New developments in the treatment of rosacea – role of once-daily ivermectin cream

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Abstract: Rosacea is a chronic dermatological disorder with a variety of clinical manifestations localized largely to the central face. The unclear etiology of rosacea fosters therapeutic difficulty; however, subtle clinical improvement with pharmacologic treatments of various drug categories suggests a multifactorial etiology of the disease. Factors that may contribute to disease pathogenesis include immune abnormality, vascular abnormality, neurogenic dysregulation, presence of cutaneous microorganisms, UV damage, and skin barrier dysfunction. The role of ivermectin in the treatment of rosacea may be as an anti-inflammatory and anti-parasitic agent targeting Demodex mites. In comparing topical ivermectin and metronidazole, ivermectin was more effective; this treatment modality boasted more improved quality of life, reduced lesion counts, and more favorable participant and physician assessment of disease severity. Patients who received ivermectin 1% cream had an acceptable safety profile. Ivermectin is efficacious in decreasing inflammatory lesion counts and erythema.

Keywords: papulopustular rosacea, topical ivermectin, metronidazole, azelaic acid, topical

Introduction
The unclear etiology of rosacea poses significant therapeutic difficulty. Several medications have been utilized in the treatment of rosacea; however, many of them do not yield adequate and persistent improvement. Variability in rosacea assessment methodologies has made comparison of treatment options more difficult. A standardized and reliable assessment tool is necessary to assess the adequacy of novel treatment options in the management of rosacea.¹ Several exacerbating factors have been identified per patient report; however, no real standard has been ascertained. Response to medications with various mechanisms of action suggests a multifactorial etiology of the disease. Topical ivermectin has emerged as a viable treatment option, which is likely to be beneficial due to its activity as an anti-inflammatory and anti-parasitic agent targeting Demodex mites which may be colonizing the pilosebaceous units of patients with the disease.²³

Background
Rosacea is a chronic dermatological disorder characterized by a variety of clinical manifestations localized to the central face. Four subtypes exist, including erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea. The main features of erythematotelangiectatic rosacea are persistent telangiectasias and redness of the central face. Papulopustular rosacea is characterized by inflammatory papules and pustules involving the central face. In addition to the inflammatory papules and pustules that are
characteristic of this subtype, patients with papulopustular rosacea may also experience the facial erythema and telangiectasias, which are typical of erythematotelangiectatic rosacea. The phymatous subtype is characterized by the thickening of the skin and bulbous facial features. Ocular rosacea, which may occur in the absence of cutaneous manifestations, is the rarest of the subtypes and involves eye symptoms such as redness and irritation. Rosacea is commonly observed in individuals with Fitzpatrick skin types 1 and 2; though the disease may be seen in individuals of darker skin types, the prevalence is far lower. Females over the age of 30 are most commonly affected, though the disease may also occur in younger age groups and males. Many individuals with rosacea do not receive adequate treatment due to lack of awareness, misdiagnosis, and noncompliance with prescribed medications.

The pathogenesis of rosacea is poorly understood. Contributing factors may include immune abnormality, vascular abnormality, neurogenic dysregulation, presence of cutaneous microorganisms, ultraviolet (UV) damage, and skin barrier dysfunction. An aberrant innate immune response may lead to chronic facial inflammation and vascular abnormalities in rosacea patients through increased production of toll-like receptor 2 and matrix metalloproteinases, which facilitate the activation of cytokines and cathelicidin peptides. This hypothesis is supported by evidence of increased baseline expression of cathelicidin and kalikrein 5 (KLK5) in patients with rosacea. Two subfamilies within the transient receptor potential family of cation channels – vanilloid and ankyrin receptors – have activity in patients with rosacea. When activated by some of the commonly identified rosacea patient triggers, including heat, capsacin, and inflammatory states, these receptors mediate sensory and inflammatory signaling processes that manifest as flushing and burning associated with rosacea. Papulopustular rosacea is a type-1 T-helper cell-mediated process with the involvement of macrophages and mast cells. Upregulation of interleukin (IL)-8 messenger RNA results in the recruitment of neutrophils manifesting clinically as inflammatory pustules.

The presence of cutaneous microorganisms has been suggested as a factor provoking cutaneous inflammation. In 35%–50% of rosacea patients, the Demodex folliculorum mite load is significantly increased at the site of disease. However, this association is controversial because unaffected individuals may also be colonized by Demodex mites. In patients with papulopustular rosacea, the Demodex density tends to be higher than that of control patients with healthy skin. The mite causes a cutaneous barrier disruption by eroding the epithelium. This in turn leads to a skin hypersensitivity that is reversible when the Demodex mite density is reduced with pharmacological agents. Biopsy characteristics in a patient colonized by Demodex tend to include a dense lymphocytic infiltrate around the follicle. It is this inflammatory response that facilitates the mite’s ability to traverse the epidermis and destroy the pilosebaceous unit. Ultimately, this breach stimulates an exaggerated immune response that induces the papules and pustules characteristic of papulopustular rosacea.

