at the pregnane X receptor; ethinyloestradiol is an agonist of the estrogen receptors	I or II	• Inexpensive • May reduce menstrual flares	• Not available in US • Risk of increased clotting	C[79]	IV, D
Finasteride	Competitive inhibitor of type 2 5α-reductase	I or II	• Multiple cases have shown improvement in 4 weeks[52]	• Sexual AEs • Gynecomastia • Recurrence after treatment cessation[52]	D	IV, D
Dutasteride	Synthetic 4-azasteroid compound that is a selective inhibitor of both the type 1 and type 2 isoforms of steroid 5α-reductase	NED	• More effective testosterone blocker than finasteride	• AEs similar and greater than finasteride • More risk of gynecomastia • Uncertain effect of blocking DHT1 • More expensive than finasteride	NR	IV, D
Leuprolide acetate, flutamide, degarelix gonadotropin-releasing hormone agonist	GnRH analog with agonist properties when pulsatile and antagonist when continuous; Nonsteroidal competitive inhibitor at androgen receptors	II or III[73]	• Strong hormonal suppression	• Not proven for HS • Extreme hormonal AEs	NR	IV, D

Retinoids						
Isotretinoin	13-*cis*-retinoic acid, binds to and activates nuclear retinoic acid receptors	NED	• Helped >20% of patients • May have greater effect in younger patients with acne[56]	• Most patients have no response • Xerosis • Needs iPledge participation • Requires laboratory monitoring • Many potential AEs	B	IV, D
Acitretin, oral alitretinoin, or etretinate	Acitretin is the free acid of etretinate, which is less lipophilic and has a shorter terminal half-life than etretinate; alitretinoin is an endogenous retinoid related to vitamin A	II or III	• Might resolve follicular occlusion • May have other positive immunologic effects • Does not require iPledge participation	• Similar AEs as isotretinoin except more prolonged risk of birth defects • Expensive • Few studies	B	IV, C
Antidiabetics						
Metformin	Biguanide; inhibits hepatic gluconeogenesis and the action of glucagon; decreases gluconeogenesis; increases glycolysis and peripheral glucose uptake (increased insulin sensitivity)	I or II	• May decrease Sartorius score and improve QoL • Few side effects	• Mixed results on efficacy	D[16]	NR
Glucagon-like peptide-1 analogues/ agonists	Increased glucose-dependent insulin release and satiety; decreased glucagon release and gastric emptying	NED	• Limited data	• Limited data on efficacy	NR	NR
Other therapies						
Zinc gluconate 90 mg	Zinc salt of gluconic acid, with two anions of gluconate for each zinc (II) cation	I[73]	• Inexpensive • Limited strong data • May decrease Sartorius score and improve QoL	• Not for severe disease • Copper should accompany it • Relapse with reduction in dose	C	III, C

Continued

Table I. Cont'd

Treatment	MOA	Severity (Hurley stage)*	Advantages†	Disadvantages†	Grade, ‖,‡	Evidence level, strength of recommendation¶,§,**,#
Botulinum toxin	Heat-labile toxin that inhibits acetylcholine release at the neuromuscular junction	NED; case reports of efficacy in II and III[80,81]	• Might alter neural factors • Alters skin flora because of decreased sweating	• Expensive, unproven	E[80]	IV, D
3 times daily wash + antibacterial soap + sodium fusidate 2% ointment	Sodium fusidate is a bacterial protein synthesis inhibitor that prevents turnover of elongation factor G from the ribosome; inhibits protein translation in Gram-positive bacteria	I[66]	• Prospective trial found decreased pain and itching as well as complete healing of many lesions[66]	• Only tested in patients with Hurley stage I axillary lesions	B	NR
IVIG	Derived from the pooled human plasma of thousands of donors; intact IgG molecules with trace amounts of IgA, soluble CD4, CD8, HLA molecules, and certain cytokines; IgG subclasses (IgG1, IgG2, IgG3, and IgG4) in IVIG products have a distribution similar to that found in normal human plasma	NED	• Might work if all else fails	• Expensive, unproven	D[82]	NR

PDGF, GCSF	PDGF induces vascular remodeling, smooth muscle cell migration, and stimulates fibroblast growth for collagen synthesis; GCSF is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells	NED; only 1 case report[83]	• Promote healing	• Expensive, unproven	E[83]	NR
Benzoyl peroxide	Releases free radical oxygen species; sebostatic, comedolytic, and inhibitory to *Propionibacterium acnes* in vivo	NED	• Established acne treatment • Prospective multi-center trial in progress[13,67]	• No published data[13]	NR	NR

AE, Adverse event; *C5a*, complement factor 5a; *cAMP*, cyclic adenosine monophosphate; *CNS*, central nervous system; *DHT1*, dihydrotestosterone 1; *GCSF*, granulocyte-macrophage colony-stimulating factor; *GI*, gastrointestinal; *GnRH*, gonadotropin-releasing hormone; *HLA*, human leukocyte antigen; *HSS*, hypersensitivity syndrome; *IgA*, immunoglobulin A; *IgG*, immunoglobulin G; *IL*, interleukin; *IVAB*, intravenous antibiotics, in particular ertapenem and ceftriaxone; *IVIG*, intravenous immunoglobulin; *K*, potassium; *MTX*, methotrexate; *NED*, not enough data; *NR*, not reported; *OCP*, oral contraceptive pill; *PDE4*, phosphodiesterase 4; *PDGF*, platelet-derived growth factor; *PKA*, protein kinase A; *QoL*, quality of life; *RB*, resistant bacteria; *SCC*, squamous cell carcinoma.

[¶]As defined by Guyatt G, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-926.

[#]Evidence level: Ia = metaanalysis of randomized controlled trials; Ib = randomized controlled trial; IIa = controlled study without randomization; IIb = quasiexperimental study; III = nonexperimental descriptive studies, such as comparative, correlation, and case-control studies; IV = expert committee reports or opinion or clinical experience of respected authorities, or both.

**Strength of recommendation: A = category I evidence; B = category II evidence or extrapolated from category I evidence; C = category III evidence or extrapolated from category I or II evidence; D = category IV evidence or extrapolated from category II or III evidence.

*As defined by Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations: part II: Topical, intralesional, and systemic medical management. J Am Acad Dermatol 2019;81:91-101.

[†]As defined by Scheinfeld N. Hidradenitis suppurativa: a practical review of possible medical treatments based on over 350 hidradenitis patients. Dermatol Online J 2013;19:1.

