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Hidradenitis Suppurativa: A Review with a Focus on Treatment Data

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic disease of the follicular unit that often leads to marked impairment of quality of life and usually affects the axillary, perineum and inframammary regions resulting in tender subcutaneous nodules, abscesses, fibrosis and sinus tract formation. New updates on HS underscores the role of various genes as well as the innate and adaptive immune response in its pathogenesis. Although every patient requires an individualized approach to treatment, topical therapy and antibiotics are mainly used for mild to moderate disease, whereas various systemic immune modulators and/or surgical approaches play a pivotal role in moderate to severe disease. New treatments using various immune modulators, laser modalities and other novel agents provide clinicians with better ways of managing HS.

Key words: hidradenitis suppurativa, antibiotics, biologics, immune modulators, lasers, surgery

Introduction

Hidradenitis suppurativa (HS) is a chronic disease of the follicular unit that results in significant impairments to quality of life and increases emergency room visits and inpatient hospitalizations.[1-3] It most commonly occurs in the axillary, inguinal, and anogenital regions in post-pubertal females.[3] HS may result in sinus tract formation and severe scarring, and is difficult to treat, with many patients never achieving complete clearance of lesions. Ongoing research and new insights into pathogenesis and treatment will hopefully improve the management of HS patients.

Epidemiology

Prevalence of HS is a matter of debate, with estimates ranging from 0.052% to 1% of the population, likely reflecting differences in research methodology and populations studied.[1,3-12] A recent population-based study in Olmsted County, Minnesota, found an overall annual age- and sex-adjusted incidence of 6 per 100,000, supporting that HS is an uncommon diagnosis.[7] Incidence appears significantly higher in women, particularly in those aged 18 to 44 years. HS may occur more commonly in certain races, but this is still unclear.[13]

A review of 846 Dutch patients identified that male sex, disease duration, obesity, pack-year smoking, and lesions in axillary, perianal, and mammary regions are significant factors for more severe disease.[8]

About one-third of HS patients report a family history of the disease, and families with an autosomal dominant mode of inheritance have been identified.[14] There may be a strong association between HS and Crohn's disease - in a recent patient questionnaire of 1,093 patients with inflammatory bowel disease, 23% of patient responded to having signs and symptoms of HS.[15] Other diseases that may occur concomitantly include acne conglobata, dissecting cellulitis, pilonidal cysts, spondyloarthritis, pyoderma gangrenosum, and synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome.[4,16,17]

Hypertension, metabolic syndrome, depression, anxiety, obesity and smoking are important co-morbidities among HS patients.[1,18-20] Furthermore, smoking and obesity are not only predictive of disease severity but are also correlated with lower rates of disease remission.[20,21]

Pathogenesis

The pathogenesis of HS is complex. Although it was previously believed to be a disorder of apocrine glands, HS is now thought of as a disorder of follicular occlusion. Whether immune dysregulation precedes or follows follicular occlusion remains to be determined, but it is evident that both play a role.[22-36]

Of note, recent data demonstrates that many familial cases of HS show mutations in gamma secretase, a protease that cleaves intramembrane receptors and regulates follicular keratinization,

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elucidating further the role of follicular occlusion in the disorder.[37-40]

Both innate and adaptive immune dysregulation has been demonstrated via decreased expression of epithelial-derived antimicrobial peptides (such as ribonuclease, human beta-defensin 3 and toll like receptor 4), which may result in excessive inflammatory response, as well as overexpression of pro-inflammatory cytokines (e.g., interleukin (IL)-1, IL-10, tumor necrosis factor (TNF)-alpha, IL-17, IL-22) in HS lesions.[22-24,26-28,33] Additional factors that contribute to HS include bacterial biofilms, abnormal secretion of apocrine glands, abnormal invaginations of the epidermis leading to sinus tract formation, and deficient numbers of sebaceous glands.[35,41-44] Hyperandrogenism and/or vitamin D deficiency may be involved, although their role is unclear at this time.[45,46]

Clinical Features

HS is characterized by recurrent inflammatory nodules, cysts, abscesses and sinus tracts in apocrine gland-bearing sites such as the axilla, groin, perianal and/or inframammary areas.[47] The lesions are frequently accompanied by chronic drainage. The clinical presentation of HS is highly variable in terms of cutaneous features, distribution, presence of complications (fistula formation, lymphedema, scrotal elephantiasis), extracutaneous features (arthritis, interstitial keratitis) and associated constitutional symptoms (i.e., fever and malaise).[47]

HS affecting the anogenital region may be difficult to differentiate from Crohn's disease, especially given the strong association between the two disorders and that they can both present clinically as fistulas and sinuses, and histologically as granulomas.[48]

Since HS is a chronic inflammatory disease, anemia and hypoproteinemia may develop. Furthermore, HS lesions can form fistulae to the rectum, vagina, urethra, peritoneum and/or bladder. Reactive arthritis and SAPHO syndrome has been described in HS patients.[49] Additionally, aggressive squamous cell carcinoma may form in areas of chronic scarring and carry a morbid prognosis.[50]

HS can be staged by either the Hurley staging system (Table 1) or the newer Sartorius system (Table 2). The Hurley system is more clinically applicable while the Sartorius system is used primarily for research.[51]

Search for biomarkers that help diagnose HS and/or correlate its severity have been undertaken. Analogous to Sartorius clinical staging, these tests remain largely for research use, since diagnosis is generally achievable via clinical findings and disease location.[52-55]

Stage	Clinical presentation
I	Abscess formation, single or multiple, without sinus tract and scarring
II	One or more widely separated recurrent abscesses with sinus tracts and scarring
III	Multiple interconnected tracts and abscesses throughout an entire area

Table 1: Hurley staging of HS

The Sartorius Hidradenitis Suppurativa Score	
Anatomic region involved (3 points per region)	Axilla Groin Genital Gluteal Inframammary Other inflammatory region
Number and score of lesions	2 points for each nodule 4 points for each fistula 1 point for each scar 1 point each for "other"
Longest distance between 2 relevant lesions	Less than 5 cm (2 points) Less than 10 cm (4 points) More than 10 cm (8 points)
Lesions clearly separated by normal skin in each region	Yes (0 points) No (6 points)

Table 2: The Sartorius Hidradenitis Suppurativa Score is comprised of counting involved regions, nodules and sinus tracts

Treatment

Treatment of HS varies widely depending on disease severity, with many treatments supported by weak scientific evidence. Topical, systemic, and surgical therapies are available and are often used in combination. The authors list their treatment ladder in Table 3. Non-pharmacologic therapies include avoidance of tight-fitting clothing, reassurance, smoking cessation, management of underlying depression and anxiety, support group referral, and weight loss.

Pain is a common problem expressed by HS patients and must be addressed.[56] Given the chronicity of HS, opioid dependence is a significant concern. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are good initial therapies,[57] while pregabalin, gabapentin, selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) may be considered as second-line agents.[58]

Antibiotics

Both topical and systemic antibiotics have been widely used for patients with HS. A randomized controlled study of 30 patients treated with topical clindamycin 1% solution found the clindamycin group did significantly better than the placebo group at 3 months.[59] In another randomized trial, Jemec et al. suggested that topical clindamycin has similar efficacy to systemic tetracycline (500 mg twice daily for 3 months).[60]

Tetracyclines are often used for mild to moderate HS, although published data (in the form of trials) regarding their efficacy is limited. We commonly prescribe doxycycline 100 mg orally once to twice daily for our HS patients, and may taper down after several months based on patient response and tolerance.[58] Two prospective trials that looked at combination treatment with systemic rifampin and clindamycin suggest this treatment might be beneficial.[61,62] However, another series reported a large proportion of patients needed to discontinue this regimen due to gastrointestinal side effects.[63]

Hidradenitis Suppurativa Treatments by Hurley Stage		
Hurley Stage I to II	Topical, injectable and intralesional	• Topical antibiotics (e.g., clindamycin 1%) • Intralesional corticosteroids • Topical resorcinol • Botulinum toxin
	Oral options	• Oral antibiotics (e.g., tetracycline agents, rifampin + clindamycin, dapsone) • Hormonal therapies (e.g., oral contraceptive pills, finasteride, spironolactone) • Metformin
	Surgical and physical options	• Less invasive surgical approaches • Laser therapy (e.g., Nd:YAG, carbon dioxide) • Cryotherapy/cryoinsufflation • Photodynamic therapy
Hurley Stage II to III	(includes Stage I to II approaches)	• More invasive surgical approaches (e.g., wide radical excision) • Systemic retinoids (e.g., acitretin) • Systemic immunosuppressants • Biological treatments (e.g., adalimumab, infliximab, ustekinumab, anakinra)
All Stages	• Weight loss • Pain control (via topical and/or oral treatments) • Smoking cessation • Zinc supplementation • Antimicrobial wash (e.g., chlorhexidine, benzoyl peroxide)	

Table 3: Treatment summary for HS by Hurley Stage

Dapsone is considered relatively ineffective for HS. A study of 24 patients treated with dapsone reported improvement in 9 (38%), while 15 (62%) did not experience any improvement.[64]

Although data supporting their efficacy is limited, antimicrobial cleansers such as chlorhexidine and benzoyl peroxide are often applied daily to affected areas.[43,57,65]

Hormonal Therapy

Anti-androgens such as spironolactone and cyproterone acetate, as well as oral contraceptives, may be considered in female patients who have a history of hormonal abnormalities or are not responding to conventional treatment(s).[66,67] A randomized controlled trial of 18 female patients who received either daily ethinyloestradiol 50 mg/norgestrel 500 mg or ethinyloestradiol 50 mg/cyproterone acetate 50 mg for 6 months demonstrated improvement in 5 patients, no change in 4, and worsening in 2.[66]