[‡]As defined by Zouboulis et al.[72]

[§]As defined by Gullive W, Zouboulis C, Prens E, Jemec GB, Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord 2016;17:343-351.

[‖]Grading criteria: A = ≥1 prospective, randomized, double-blind, controlled trial without major design flaws; B = prospective clinical trial with ≥20 subjects; C = clinical trial with <20 subjects or ≥20 cases in the literature; D = series with ≥5 subjects who responded; E = anecdotal case reports with <5 subjects.

Table II. Surgical therapies for hidradenitis suppurativa

Procedure	Severity (Hurley stage)	Advantages	Disadvantages	Evidence level, strength of recommendation*†
Surgery				
Deroofing	I or II[18,84]	• Minimally invasive • Preserves unaffected tissues[85] • Provides immediate relief[84,86]	• Does not permanently remove inflammation • High rate of recurrence and infection[84,86]	IV, D
Incision and drainage	I or II[86]	• Minimally invasive • Provides immediate relief from a tense abscess	• Cannot be performed on solid lesions[86] • High rate of recurrence and infection[84,86]	III, C
Excision with primary closure	II or III (occasionally I)[87]	• Low morbidity • Rapid wound healing • High patient satisfaction rate[88]	• Moderate recurrence rate[89] • Postoperative complications may include suture dehiscence, bleeding, and infection[88]	III, C
Excision with second intention healing	II or III (occasionally I)[87]	• No entrapment of epithelial strands or debris, as can occur after primary closure[87] • Favorable cosmetic results[90]	• Moderate recurrence rate[87]	IIb, B
Wide excision	II or III (occasionally I)[87]	• Only known treatment that can be curative[18] • Associated with the lowest rates of recurrence[84] • Early excision allows for the best chance of reduced pain and disability[84]	• Associated with greater postoperative morbitity[85]	IIb, B
Reconstruction with flap plasty	II or III (occasionally I)[87]	• Considered the best option for closing wounds if repair is indicated[18]	• Associated with greater postoperative morbitity[85]	Ia/IIa, A/B
STEEP	II or III[91]	• Spares subcutaneous fat • Low recurrence rates • Relatively short healing time[91]	• Contracture formation possible[91]	IV, D[91,92]

Laser				
Nd:YAG	I or II[93]	• Reduces the number of hair follicles and sebaceous glands in the treated areas[93] • Decreases inflammation and scarring of lesions[93,84] • May prevent new eruptions[94] • Less invasive than surgery[95]	• Many patients experience pain related to treatment • Some patients report no change in symptoms after treatment[94]	Ib, A
Intralesional laser (630-nm)	Hurley stage unclear; modified Sartorius score range 8-59[96]	• Improved effect with photosensitizers, such as methylene blue gel, psoralen bath solution, or with activation by ultraviolet A	• Increased depth of lesions make it less effective for HS compared with other skin conditions like acne[6]	NED
IPL	I or II[93]	• Decreases inflammation of lesions • Less invasive than surgery[95]	• Requires multiple treatments • Can cause erythema, irritation, or burning[97]	IV, D
CO_2	II or III[93]	• Tissue sparing ability • Heal with less disfiguring consequences compared with surgical excision[93]	• Recurrence likely • Complications include scar contracture, restricted range of motion, and delayed wound healing[84] • Limited evidence showing success[93]	Ib, A

CO_2, Carbon dioxide; *IPL*, intense pulsed light; *Nd:YAG*, neodymium-doped:yttrium aluminum garnet; *NED*, not enough data; *STEEP*, skin-tissue sparing excision with electrosurgical peeling.

*As defined by Gullive W, Zouboulis C, Prens E, Jemec GB, Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord 2016;17:343-51. Evidence level: Ia = metaanalysis of randomized controlled trials; Ib = randomized controlled trial; IIa = controlled study without randomization; IIb = quasiexperimental study; III = nonexperimental descriptive studies, such as comparative, correlation, and case-control studies; IV = expert committee reports or opinion or clinical experience of respected authorities, or both.

†As defined by Guyatt G, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6. Strength of recommendation: A = category I evidence; B = category II evidence or extrapolated from category I evidence; C = category III evidence or extrapolated from category I or II evidence; D = category IV evidence or extrapolated from category II or III evidence.

responders" who achieved a ≥25% reduction in the number of total abscesses.[30] In an open-label extension of both trials, all patients were followed for ≥96 weeks. Of the 88 patients receiving 40 mg ADA weekly, HiSCR was improved at week 36 (62.5% HiSCR) and maintained at week 168 (52.3% HiSCR).[30] Of a subset of responders and partial responders, the HiSCR rate was improved at week 36 (79.4%) and maintained by week 168 (57.1%).[30] In both the responders and partial responders, there was a clinically significant improvement in quality of life at week 72. Even if patients did not meet HiSCR at week 12, the open-label extension results suggest patients might still benefit from long-term use.[30] In October 2018, ADA was approved by the US Food and Drug Administration for the treatment of HS in patients ≥12 years of age.[31]

ADA efficacy might be related to mTORC1 signaling,[26] which is important for innate and adaptive immunity and T_H17 differentiation.[32] In a study of 13 patients given the standard HS dose of ADA, *MTOR* gene expression was significantly reduced in lesional skin at week 16.[26] mTORC1 phosphorylates the effector protein S6 kinase beta-1 (S6K1), and therefore this study also analyzed S6K1 and activated P-S6K1 protein levels. After 16 weeks, both S6K1 and P-S6K1 levels were significantly reduced in patients with HS.[26]

Infliximab is a chimeric monoclonal antibody that inhibits TNF-α by binding soluble and bound TNF-α, reducing circulating TNF-α and inducing apoptosis in cells with bound TNF-α.[15,25,29] In a phase II randomized, double-blind, crossover study, 38 patients with moderate to severe HS received 5 mg/kg of intravenous infliximab on weeks 0, 2, 4, 6, 14, and 22. By week 8, 60% of patients had a 25% to <50% decrease in HS severity compared with 5.6% of patients in the placebo group.[25] The infliximab group also demonstrated reduced inflammatory markers compared with the placebo group at week 8 as well as significant improvements in mean Dermatology Life Quality Index (DLQI) and visual analog scores.[25,27] However, "wearing off effects" occurred during the maintenance period 4 weeks after each infusion,[13] suggesting that shorter intervals between infusions might be more effective.