Finasteride has been suggested as another treatment option in HS. A series of 3 pediatric patients receiving finasteride for HS showed marked reduction in the amount and severity of flares.[68] A similar trial of 7 patients showed complete healing of lesions in 3 patients and reduction in suppuration and inflammation in the remaining 4 patients.[69]

Biologics

Tumor Necrosis Factor-Alpha (TNF-α) Inhibitors

Biologic agents are increasingly utilized in the management of moderate to severe HS (Table 3). Among TNF-α inhibitors, infliximab is one of the better studied medications. A randomized double-blind, placebo-controlled trial, in which 38 subjects received infliximab (5 mg/kg) infusions at 0, 2 and 6 weeks compared to placebo, showed that 60% of patients in the infliximab group compared to 5.6% of patients in the placebo group achieved 25-50% decrease in their severity scores at 8 weeks.[70] A long-term study of 10 patients who received infliximab every 8 weeks after an initial loading regimen found 2 patients (20%) had no response to treatment after five doses and 5 (50%) patients experienced disease recurrence after a median treatment period of 37 weeks.[71] Another prospective cohort trial with more frequent dosing (every 4 weeks) found that 9 of 11 patients (mean follow-up of 60.3 months) had measurable improvement after undergoing treatment. Two patients failed treatment at 12 and 19 months.[65]

Adalimumab, unlike infliximab, is self-administered by the patient.[72,73] In a double-blind, randomized, controlled trial, 15 patients received adalimumab 80 mg subcutaneously (SC) at baseline followed by 40 mg SC every other week for 12 weeks. A significantly better reduction in Sartorius score was seen at 12 weeks in the treatment group compared to placebo.[74] A recent large multicenter study demonstrated that weekly dosing of adalimumab achieved better clinical outcomes than bi-monthly dosing.[75]

Etanercept is considered inefficacious for HS. A double-blind, placebo-controlled study of 20 patients in which etanercept 50 mg was administered twice weekly for 3 months, followed by open-label etanercept 50 mg twice weekly for an additional 3 months found no significant difference in outcomes between groups.[76]

Other Biologics

Ustekinumab, an IL-12/IL-23 antibody, may also be efficacious for moderate to severe HS. In a small prospective trial, 3 patients received three 45 mg SC injections at 0, 1 and 4 months. At 6 months, 1 patient had remission of disease, the second patient improved, and the third had no response.[77]

Most recently, 5 patients receiving anakinra, an antibody directed against IL-1, showed mean decrease in modified Sartorius score of 34.8 points.[78] A report of the related agent, canakinumab, also demonstrated good response.[79]

Immunosuppressants

Cyclosporine has been used in severe HS recalcitrant to other therapies, though data is scant and mostly case reports.[80] Two case reports suggest that prednisone may be used in those patients who have concomitant pyoderma gangrenosum or arthritis.[81,82] Methotrexate is of limited value in the management of HS.[83]

In our experience, intralesional triamcinolone at concentrations ranging from 5 mg/cc to 10 mg/cc can help with acutely inflamed nodules and cysts, as well as with scar formation. It is important to be confident that these are not injected into infectious abscesses prior to administration.[58]

Retinoids

Isotretinoin has demonstrated mixed results for the management of HS. In a retrospective trial of 68 patients, only 48 actually completed the trial (29.4% dropped out due to side effects and/or lack of efficacy). Sixteen patients (23.5%) had clearance of lesions, 14 patients (20.6%) had marked improvement, 11 (16.2%) patients improved, and 7 (10.3%) experienced no change in their disease.[84] A later retrospective report with 88 patients found that only 14 patients (16.1%) noted improvement, 67 patients (77%) had no change, and 6 patients (6.9%) experienced disease worsening.[85]

Many providers feel acitretin is more effective than isotretinoin in the treatment of HS, probably based upon initially favorable reports. Boer et al. found in their retrospective trial of 12 patients that 10 had marked improvement or complete disease resolution and the remaining 2 improved from baseline. However, Mutasiak et al. reported less favorable results in a prospective trial of 17 patients. Eight patients exhibited a 50% reduction in HS severity index. However, 8 patients (47%) dropped out of the study due to lack of efficacy or adverse effects.[86]

Alitretinoin has a similar pharmacologic mechanism to acitretin, but a much shorter half-life and, thus, may carry a lower teratogenic risk. In one trial, 14 female patients of childbearing age received alitretinoin (10 mg daily) for 24 weeks with significant improvement in Sartorius and Dermatology Life Quality Index (DLQI) scores recorded in 78.5% of cases.[87]

Surgery

Surgery is frequently performed to control moderate and severe HS. The type of surgery depends on the severity and location of the disease and can be limited or extensive.[88] In one trial, 73 patients underwent a deroofing procedure (in which the roof of a lesion is surgically removed and the floor of the lesion is left exposed to heal by second intention) and were followed for a median of 34 months; 83% of patients showed no recurrence.[89]