Etanercept is a recombinant human TNF-α receptor p75-Fc fusion protein that competitively binds membrane-bound TNF-α receptors. In a phase II open-label trial of 15 patients receiving etanercept 50 mg weekly for 12 weeks, 10 participants completed the 12-week treatment period, while 5 participants withdrew before completion. The results showed no clinically significant decrease in DLQI after treatment. Although 29% of patients reported moderate improvement in their disease, no participants had complete remission at 12 weeks.[33]

Golimumab is a human anti—TNF-α monoclonal antibody that binds to soluble and membrane-bound TNF-α. One published case describes a 51-year-old woman with severe HS, type II diabetes, and psoriatic arthritis. Initial treatment with 40 mg ADA every-other-week and 15 mg methotrexate weekly for her psoriatic arthritis had no impact on her HS. A subsequent change to anakinra 100 mg daily for 5 months flared both her HS and arthritis. A trial of golimumab 50 mg once a month for 8 months flared her HS further, though her arthritis improved.[34]

Interleukin-17 inhibitors

Secukinumab is a monoclonal antibody against interleukin-17A (IL-17A). A published case of a 47-year-old man describes patient-reported improvements in abscess and inflammatory nodule count as well as pain score, but these were not paralleled by the physician's clinical scores.[25,35] Another report of a 24-year-old woman describes an almost complete resolution of nodules at 8 weeks after secukinumab 300 mg weekly for 1 month. Throughout the treatment period, there was a continuous reduction in HSS, serum amyloid A level, white blood cell count, and C-reactive protein level.[36] Serum amyloid A is an acute-phase protein that increases significantly in response to inflammatory stimuli. The treatment-induced reduction in serum amyloid A and C-reactive protein suggests a decrease in inflammation. A single-arm, open-label, pilot study of secukinumab for patients with HS has been completed,[37] and a phase III, multicenter, randomized, double-blind, placebo-controlled study is underway.[38]

Ixekizumab is another monoclonal antibody that selectively binds IL-17A. One published case describes a 46-year-old man with HS and comorbid psoriasis and psoriatic arthritis who had a decrease in Sartorius score (54 to 16) and DLQI (20 to 3) after 4 weeks of treatment with ixekizumab (160 mg at week 0, 80 mg every-other-week for 12 weeks, then 80 mg every 4 weeks).[39] At 20 weeks, efficacy was maintained and there were no side effects.

IL-12/23 inhibitors

Ustekinumab is a monoclonal antibody against IL-12/IL-23, which function within the T_H1 and T_H17 pathways, respectively.[25] One phase II, prospective, uncontrolled, open-label study of ustekinumab treatment in 17 patients with moderate-to-severe HS suggests limited benefit.[40,41] Guselkumab is a monoclonal antibody that specifically targets IL-23. A

phase II, multicenter, randomized, placebo-controlled, double-blind, proof of concept study to evaluate guselkumab for the treatment of moderate-to-severe HS is underway.[42]

Other biologics

Anakinra is a humanized monoclonal antibody targeting the IL-1 receptor. A study of 20 patients with HS found 7 of 9 patients in the treatment group receiving 100 mg anakinra subcutaneously once daily for 12 weeks achieved HiSCR compared with 3 of 10 patients receiving placebo.[43] An open-label phase II, nonrandomized trial with 6 moderate-to-severe patients with HS demonstrated a significant reduction of Sartorius score after daily anakinra for 8 weeks.[25,44] In a double-blind, randomized, placebo-controlled trial with 20 Hurley stage II or III patients, HiSCR improved in 78% of patients in the anakinra arm compared with 30% in the placebo arm at week 12.[25,45] However, at 24 weeks, the HiSCR difference was not significant between the treatment and placebo groups.[25] A significant decrease in serum levels of interferon-gamma and an increase in IL-22 was also observed in the treatment group after 12 weeks.[43]

MABp1 is a monoclonal antibody against IL-1α. A prospective, double-blind, 1:1 randomized, placebo-controlled study in 20 moderate-to-severe patients with HS was completed.[46] All patients either failed or had a contraindication to ADA. Sixty percent of MABp1-treated patients achieved HiSCR at week 12 compared with 10% of placebo patients.[16,46] MABp1 efficacy was maintained at week 24, while there was no maintenance of efficacy in the placebo group. More than 80% (85.7%) of MABp1-treated patients reported improvement in visual analog scores versus 20% of the placebo group. In the MABp1 group, ultrasonography found decreased neovascularization and lesion depth while serum analysis demonstrated decreased circulating IL-8 and production of IL-8 by whole blood.[46]

Growing evidence suggests that multiple immunologic pathways are implicated in HS; simultaneously targeting different pathways might provide better outcomes,[47] but there is controversy regarding the safety of using multiple biologics concurrently. In rheumatoid arthritis, concomitant therapy with etanercept and anakinra resulted in more adverse events.[47] However, rheumatoid arthritis analyses may not be applicable to HS.[47] Moreover, 2 biologics have been safely and effectively used for the treatment of other diseases (eg, TNF-α and IL-12/23 therapy for psoriasis and palmoplantar pustulosis),[47-49] and anecdotal evidence suggests that this method of therapy has been successful in patients with HS.[47] Indeed, combination therapies using multiple immunosuppressive agents like ADA plus mycophenolate or methotrexate appear to provide better responses than ADA alone (authors' unpublished data).

Table III summarizes other biological therapies and new small molecules for HS.

OTHER THERAPIES

Key points

- **Ethinyloestradiol, noregestrol, and cyproterone acetate have not been effective for HS treatment, but finasteride might decrease symptoms**
- **Systemic retinoids might decrease symptoms in younger patients with HS with acne and lower body weight**
- **For mild HS, a combination of antibacterial soap, warm compresses, and sodium dusidate 2% ointment may decrease lesion size and symptoms**

Hormonal therapies

The evidence for hormonal therapy in HS is limited by small sample sizes, variable outcome measures and methods, and reporting bias.[50] The only randomized controlled, double-blinded, crossover study of hormonal therapy in HS compared 50 μg ethinyloestradiol/500 μg noregestrol on days 5 to 25 of the menstrual cycle to 50 μg ethinyloestradiol on days 5 to 25 and 50 μg cyproterone acetate on days 5 to 14 of the menstrual cycle.[51] Both groups had decreased plasma testosterone and visual analogue scales, and there was no clinically significant difference between the 2 treatments.[8,51] However, both groups had significantly decreased HS severity; 29% of patients cleared after having continuous disease for $\leq$20 years.[51]

Finasteride is a selective competitive inhibitor of type II 5α-reductase.[52,53] Case reports have reported improvement of moderate-to-severe HS within 4 weeks of finasteride treatment, but recurrences were reported after treatment cessation.[52]