A study comparing recurrence rates of HS after incision and drainage (limited excision and wide radical excision) found that all cases recurred (median time = 3 months), 42.8% recurred in the local excision (median time = 11 months), and 27% recurred in the wide excision group (median time = 20 months).[90]

Alharabi et al. conducted a retrospective analysis of 50 operative procedures for 32 patients who underwent wide surgical excision. Twenty six patients (81.25%) showed no recurrence after surgery.[91]

Lasers and Lights

Various laser and light treatments, alone or in combination with surgery and/or systemic therapy, have been suggested in the management of HS. Photodynamic therapy (PDT) has been reported several times. The range of results have been described as good[92-94] to mediocre[95,96] in terms of efficacy. In general, evidence regarding PDT for HS is of such limited or poor quality that meaningful conclusions are not ascertainable.

Bath psoralen + ultraviolet A (PUVA) was undertaken in a retrospective trial with 13 patients receiving bath PUVA twice weekly. Five patients had clearance or near clearance of their lesions, 4 patients had moderate clearance, and 4 had minimal to no response. Among the 5 patients in which clearance or near clearance was documented, the response was sustained for at least a 3-month follow-up period.[97]

Long-pulsed neodymium:yttrium-aluminum-garnet laser (Nd:YAG) has demonstrated promising results in a randomized trial. Mahmoud et al. enrolled 22 subjects who received monthly Nd:YAG laser sessions for 4 months and reported a 72.7% mean improvement on the laser-treated side compared to 22.9% on the control side.[98] A subsequent trial of 19 patients showed a mean 31.6% reduction in Lesion Area and Severity Index (LASI) over all anatomic sites 2 months following treatment.[99]

Intense pulse light has also been used. In a prospective trial, 18 patients were randomized to treatment on one side of the axillae, groin, or inframammary region two times per week for 4 weeks. There was significant reduction in Sartorius score of 55% after completion of treatment compared to 10% on the untreated side. Patients maintained a 33% reduction in their Sartorius score compared to 3% on the untreated side at 12 months.[100]

Lastly, several studies show that carbon dioxide (CO2) laser ablation is an efficacious treatment in HS.[101-103] In a trial by Hazen et al., all (61) patients who underwent CO2 laser ablation followed by marsupialization had clearance of treated areas. Of note, 17 patients (28%) experienced postsurgical hypertrophic granulation tissue appearing approximately 5 weeks after surgery.[104]

Other Treatments

Cryoinsufflation

Cryoinsufflation, a modified spray cryotherapy performed by injecting liquid nitrogen through a needle directly into HS tracts, has been recently described. Results are restricted to a single patient experience.[105]

Botulinum Toxin

One case report of a patient with moderate HS who underwent four treatments of 50 units of botulinum toxin type A (100 units

Biologics	Author and Trial Design	N	Dose/Frequency	Follow-up from Treatment Initiation	Result
Adalimumab	Miller et al. (2011), double-blind randomized controlled trial	15	Adalimumab 80 mg SC at baseline followed by 40 mg SC EOW	12 weeks	Reduction in Sartorius score of 10.7 points at 6 weeks and 11.3 points at 12 weeks was seen in the treatment group compared to 7.5 points and 5.8 points in the placebo group, respectively
	Kimball et al. (2012), phase 2, parallel, randomized, placebo-controlled trial consisting of a blinded 16-week period (period 1) and an open-label 36-week period (period 2)	154	Adalimumab, 40 mg/wk; adalimumab, 40 mg EOW; or placebo. All patients received adalimumab, 40 mg EOW, at the beginning of period 2 but switched to weekly dosing if the response was suboptimal at weeks 28 or 31	16 weeks	At week 16, 3.9% of patients receiving placebo (2 of 51), 9.6% of patients receiving adalimumab EOW (5 of 52), and 17.6% of patients treated weekly (9 of 51) achieved minimal or mild HS-PGA score by week 16
Infliximab	Paradela et al. (2012), prospective trial	10	Infliximab 5mg/kg every 8 weeks after initial standard loading dose	37 weeks	2 patients (20%) had no response to treatment after 5 doses; 5 (50%) patients experienced disease recurrence
	Grant et al. (2010), randomized double-blind placebo-controlled crossover trial	38	Infliximab 5mg/kg infusions at 0, 2 and 6	8 weeks	60% of patients in the infliximab group compared to 5.6% of patients in the placebo group achieved 25%-50% decrease in in their severity scores
	Moriarty et al. (2014), prospective cohort trial	11	Infliximab 5mg/kg infusion every 4 weeks after initial standard loading dose	60.3 months	9 patients had measurable improvement after undergoing treatment; 2 had treatment failure at 12 and 19 months
Ustekinumab	Gulliver (2012), prospective cohort trial	3	Ustekinumab 45 mg SC injections at 0, 1 and 4 months	6 months	1 patient had remission of disease, the second patient improved, and the third had no response
Etanercept	Adams et al. (2010), double-blind, placebo-controlled study	20	Etanercept 50 mg SC was administered twice weekly for 3 months, followed by open-label etanercept 50 mg SC, twice weekly for an additional 3 months	6 months	No statistically significant difference among PGA, patient global assessment, and DLQI at 12 or 24 weeks between treatment and placebo groups
Anakinra	Leslie (2014), prospective cohort	5	Anakinra 100 mg SC daily	8 weeks	Mean decrease in modified Sartorius score of 34.8 points

Table 4: Summary of trials for biologics used in HS
N = number of patients, SC = subcutaneous, DLQI = dermatologic quality of life Index, PGA = physician global assessment, EOW = every other week dosing

dissolved in 4 mL of 0.9% sodium chloride solution) injected to each axilla (administered over 3 years) achieved lesion clearance following the second treatment (6 months) with maintenance of remission 1 year after completion of treatment.[106]

Zinc

A study of 22 patients with mild to moderate HS receiving zinc gluconate (90 mg/day) for at least 6 months (with a mean follow-up of 23.7 months) demonstrated a positive response in all patients with complete remission in 8 and partial remission in 14 patients.[107]

Metformin

Eighteen of 25 (72%) patients who received metformin (500 mg daily to 500 mg three times daily) had a mean reduction in their Sartorius sore of 12.7 at 24 weeks of treatment. Seven patients had no response.[108]

Conclusion

HS is associated with significant morbidity and health care costs. Many treatments are available to meet the needs of these patients, though more data is warranted to determine optimal management algorithms. Care needs to be individualized to each patient's situation and preferences, with a strong emphasis on improving quality of life and management of related comorbidities.

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Ivermectin 1% Cream for Rosacea

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ABSTRACT

The etiology of papulopustular rosacea (PPR) is not well understood yet appears to involve both the innate and adaptive immune response in addition to possible infestation with Demodex *mites. Current treatments for PPR consist mainly of antibiotics. Ivermectin cream 1%, a new topical treatment for PPR, possesses both anti-inflammatory and anti-parasitic properties. After 12 weeks of treatment, subjects treated with ivermectin cream 1% had significantly greater reductions in PPR symptoms and enhanced disease-related quality of life improvements compared to subjects who received vehicle. Furthermore, PPR symptoms continued to improve with prolonged treatment (40 weeks). Ivermectin cream 1% offers a multi-pronged approach to combat the complex pathophysiology of rosacea.*

Key words: anti-parasitic, avermectin, Demodex, erythema, inflammation, insecticide, papulopustular rosacea, Rosiver®, Soolantra®, topical ivermectin

Introduction

Rosacea is a chronic inflammatory condition affecting the central facial skin of the cheeks, nose, chin and forehead. Rosacea typically affects females approximately 30 years of age and increases in severity throughout the lifespan.[1] The exact cause of rosacea is unknown and its pathogenesis is not well understood.[2,3] Innate and adaptive immune responses, vascular abnormalities, dermal microorganism imbalances, and environmental factors may interact to produce chronic inflammation and the development of fibrosis.[2] Four subtypes of rosacea have been identified: 1) erythematotelangiectatic rosacea, 2) papulopustular rosacea (PPR), 3) phymatous rosacea, and 4) ocular rosacea[2]; yet, whether these represent a distinct variation or a continuum of disease severity remains a matter of debate.[2] PPR, previously known as acne rosacea, is characterized by erythema, telangiectasia, papules, pustules, edema, and sometimes pain, stinging or burning.[4] Patients report that symptoms are a cause of low self-esteem, as they are a source of shame, embarrassment, and physical discomfort.[5] Treatment is strongly encouraged to moderate the detrimental effect on patient quality of life (QoL) and to prevent the condition from worsening. Few therapeutic alternatives exist for the treatment of PPR. There is some evidence supporting the efficacy of azelaic acid, topical metronidazole and sub-antimicrobial dose doxycycline in the treatment of moderate to severe rosacea, although it remains unclear which agent is most effective.[6]

Ivermectin is derived from avermectin, a class of broad-spectrum anti-parasitic agents isolated from the fermentation of *Streptomyces avermitilis*.[7] Ivermectin possesses both anti-parasitic and anti-inflammatory properties and has been shown to reduce the number of *Demodex* mites in demodicidosis and blepharitis and to inhibit the production of lipopolysaccharide inflammatory cytokines, such as tumor necrosis factor-alpha and interlukin (IL)-1b, while upregulating the production of the anti-inflammatory cytokine IL-10.[8] Because PPR is recognized as an inflammatory condition whose pathogenesis may involve parasitic infestation with *Demodex* mites, vehicle-controlled and active comparator trials were undertaken to evaluate the efficacy and safety of topical ivermectin 1% cream in the treatment of PPR.