Spironolactone is a potassium-sparing diuretic that has antiandrogenic properties. It blocks mineralocorticoid receptors, inhibiting androgen production, and has moderate affinity for both progesterone and androgen receptors.[54] In a small case series of patients with HS with mild-to-moderate disease, 17 of 20 patients taking spironolactone 100 to 150 mg daily showed reduced PGA after 3 months. No cases were completely cleared and only 3 were severe at baseline.[8,55] This

Table III. Other biologic therapies and new small molecules for hidradenitis suppurativa

Drug and dose (if applicable)	MOA	Study no.	Trial type	Patients, n	Disease severity	Outcome
Etanercept 50 mg SQ	Fusion protein that binds and inhibits both TNF-α and TNF-β	NCT00107991	Phase II open-label; 12 weeks	15	Moderate to severe	Failed to show a clinically significant decrease in PGA score and DLQI at 12 weeks[98]
CJM-112	Monoclonal antibody against IL-17A	NCT02421172	Phase II randomized, double-blind, placebo-controlled, multiple dose study	66	Moderate to severe	No published results[99]
Bimekizumab	Monoclonal antibody against IL-17A and IL-17F	NCT03248531	Phase II multicenter double-blind placebo-controlled trial comparing with adalimumab	157	Moderate to severe	No published results[100]
Ustekinumab 45 mg or 90 mg on weeks 0, 4, 16, and 28	Monoclonal antibody against p40 subunit of IL-12 and IL-23	NCT01704534	Phase II prospective, uncontrolled, open-label study; 40 weeks	17	Moderate to severe	Sartorius score was markedly (n = 6), moderately (n = 8), and mildly improved (n = 1), no change, or worsening (n = 2); mean Sartorius score of the whole population decreased from a baseline of 112.12 to 60.18 after 40 weeks[40]; in addition, by week 40, 8 of 17 patients achieved HiSCR-50
MEDI8968	Antibody to the IL-1 receptor	NCT01838499	Phase IIa Randomized, Double-Blind, Placebo-controlled, Multicenter Study	224	Moderate to Severe	23.6% of patients in the MEDI8968 group had improved PGA compared with 18.5% of patients in the placebo group; 43.6% of patients dropped out of the experimental group because of a lack of improvement and trial terminated early because of a lack of efficacy[16]

Bermekimab 400 mg	Monoclonal antibody against IL-1α	NCT03512275	Phase II multicenter open-label study	20	Moderate to severe	No published results[101]
Adalimumab	Human monoclonal antibody against TNF-α	PIONEER I (NCT01468207)	Phase III multicenter, double-blinded, placebo-controlled, randomized trial	307	Mild to severe	41.8% of patients receiving ADA compared with 26.0% of patients in the placebo group achieved a clinical response (P = .003)[29]
		PIONEER II (NCT01468233)	Phase III multicenter, double-blinded, placebo-controlled, randomized trial	326	Mild to severe	58.9% of patients receiving ADA compared with 27.6% of patients in the placebo group achieved a clinical response (P = .001); patients receiving ADA had significantly greater improvement in lesions, pain, and modified Sartorius score compared with the placebo group[29]
		NCT02904902	Phase III multicenter, open-label, single arm study	15	Moderate to severe	No published results[102]
		NCT02808975	Phase IV, double-blind, randomized, placebo-controlled, multicenter study	200	Moderate to severe	No published results[103]
		NCT03001115	Postmarketing cohort study	300	Severe	No published results[104]
IFX 5 mg/kg at weeks 0, 2, 6, then every 8 weeks thereafter	Chimeric monoclonal antibody against TNF- α	NCT00795574	Phase II, randomized, double-blind, placebo-controlled crossover trial	38	Moderate to severe	60% of patients treated with IFX showed a 25% to <50% improvement, 26.7% showed a ≥50% improvement, and 13.3% showed a <25% improvement in HSSI score 8 weeks after the initial dose[105]

Continued

Table III. Cont'd

Drug and dose (if applicable)	MOA	Study no.	Trial type	Patients, n	Disease severity	Outcome
Anakinra 100 mg/ 0.67 mL injected SQ once daily	Humanized monoclonal antibody against the IL-1 receptor	NCT01516749	Phase II, open-label, proof-of-concept, nonrandomized study	6	Moderate to severe	Patients showed a significant reduction of Sartorius score after anakinra was given daily for 8 weeks (P = .024)[44]
		NCT01558375	Phase II, double-blind, randomized, controlled clinical trial	20	Moderate to severe	HiSCR improved at week 12 in 78% of patients in the anakinra arm compared with 30% in the placebo arm[43]
Secukinumab 300 mg every 2 weeks or every 4 weeks	Monoclonal antibody against IL-17A	NCT03713632	Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group study	Estimated enrollment: 471	Moderate to severe	No published results[38]
Guselkumab	Monoclonal antibody against IL-23	NCT03628924	Phase II multicenter, randomized, placebo-controlled, double-blind, proof-of-concept study	Estimated enrollment: 180	Moderate to severe	No published results[42]
Apremilast	PDE4 inhibitor that blocks cAMP degradation, which drives activation of PKA. In turn, it reduces production of TNF- α, IL-12p40, and IL-17, and increases IL-10.	NCT03049267	Phase I double-blind, randomized placebo-controlled clinical trial	20	Moderate	No published results[106]
		NCT02695212 10 mg/days 1-6, 30 mg twice daily at day 6 onwards	Phase II single center open-label clinical trial	20	Moderate	No published results[107]
		N/A; no clinical trial underway	Case series	9	Moderate to severe	Significant improvement in Sartorius score in addition to decreased VAS pain score and DLQI[108]
IFX-1	Monoclonal antibody against C5a	NCT03001622	Phase II open-label clinical trial	12	Moderate to severe	No published results[109]
INCB054707	JAK inhibitor	NCT03569371	Phase II open-label, single arm study	10	Moderate to severe	No published results[110]

C5a, Complement factor 5a; *cAMP*, cyclic adenosine monophosphate; *DLQI*, Dermatology Life Quality Index; *HiSCR*, Hidradenitis Suppurativa Clinical Response; *HSSI*, Hidradenitis Suppurativa Severity Index; *IFX*, infliximab; *IL*, interleukin; *JAK*, Janus kinase; *MOA*, mechanism of action; *PDE4*, phosphodiesterase 4; *PGA*, Physician's Global Assessment; *PKA*, protein kinase A; *SQ*, subcutaneous; *TNF*, tumor necrosis factor; *VAS*, visual analog scale.

medication may benefit women who report flares associated with menses.[8]

Retinoids

Retinoids have long been used for HS despite their questionable efficacy.[13] One chart review investigated the response of 25 patients with HS (11 with Hurley stage I, 7 with stage II, and 7 with stage III) to isotretinoin, with an average dose of 0.45 mg/kg/day for 6.8 months.[56] Eight patients had no response, 8 had a partial response, and 9 had a complete response. Acne was most prevalent in complete responders and least common in nonresponders. Moreover, out of the complete responders, two-thirds of patients had Hurley stage I disease, and one third of patients had stage II.[56] Complete responders were an average of 7.5 years younger than nonresponders. Response was also better in patients who weighed less.[56] This study suggests that isotretinoin may benefit less severe patients with acne who are younger and weigh less.