Pivotal Phase 3 Studies

Two pivotal phase 3 trials assessed the efficacy and safety of ivermectin cream 1% for moderate to severe PPR.[9] These trials were part of a larger study comprised of a second long-term active comparator trial[10] and a 4 week follow-up safety study. The pivotal phase 3 studies were identically designed multicenter, randomized, double-blind, vehicle-controlled trials that enrolled participants aged 18 years or older with moderate to severe PPR and 15-70 inflammatory facial lesions.[9] Subjects were randomized in a 2:1 ratio to receive either ivermectin 1% cream or vehicle cream for 12 weeks. Participants were instructed to apply their respective cream to the face once daily at bedtime while avoiding the upper and lower eyelids and lips. Participants were also asked to avoid known rosacea triggers, such as specific foods and environments, whenever possible. Evaluations occurred at baseline and at weeks 2, 4, 8 and 12. Co-primary efficacy outcomes for this study included the percentage of participants who achieved an Investigator Global Assessment (IGA) of "clear" or "almost clear" and mean change in inflammatory lesion counts between groups at week 12. Other efficacy outcomes were percent change in inflammatory lesion counts from baseline, subjective assessment of rosacea improvement, and QoL scores on the Dermatology Life Questionnaire Index (DLQI) and the Rosacea Quality of Life Index (RosaQoL™). Adverse events (AEs) and laboratory parameters (hematology and blood chemistry) were also monitored.

Study 1 enrolled 683 participants and Study 2 enrolled 688 participants, the majority of whom were female (Study 1: 68.2%

	Study 1		Study 2	
	Ivermectin 1% cream (n=451)	Vehicle (n=232)	Ivermectin 1% cream (n=459)	Vehicle (n=229)
IGA 'clear' or 'almost clear'	38.4%†	11.6%	40.1%†	18.8%
Reduction in inflammatory lesion count from baseline	76.0%†	50.0%	75.0%†	50.0%
Subjective rosacea improvement 'excellent' or 'good'	69.0%†	38.6%	66.2%†	34.4%

Table 1: Efficacy endpoints for the pivotal phase 3 trials of ivermectin 1% cream vs. vehicle
IGA = Investigator global assessment; †P<0.001

and Study 2: 66.7%) and approximately 50 years of age on average. Participants in Study 1 had an average of 30.9 lesions, while subjects in Study 2 had an average 32.9 inflammatory lesions at baseline. The proportion of participants with an IGA of 'severe' was 18% and 24.1% in Studies 1 and 2, respectively. There were no differences in DLQI scores between treatment groups at baseline.

Efficacy results are presented in Table 1. In both studies, a significantly higher percentage of participants who received ivermectin 1% had an IGA of 'clear' or 'almost clear' at week 12 compared to vehicle (P<0.001) and the significant difference between active and control arms was noted at week 4 (10.9% and 11.8% vs. 5.6% and 5.7%, respectively; P<0.05 for both). The mean difference in inflammatory lesion counts between ivermectin 1% and vehicle from baseline to week 12 was -8.13 and -8.22 for Studies 1 and 2, respectively (ivermectin 1% vs. vehicle, both P<0.001). There was also a significant difference in the median reduction in lesion count from baseline between the ivermectin 1% and vehicle groups (both studies P<0.001) observed as early as week 2. In both studies, a significantly higher proportion of participants who received ivermectin 1% cream reported improvement of their rosacea symptoms as 'excellent' or 'good' compared to participants who received vehicle (P<0.001). QoL scores also improved in the ivermectin 1% groups compared to vehicle at the end of 12 weeks. In both studies, a significantly greater proportion of participants in the ivermectin 1% group (approximately 53%) than the vehicle group (approximately 35%) considered their rosacea had no effect on their QoL (P<0.001). Improvement in RosaQoL scores was also significantly higher for ivermectin 1% compared to vehicle (-0.64 ± 0.7 and -0.60 ± 0.6 vs. -0.35 ± 0.5 in both vehicle groups; P=0.001 for Studies 1 and 2).

For Studies 1 and 2, no serious treatment-related AEs were reported in either the ivermectin 1% cream or vehicle groups. Burning (1.8% for ivermectin 1% cream and 2.6% for vehicle) was the most commonly reported treatment-related AE in Study 1, while pruritus and dry skin were the most commonly reported treatment-related AEs in Study 2 (pruritus: 0.7% vs. 0% and dry skin: 0.7% vs. 0.9% for ivermectin 1% cream vs. vehicle). Furthermore, treatment-related AEs with active drug were less than with vehicle alone. Laboratory tests showed no clinically significant abnormalities.

Ivermectin 1% Cream vs. Azelaic Acid 15% Gel

Ivermectin 1% cream was then evaluated against azelaic acid 15% gel in a 40 week extension study.[10] In this continuation of the pivotal phase 3 trials, participants with PPR originally assigned to ivermectin 1% cream once daily in the 12-week study continued to be treated as such and participants initially randomized to vehicle were switched to azelaic acid 15% gel twice daily for 40 weeks. Efficacy was assessed at 4 week intervals using the IGA. Safety assessments were comprised of documentation of AEs, tolerability signs and symptoms, and laboratory tests.