Although isotretinoin is not recommended by the European Treatment Guidelines for HS, it might be helpful for patients with inflammatory, migratory, and furunculoid lesions.[57] A few studies from 1-2 decades ago found a response rate to isotretinoin in Patients with HS of about 16%.[57] A more recent review found a relatively high response rate to acitretin/etretinate among patients with HS (7 independent studies comprising a total of 32 patients demonstrated a significant response in 65.6%).[57,58] Isotretinoin appears to be ineffective for treating sinus tracts and tunnels.[59]

Antidiabetic medications

Antidiabetic drugs, specifically metformin, have garnered attention because they inhibit the proliferation of proinflammatory cytokines of human keratinocytes in vitro through an mTOR signaling pathway.[60] Metformin decreases hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake and utilization,[61,62] and it has been shown to act as an antiandrogenic agent that may influence the expression of genes involved in HS.[62]

A pilot study found metformin effective in treating recalcitrant HS.[63] In addition, 22 women and 3 men treated with metformin showed a statistically significant reduction in average Sartorius score of 7.64 at week 12 and 12.78 at week 24.[8,62] Other metformin studies in patients with HS have yielded mixed results.[13] Glucagon-like peptide-1 analogues and agonists (eg, liraglutide) have also been considered for HS treatment. Although there is less research on the efficacy of these drugs,[64] some studies suggest potential benefit.[20]

Zinc glutamate has a regulatory role in innate and adaptive immunity and may have a potential benefit in patients with HS.[13] In a small pilot study of patients with Hurley stage I and II HS, zinc glutamate was somewhat effective, but relapses occurred when the dose was reduced from 90 mg to 20 to 60 mg.[13] A combination of oral zinc gluconate and topical triclosan was evaluated for HS treatment in a retrospective study of 66 patients. After 3 months of treatment, Sartorius score and DLQI were reduced from 32.5 to 25 and 12.5 to 8, respectively.[65]

Topicals

Few studies have investigated washes for HS treatment. One prospective trial of 627 patients with Hurley stage I axillary disease tested the efficacy of a three times daily wash with antibacterial soap, warm compress for 10 minutes, and the application of topical sodium dusidate 2% ointment. Patients did not shave. Before treatment, 100% of patients reported armpit pain and 77% had itching. Complete healing was reported in 361 patients at week 2 and 114 patients at week 4.[66]

Benzoyl peroxide is an established acne treatment that is being tested for HS. One prospective 16-week multicenter, single-blinded, randomized controlled trial is comparing provodine topical cream and 10% benzoyl peroxide in 25 patients with HS. There are no published data from this trial to date.[13,67]

In conclusion, at the time of this article's submission, there were 33 HS active clinical trials (ie, not yet recruiting, recruiting, enrolling by invitation, or active but not recruiting).[68] The British Association of Dermatologists guidelines for the management of HS[69] and the North American clinical management guidelines for HS[50] have recently been updated. Although the treatment of HS remains difficult, a clearer understanding of the immunopathogenesis of this disease will likely lead to more efficacious therapies. With so many trials currently enrolling patients or doing so on the horizon,[70] practitioners will hopefully have more tools in their armamentarium supported by more rigorously derived data.

REFERENCES

1. Ingram JR, Woo PN, Chua SL, et al. Interventions for hidradenitis suppurativa. *Cochrane Database Syst Rev*. 2015; 10:CD010081.
2. Ingram JR, McPhee M. Management of hidradenitis suppurativa: a U.K. survey of current practice. *Br J Dermatol*. 2015; 173:1070-1072.
3. Jemec GB, Wendelboe P. Topical clindamycin versus systemic tetracycline in the treatment of hidradenitis suppurativa. *J Am Acad Dermatol*. 1998;39:971-974.