Six hundred and twenty-two and 683 participants enrolled in the 40-week extension studies (see previous section for participant demographics). The efficacy of ivermectin 1% cream increased over time as IGA scores of 'clear' and 'almost clear' increased from 38.4% to 71.1% by the end of Study 1 and from 40.1% to 76% by the end of Study 2; 59.4% and 57.9% of participants who received azelaic acid had an IGA of 'clear' or 'almost clear' by the end of Studies 1 and 2, respectively. No statistical comparisons were made because of the differing treatments lengths between the ivermectin 1% and azelaic acid 15% groups. Furthermore, because the ivermectin group had already been treated with ivermectin for 3 months, while the azaleic acid group had previously received vehicle, baseline factors may not have been comparable between groups.

The incidence of treatment-related AEs in the ivermectin 1% cream and azelaic acid 15% gel groups was 1.9% vs. 6.7% and 2.1% vs. 5.8% in Studies 1 and 2, respectively. No severe or serious AEs were deemed related to ivermectin 1% cream in Studies 1 or 2 and no serious AEs were considered related to azelaic acid 15% gel in either study; however, 1 severe case of skin irritation was considered related to azelaic acid in Study 2. In Study 1, 4 participants in the azelaic acid group and 5 in the ivermectin group discontinued the study as a result of AEs. In Study 2, 5 participants in the azelaic acid group and 3 in the ivermectin group discontinued the study due to AEs. None of the AEs in either study were considered related to ivermectin 1% cream; however, in the azaleic acid group, 3 AEs in Study 1 and 4 AEs in Study 2 were considered related to azaleic acid (Study 1: skin irritation, eye and skin irritation, and skin pain and burning; Study 2: skin irritation, skin burning, skin discomfort, and skin burning and pruritus).

Ivermectin 1% Cream vs. Metronidazole 0.75% Cream

Another phase 3, investigator-blinded, randomized trial conducted in Europe explored the efficacy and safety of ivermectin 1% cream compared to metronidazole 0.75% cream for the treatment of moderate to severe PPR (Table 2).[1] Nine-hundred and sixty-two participants age 18 years or older with

moderate or severe PPR and presenting with 15-70 facial lesions were randomized 1:1 to receive either ivermectin 1% cream (n=478) once daily or metronidazole 0.75% gel (n=484) twice daily for 16 weeks. Treatments were applied to the entire face, avoiding the upper and lower eyelids and lips. Participants were also asked to avoid known rosacea triggers. Study visits were at baseline and at weeks 3, 6, 9, 12 and 16. Efficacy endpoints included inflammatory lesion counts, the IGA, participants' subjective evaluation of rosacea improvement, and the DLQI. The safety evaluation consisted of AE assessments over the course of the study, as well as local tolerance and laboratory parameters.

	Ivermectin 1% cream (n=478)	Metronidazole 0.75% cream (n=484)
IGA 'clear' or 'almost clear'	84.9%†	75.4%
Reduction in inflammatory lesion count from baseline	83.0%†	73.7%

Table 2: Efficacy endpoints for the phase 3 trial of ivermectin 1% cream vs. metronidazole 0.75% cream
IGA = Investigator global assessment; †P<0.001

At baseline, the majority of participants had moderate rosacea (16.7% severe) with an average 32.5 inflammatory lesions. Participants had a mean age of 52 years and were primarily female (65.2%). In terms of efficacy at week 16, ivermectin was significantly more effective than metronidazole 0.75% cream in reducing the percentage of inflammatory lesions (83% vs. 73.7%; P<0.001) with a significant difference between the two treatments observed at week 3. The IGA of disease severity was also significantly better for ivermectin 1% cream compared to metronidazole 0.75%, with 84.9% of the ivermectin 1% cream and 75.4% of the metronidazole 0.75% cream groups rated as 'clear' or 'almost clear' at week 16 (P<0.001), with the greatest difference in IGA noted at week 12. Approximately 86% of the ivermectin group rated their global improvement as 'excellent' or 'good' compared to 74.8% in the metronidazole 0.75% group. Although the DLQI scores were similar between treatment groups at baseline (6.93 and 6.05 for ivermectin and metronidazole, respectively), participants treated with ivermectin 1% cream showed a greater improvement in QoL as indicated by a reduction in their DLQI scores (-5.18 vs. -3.92; P<0.01).

A similarly low proportion of participants experienced a treatment-related AE (1.9% in the ivermectin 1% cream group and 2.5% in the metronidazole 0.75% group). The most common treatment-related AE was skin irritation experienced by 3 and 4 participants in the ivermectin 1% cream and metronidazole 0.75% cream groups, respectively. Three participants in the ivermectin 1% cream group discontinued the study because of skin irritation and hypersensitivity, while 10 participants in the metronidazole 0.75% cream group discontinued the study due to skin irritation, allergic dermatitis, aggravation of rosacea, erythema, pruritus and feeling hot. Worsening of local tolerance parameters from baseline was more pronounced in the metronidazole 0.75% group than the ivermectin 1% cream group for stinging/burning (15.5% vs. 11.1%), dryness (12.8% vs. 10%), and itching (11.4% vs. 8.8%). No clinically significant abnormalities in laboratory parameters were found.