4. Pradhan S, Madke B, Kabra P, Singh AL. Anti-inflammatory and immunomodulatory effects of antibiotics and their use in dermatology. *Indian J Dermatol*. 2016;61:469-481.
5. van der Zee HH, Boer J, Prens EP, Jemec GBE. The effect of combined treatment with oral clindamycin and oral rifampicin in patients with hidradenitis suppurativa. *Dermatology*. 2009;219:143-147.
6. Robert E, Bodin F, Paul C, et al. Non-surgical treatments for hidradenitis suppurativa: a systematic review. *Ann Chir Plast Esthet*. 2017;62:274-294.
7. Bettoli V, Join-Lambert O, Nassif A. Antibiotic treatment of hidradenitis suppurativa. *Dermatol Clin*. 2016;34:81-89.
8. Orenstein LA, Micheletti RG. Medical management of hidradenitis suppurativa. *Semin Cutan Med Surg*. 2017;36:62-66.
9. Andersen RK, Jemec GBE. Treatments for hidradenitis suppurativa. *Clin Dermatol*. 2017;35:218-224.
10. Fischer AH, Haskin A, Okoye GA. Patterns of antimicrobial resistance in lesions of hidradenitis suppurativa. *J Am Acad Dermatol*. 2017;76:309-313.e2.
11. Scheinfeld N. Why rifampin (rifampicin) is a key component in the antibiotic treatment of hidradenitis suppurativa: a review of rifampin's effects on bacteria, bacterial biofilms, and the human immune system. *Dermatol Online J*. 2016;22.
12. Braunberger TL, Nartker NT, Nicholson CL, et al. Ertapenem - a potent treatment for clinical and quality of life improvement in patients with hidradenitis suppurativa. *Int J Dermatol*. 2018;57:1088-1093.
13. van Straalen KR, Schneider-Burrus S, Prens EP. Current and future treatment of hidradenitis suppurativa [E-pub ahead of print]. *Br J Dermatol*. https://doi.org/10.1111/bjd.16768. Accessed October 23, 2019.
14. Wong D, Walsh S, Alhusayen R. Low-dose systemic corticosteroid treatment for recalcitrant hidradenitis suppurativa. *J Am Acad Dermatol*. 2016;75:1059-1062.
15. Shanmugam VK, Zaman NM, McNish S, Hant FN. Review of current immunologic therapies for hidradenitis suppurativa. *Int J Rheumatol*. 2017;2017:8018192.
16. Theut Riis P, Thorlacius LR, Jemec GB. Investigational drugs in clinical trials for hidradenitis suppurativa. *Expert Opin Investig Drugs*. 2018;27:43-53.
17. University of North Carolina Chapel Hill. A randomized controlled trial evaluating the efficacy of intralesional triamcinolone in hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT02781818. Accessed October 23, 2019.
18. Scuderi N, Monfrecola A, Dessy LA, Fabbrocini G, Megna M, Monfrecola G. Medical and surgical treatment of hidradenitis suppurativa: a review. *Skin Appendage Disord*. 2017;3:95-110.
19. Kromann CB, Ibler KS, Kristiansen VB, Jemec GBE. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. *Acta Derm Venereol*. 2014;94:553-557.
20. Jennings L, Nestor L, Molloy O, Hughes R, Moriarty B, Kirby B. The treatment of hidradenitis suppurativa with the glucagon-like peptide-1 agonist liraglutide. *Br J Dermatol*. 2017;177:858-859.
21. Golbari NM, Lee Porter M, Kimball AB. Response to: remission of hidradenitis suppurativa after bariatric surgery. *JAAD Case Rep*. 2018;4:278-279.
22. Garg A, Papagermanos V, Midura M, Strunk A. Incidence of hidradenitis suppurativa among tobacco smokers: a population-based retrospective analysis in the U.S.A. *Br J Dermatol*. 2018;178:709-714.
23. Garg A, Besen J, Legler A, Lam CS. Factors associated with point-of-care treatment decisions for hidradenitis suppurativa. *JAMA Dermatol*. 2016;152:553-557.
24. Micheletti R. Tobacco smoking and hidradenitis suppurativa: associated disease and an important modifiable risk factor. *Br J Dermatol*. 2018;178:587-588.
25. Maarouf M, Clark AK, Lee DE, Shi VY. Targeted treatments for hidradenitis suppurativa: a review of the current literature and ongoing clinical trials. *J Dermatolog Treat*. 2018;29:441-449.
26. Balato A, Caiazzo G, Annunziata MC, et al. Anti-TNFα therapy modulates mTORC1 signalling in hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. 2019;33:e43-e45.
27. van Rappard DC, Mekkes JR, Tzellos T. Randomized controlled trials for the treatment of hidradenitis suppurativa. *Dermatol Clin*. 2016;34:69-80.
28. Kimball AB, Kerdel F, Adams D, et al. Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med*. 2012;157:846-855.
29. Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med*. 2016;375:422-434.
30. Zouboulis CC, Okun MM, Prens EP, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. *J Am Acad Dermatol*. 2019;80:60-69.e2.
31. Humira [package insert]. North Chicago, IL: AbbVie Inc.
32. De Vita V, Melnik BC. The magnitude of mTORC1 signalling may predict the response to isotretinoin treatment in patients with hidradenitis suppurativa. *Dermatology*. 2017;233:399-400.
33. Lee RA, Dommasch E, Treat J, et al. A prospective clinical trial of open-label etanercept for the treatment of hidradenitis suppurativa. *J Am Acad Dermatol*. 2009;60:565-573.
34. van der Zee HH, Prens EP. Failure of anti-interleukin-1 therapy in severe hidradenitis suppurativa: a case report. *Dermatology*. 2013;226:97-100.
35. Thorlacius L, Theut Riis P, Jemec GBE. Severe hidradenitis suppurativa responding to treatment with secukinumab: a case report. *Br J Dermatol*. 2018;179:182-185.
36. Schuch A, Fischer T, Boehner A, Biedermann T, Volz T. Successful treatment of severe recalcitrant hidradenitis suppurativa with the interleukin-17A antibody secukinumab. *Acta Derm Venereol*. 2018;98:151-152.
37. Tufts Medical Center. Exploratory trial evaluating cosentyx (secukinumab) for patients with moderate-to-severe hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT03099980. Accessed October 23, 2019.
38. Novartis Pharmaceuticals. Study of efficacy and safety of two secukinumab dose regimens in subjects with moderate to severe hidradenitis suppurativa (HS) (SUNRISE). Available at: https://clinicaltrials.gov/ct2/show/NCT03713632. Accessed October 23, 2019.
39. Odorici G, Pellacani G, Conti A. Ixekizumab in hidradenitis suppurativa: a case report in a psoriatic patient [E-pub ahead of print]. *G Ital Dermatol Venereol*. https://doi.org/10.23736/S0392-0488.18.06135-7. Accessed October 23, 2019.
40. Blok JL, Li K, Brodmerkel C, Horvátovich P, Jonkman MF, Horváth B. Ustekinumab in hidradenitis suppurativa: clinical results and a search for potential biomarkers in serum. *Br J Dermatol*. 2016;174:839-846.
41. University Medical Center Groningen. A proof of concept study to evaluate the effectiveness of ustekinumab in hidradenitis suppurativa (HiTS). Available at: https://clinicaltrials.gov/ct2/show/NCT01704534. Accessed October 23, 2019.