Discussion

Ivermectin 1% cream is markedly more effective than vehicle in reducing inflammatory lesions of rosacea as it results in a significant reduction in lesion counts after only 2 weeks of treatment and produces substantially greater improvements in IGA ratings of 'clear' or 'almost clear' as early as week 4.[9] The efficacy of ivermectin 1% cream increases with prolonged treatment as evidenced in the 40 week trials.[10] Also, when compared to the standard treatment for PPR, metronidazole 0.75% cream, topical ivermectin was markedly superior to metronidazole in terms of reducing inflammatory lesions and IGA ratings.[1] Ivermectin 1% cream had a significantly greater positive impact on patient QoL compared to vehicle or metronidazole 0.75%.[1,9] Ivermectin 1% cream was well-tolerated and demonstrated a favorable safety profile across phase 3 studies, with skin irritation being the most common treatment-related AE.

In phase 3 trials, ivermectin 1% cream produced greater objective and subjective outcomes and improvements in disease-specific QoL over vehicle and an active comparator. Topical ivermectin represents a novel approach to the treatment of PPR that appears to confer superior efficacy and tolerability as compared to current treatment options, while offering the added convenience of once daily dosing. Since ivermectin possesses both anti-parasitic and anti-inflammatory properties, its effectiveness in treating PPR may be attributed to its ability to combat several pathogenic factors linked to the condition. Further studies are needed to elucidate the contribution of the anti-parasitic versus the anti-inflammatory modes of action of ivermectin.

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Update on Drugs

Name/Company	Approval Dates/Comments
Deoxycholic acid injection *Kybella*™ Kythera Biopharmaceuticals	The US FDA approved this first-in-class adipolytic agent in April 2014 for treating adults with moderate to severe submental (under the chin) fat. Treatment of fat outside of the submental area is not approved and not recommended. Deoxycholic acid (ATX-101) is an injectable treatment for the reduction of submental fullness, which commonly presents as a double chin. ATX-101 is a cytolytic drug identical to the deoxycholic acid that is produced in the body, which helps the body to absorb fats. When properly injected into the submental region, the drug destroys fat cells; however, it can also destroy other types of cells. Patients may receive up to 50 injections in a single treatment, with up to six single treatments administered no less than 1 month apart.
Ivermectin 1% cream *Rosiver*® Galderma Canada Inc.	Health Canada approved ivermectin 1% cream in April 2015 for the once daily topical treatment of inflammatory lesions, or bumps and pimples, of rosacea. The exact cause of rosacea is unknown, but multiple triggers have been implicated, including the over-proliferation of *Demodex* mites in the skin. Ivermectin has both anti-inflammatory and antiparasitic activity. FDA approval was gained in December 2014 and is marketed in the US under the trade name Soolantra®.
Adalimumab SC injection *Humira*® AbbVie Inc.	The FDA has granted adalimumab, a TNF-α inhibitor, Orphan Drug Designation in May 2015 for the investigational treatment of moderate to severe hidradenitis suppurativa (acne inversa, HS) (Hurley Stage II and Hurley Stage III disease). The etiology of HS is not well understood, but both dysregulation of the inflammatory cascade in the hair follicle and wound healing have been implicated. The anti-inflammatory effects of TNF-α inhibition are believed to influence the pathogenic mechanisms in HS.
Apremilast tablets *Otezla*® Celgene Corporation	In June 2015, Health Canada approved an expanded indication for apremilast, an oral phosphodiesterase-4 inhibitor, which was initially approved in November 2014 for treating patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. The new indication is for the treatment of patients with psoriatic arthritis.
Dermal filler with calcium hydroxylapatite (CaHA) *Radiesse*® Merz North America	The FDA approved this dermal filler in June 2015 for hand augmentation to correct volume loss in the dorsum of the hands. Treatment provides an immediate volumizing effect and can help to reduce the prominence of tendons and veins in the hands, with results lasting up to 1 year.

In Memoriam

Our hearts are heavy with the passing of our founder and 20-year Editor-in-Chief, W. Stuart Maddin, on May 21, 2015. The life of Stuart Maddin is a singular example of a great leader, visionary, innovator, and mentor. Those fortunate enough to have been touched by his unflagging spirit will continue to draw inspiration from his wisdom and tenacity. As an ambassador for dermatology, his global reach in this special discipline spanned over 60 years, and his legacy is beyond measure and compare.

Passing the Torch

Starting in June 2015, *Skin Therapy Letter* will be guided by our new Editor-in-Chief, D. Richard Thomas, MD, who will take over from Stuart Maddin. The staff and Editorial Board are both pleased to have such an excellent individual taking the reins to serve the dermatologic community in this role.