42. Janssen Research and Development. A study to evaluate the efficacy, safety, and tolerability of guselkumab for the treatment of participants with moderate to severe hidradenitis suppurativa (HS) (NOVA). Available at: https://clinicaltrials.gov/ct2/show/NCT03628924. Accessed October 23, 2019.
43. Tzanetakou V, Kanni T, Giatrakou S, et al. Safety and efficacy of anakinra in severe hidradenitis suppurativa: a randomized clinical trial. *JAMA Dermatol*. 2016;152:52-59.
44. University of California San Francisco. Anakinra as a treatment for hydradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT01516749. Accessed October 23, 2019.
45. University of Athens. Anakinra in hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT01558375. Accessed October 23, 2019.
46. Kanni T, Argyropoulou M, Spyridopoulos T, et al. MABp1 targeting IL-1α for moderate to severe hidradenitis suppurativa not eligible for adalimumab: a randomized study. *J Invest Dermatol*. 2018;138:795-801.
47. Naik HB, McGinness A, Shinkai K. Concurrent anticytokine biologics for the management of severe hidradenitis suppurativa: are they safe and effective? *Cutis*. 2018;101:163-164, 176.
48. Babalola O, Lakdawala N, Strober BE. Combined biologic therapy for the treatment of psoriasis and psoriatic arthritis: a case report. *JAAD Case Rep*. 2015;1:3-4.
49. Torre KM, Payette MJ. Combination biologic therapy for the treatment of severe palmoplantar pustulosis. *JAAD Case Rep*. 2017;3:240-242.
50. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations: part II: topical, intralesional, and systemic medical management. *J Am Acad Dermatol*. 2019;81:91-101.
51. Mortimer PS, Dawber RP, Gales MA, Moore RA. A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa. *Br J Dermatol*. 1986;115:263-268.
52. Khandalavala BN, Do MV. Finasteride in hidradenitis suppurativa: a ''male'' therapy for a predominantly ''female'' disease. *J Clin Aesthet Dermatol*. 2016;9:44-50.
53. Randhawa HK, Hamilton J, Pope E. Finasteride for the treatment of hidradenitis suppurativa in children and adolescents. *JAMA Dermatol*. 2013;149:732-735.
54. Karagiannidis I, Nikolakis G, Sabat R, Zouboulis CC. Hidradenitis suppurativa/acne inversa: an endocrine skin disorder? *Rev Endocr Metab Disord*. 2016;17:335-341.
55. Lee A, Fischer G. A case series of 20 women with hidradenitis suppurativa treated with spironolactone. *Australas J Dermatol*. 2015;56:192-196.
56. Huang CM, Kirchhof MG. A new perspective on isotretinoin treatment of hidradenitis suppurativa: a retrospective chart review of patient outcomes. *Dermatology*. 2017;233:120-125.
57. Boer J. Are there indications for isotretinoin treatment of hidradenitis suppurativa? *Dermatology*. 2017;233:111-112.
58. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol*. 2015;29:619-644.
59. Lipsker D, Severac F, Freysz M, et al. The ABC of hidradenitis suppurativa: a validated glossary on how to name lesions. *Dermatology*. 2016;232:137-142.
60. Liu Y, Yang F, Ma W, Sun Q. Metformin inhibits proliferation and proinflammatory cytokines of human keratinocytes in vitro via mTOR-signaling pathway. *Pharm Biol*. 2016;54:1173-1178.
61. Vilanova I, Hernández JL, Mata C, et al. Insulin resistance in hidradenitis suppurativa: a case-control study. *J Eur Acad Dermatol Venereol*. 2018;32:820-824.
62. Bubna AK. Metformin - for the dermatologist. *Indian J Pharmacol*. 2016;48:4-10.
63. Verdolini R, Clayton N, Smith A, Alwash N, Mannello B. Metformin for the treatment of hidradenitis suppurativa: a little help along the way. *J Eur Acad Dermatol Venereol*. 2013;27:1101-1108.
64. Emtestam L, Sartorius K. Interleukin-36 cytokine family signalling in hidradenitis suppurativa. *Br J Dermatol*. 2018;178:591-592.
65. Hessam S, Sand M, Meier NM, Gambichler T, Scholl L, Bechara FG. Combination of oral zinc gluconate and topical triclosan: an anti-inflammatory treatment modality for initial hidradenitis suppurativa. *J Dermatol Sci*. 2016;84:197-202.
66. Shirah BH, Shirah HA. Effective modified conservative tissue preserving protocol to treat stage I axillary hidradenitis suppurativa: a prospective cohort study of 627 patients with five years follow-up. *J Dermatolog Treat*. 2017;28:458-463.
67. Henry Ford Health System. An investigation into the efficacy of provodine topical cream as compared to 10% benzoyl peroxide wash for the treatment of hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT01818167. Accessed October 23, 2019.
68. clinicaltrials.gov. website. Available at: https://clinicaltrials.gov/ct2/results?cond=Hidradenitis+Suppurativa&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=. Accessed October 23, 2019.
69. Ingram JR, Collier F, Brown D, et al. British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. *Br J Dermatol*. 2019;180:1009-1017.
70. U.S. National Library of Medicine. Hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/results?cond=Hidradenitis+Suppurativa&term=&cntry=&state=&city=&dist=. Accessed February 12, 2019.
71. Hambly R, Kirby B. Prolonged clindamycin and rifampicin for hidradenitis suppurativa: resist to prevent resistance. *Br J Dermatol*. 2019;180:702-703.
72. Zouboulis CC, Bechara FG, Dickinson-Blok JL, et al. Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization - systematic review and recommendations from the HS ALLIANCE working group. *J Eur Acad Dermatol Venereol*. 2019;33:19-31.
73. Scheinfeld N. Hidradenitis suppurativa: a practical review of possible medical treatments based on over 350 hidradenitis patients. *Dermatol Online J*. 2013;19:1.
74. Deckers IE, Prens EP. An update on medical treatment options for hidradenitis suppurativa. *Drugs*. 2016;76:215-229.
75. Melnik BC, John SM, Chen W, Plewig G. T helper 17 cell/regulatory T-cell imbalance in hidradenitis suppurativa/acne inversa: the link to hair follicle dissection, obesity, smoking and autoimmune comorbidities. *Br J Dermatol*. 2018;179:260-272.
76. University of Pittsburgh. Hydroxychloroquine for the treatment of hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT03275870. Accessed October 23, 2019.
77. Golbari NM, Porter ML, Kimball AB. Antiandrogen therapy with spironolactone for the treatment of hidradenitis suppurativa. *J Am Acad Dermatol*. 2019;80:114-119.

78. Massachusetts General Hospital. A study to examine the safety and efficacy of drospirenone and ethinyl estradiol (YAZ) versus placebo in HS. Available at: https://clinicaltrials.gov/ct2/show/NCT00722800. Accessed October 23, 2019.
79. Ingram JR, Woo PN, Chua SL, et al. Interventions for hidradenitis suppurativa: a Cochrane systematic review incorporating GRADE assessment of evidence quality. *Br J Dermatol*. 2016;174:970-978.
80. Khoo ABS, Burova EP. Hidradenitis suppurativa treated with Clostridium botulinum toxin A. *Clin Exp Dermatol*. 2014;39:749-750.
81. Shi W, Schultz S, Strouse A, Gater DR. Successful treatment of stage III hidradenitis suppurativa with botulinum toxin A. *BMJ Case Rep*. 2019;12:e226064.
82. Goo B, Chung HJ, Chung WG, Chung KY. Intramuscular immunoglobulin for recalcitrant suppurative diseases of the skin: a retrospective review of 63 cases. *Br J Dermatol*. 2007;157:563-568.
83. Sharon-Guidetti A, Ziv Y, Kummer E, Yogev R, Halevy A. Granulocyte-macrophage colony-stimulating factor for perianal hidradenitis suppurativa: report of a case. *Dis Colon Rectum*. 2006;49:682-684.
84. Smith MK, Nicholson CL, Parks-Miller A, Hamzavi IH. Hidradenitis suppurativa: an update on connecting the tracts. *F1000Res*. 2017;6:1272.
85. Scholl L, Hessam S, Bergmann U, Bechara FG. Surgical treatment of sinus tracts and fistulas in perianal hidradenitis suppurativa. *J Cutan Med Surg*. 2018;22:239-241.
86. Janse I, Bieniek A, Horváth B, Matusiak Ł. Surgical procedures in hidradenitis suppurativa. *Dermatol Clin*. 2016;34:97-109.
87. Deckers IE, Dahi Y, van der Zee HH, Prens EP. Hidradenitis suppurativa treated with wide excision and second intention healing: a meaningful local cure rate after 253 procedures. *J Eur Acad Dermatol Venereol*. 2018;32:459-462.
88. van Rappard DC, Mooij JE, Mekkes JR. Mild to moderate hidradenitis suppurativa treated with local excision and primary closure. *J Eur Acad Dermatol Venereol*. 2012;26:898-902.
89. Mehdizadeh A, Hazen PG, Bechara FG, et al. Recurrence of hidradenitis suppurativa after surgical management: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2015;73(5 suppl 1):S70-S77.
90. Bieniek A, Matusiak Ł, Chlebicka I, Szepietowski JC. Secondary intention healing in skin surgery: our own experience and expanded indications in hidradenitis suppurativa, rhinophyma and non-melanoma skin cancers. *J Eur Acad Dermatol Venereol*. 2013;27:1015-1021.
91. Blok JL, Spoo JR, Leeman FWJ, Jonkman MF, Horváth B. Skin-tissue-sparing excision with electrosurgical peeling (STEEP): a surgical treatment option for severe hidradenitis suppurativa Hurley stage II/III. *J Eur Acad Dermatol Venereol*. 2015;29:379-382.
92. Blok JL, Boersma M, Terra JB, et al. Surgery under general anaesthesia in severe hidradenitis suppurativa: a study of 363 primary operations in 113 patients. *J Eur Acad Dermatol Venereol*. 2015;29:1590-1597.
93. John H, Manoloudakis N, Stephen Sinclair J. A systematic review of the use of lasers for the treatment of hidradenitis suppurativa. *J Plast Reconstr Aesthet Surg*. 2016;69:1374-1381.
94. Mahmoud BH, Tierney E, Hexsel CL, Pui J, Ozog DM, Hamzavi IH. Prospective controlled clinical and histopathologic study of hidradenitis suppurativa treated with the long-pulsed neodymium:yttrium-aluminium-garnet laser. *J Am Acad Dermatol*. 2010;62:637-645.
95. Negus D, Ahn C, Huang W. An update on the pathogenesis of hidradenitis suppurativa: implications for therapy. *Expert Rev Clin Immunol*. 2018;14:275-283.
96. Valladares-Narganes LM, Rodríguez-Prieto MA, Blanco-Suárez MD, Rodriguez-Lage C, García-Doval I. Treatment of hidradenitis suppurativa with intralesional photodynamic therapy using a laser diode attached to an optical cable: a promising new approach. *Br J Dermatol*. 2015;172:1136-1139.
97. Theut Riis P, Saunte DM, Sigsgaard V, Wilken C, Jemec GBE. Intense pulsed light treatment for patients with hidradenitis suppurativa: beware treatment with resorcinol. *J Dermatolog Treat*. 2018;29:385-387.
98. University of Pennsylvania. Etanercept for treatment of hidradenitis. Available at: https://clinicaltrials.gov/ct2/show/NCT00107991. Accessed October 23, 2019.
99. Novartis Pharmaceuticals. Efficacy, safety, and pharmacokinetics study of CJM112 in hidradenitis suppurativa patients. Available at: https://clinicaltrials.gov/ct2/show/NCT02421172. Accessed October 23, 2019.
100. UCB Pharma. A study to test the efficacy, safety and pharmacokinetics of bimekizumab in subjects with moderate to severe hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT03248531. Accessed October 23, 2019.
101. XBiotech Inc. A study of bermekimab in patients with hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT03512275. Accessed October 23, 2019.
102. AbbVie. Open-label study of adalimumab in Japanese subjects with hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT02904902. Accessed October 23, 2019.
103. AbbVie. Safety and efficacy of Humira (Adalimumab) for hidradenitis suppurativa (HS) peri-surgically (SHARPS Study) (SHARPS). Available at: https://clinicaltrials.gov/ct2/show/NCT02808975. Accessed October 23, 2019.
104. AbbVie. Post-marketing surveillance of adalimumab in Korean hidradenitis suppurativa subjects (HS rPMS). Available at: https://clinicaltrials.gov/ct2/show/NCT03001115. Accessed October 23, 2019.
105. Grant A, Gonzalez T, Montgomery MO, Cardenas V, Kerdel FA. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol*. 2010;62:205-217.
106. Erasmus Medical Center. Short-term Safety, efficacy and mode of action of apremilast in moderate suppurative hidradenitis (SMASH). Available at: https://clinicaltrials.gov/ct2/show/NCT03049267. Accessed October 23, 2019.
107. Florida Academic Dermatology Centers. Single center study of apremilast for the treatment of hidradenitis suppurativa (HS). Available at: https://clinicaltrials.gov/ct2/show/NCT02695212. Accessed October 23, 2019.
108. Weber P, Seyed Jafari SM, Yawalkar N, Hunger RE. Apremilast in the treatment of moderate to severe hidradenitis suppurativa: a case series of 9 patients. *J Am Acad Dermatol*. 2017;76:1189-1191.
109. InflaRx GmbH. Studying complement inhibition in patients with moderate to severe hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT03001622. Accessed October 23, 2019.
110. Incyte Corporation. A study of the safety of INCB054707 in participants with hidradenitis suppurativa. Available at: https://clinicaltrials.gov/ct2/show/NCT03569371. Accessed October 23, 2019.