Staphylococcus epidermidis, Helicobacter pylori, and Bacillus oleronius may play a role in disease development and persistence. The non-hemolytic S. epidermidis is part of normal skin flora. However, in patients with papulopustular rosacea, the isolates were found to be beta hemolytic and thus more likely to produce virulence factors that stimulate the immune system. It is controversial whether there is a higher prevalence of H. pylori seropositivity in patients with rosacea. B. oleronius, which was isolated from a Demodex mite from an individual with papulopustular rosacea, happens to be sensitive to antibiotics commonly used to treat rosacea. This finding may suggest a role of this bacterium in rosacea pathogenesis. The distribution of rosacea in sun-exposed areas and the reported exacerbation of disease with sun exposure have inspired the theory that ultraviolet radiation may also be a contributing factor. Ultraviolet radiation increases reactive oxygen species that in turn stimulates inflammatory cytokines such as KLK 5 and cathelicidin. Patients with erythematotelangiectatic and papulopustular rosacea subtypes have increased transepidermal water loss and increased reactivity to the lactic acid stinging test demonstrating impaired skin barrier function.

Oral medications, topical medications, and light-based treatments have utility in rosacea therapy. Oral antibiotics with anti-inflammatory activity, including doxycycline, tetracycline, and minocycline, have had tremendous utility in the realm of rosacea therapy. Each of these medications has dose- and concentration-dependent antimicrobial activity; however, the anti-inflammatory activity of these medications occurs at lower doses than that which is required for antibacterial effect. This is advantageous because the therapeutic benefit of these sub-antimicrobial dose tetracyclines in the treatment of rosacea, an inflammatory skin condition, can be achieved without the risk of promoting the emergence of antibiotic-resistant bacteria. Isotretinoin may also be used off-label and in low doses to treat rosacea.

Topical rosacea therapies include metronidazole, azelaic acid, sodium sulfacetamide, erythromycin, oxymetazoline, calcineurin inhibitors such as pimecrolimus and tacrolimus,
Topical anti-parasitic agents like ivermectin 1% cream have therapeutic benefit most likely owing to their activity against *Demodex* mites. Ivermectin is a macrocyclic lactone with broad-spectrum activity against multiple parasitic organisms, including onchocerciasis, strongyloidiasis, pediculosis, and scabies. Similarly, ivermectin eradicates *Demodex* mites that reside in the pilosebaceous units of patients with papulopustular rosacea. The anti-inflammatory effects of ivermectin are achieved through decreasing neutrophil phagocytosis and chemotaxis, inhibiting inflammatory cytokines such as IL-1β and TNF-alpha, and upregulating the anti-inflammatory cytokine IL-10. It is presumed that these are the mechanisms by which ivermectin exerts its therapeutic effect in rosacea patients. Ivermectin is metabolized hepatically by CYP3A4 and has a half-life elimination of approximately 6.5 days. Peak serum concentration is achieved at approximately 10 hours post-application. Ivermectin is categorized as Pregnancy Category C, but teratogenic effects involving the drug were observed in animal reproduction following administration of the oral drug formulation. Systemic absorption of the drug is significantly lower with use of the topical formulation as directed.

**Results**

**Clinical studies**

The results of two identical 12-week duration, Phase III, randomized, double-blinded studies showed superior efficacy and comparable safety of ivermectin 1% cream applied once daily as compared to vehicle control in the treatment of papulopustular rosacea. The Investigator’s Global Assessment of Rosacea Severity (IGA-RS) was used as the efficacy assessment parameter. The achievement of IGA success, defined by the study as “clear” or “almost clear” rosacea severity grades, was 38.4% and 40.1% for study 1 and study 2, respectively, with the use of ivermectin 1% compared to 11.6% and 18.8% for study 1 and study 2, respectively, with the use of the vehicle control. Safety of the ivermectin 1% cream was assessed by incidence of adverse events. The incidence of adverse events with the use of ivermectin 1% cream versus the use of the vehicle control was comparable in studies 1 and 2. For ivermectin 1%, the incidence of adverse events in studies 1 and 2 was 40.5% and 36.5%, respectively. For the vehicle control, the incidence of adverse events in studies 1 and 2 was 39.4% and 36.5%, respectively. In a 40-week, investigator-blinded, active controlled extension of the aforementioned studies 1 and 2, subjects who initially received ivermectin 1% cream once daily continued this regimen while subjects who initially received the vehicle...
### Table 1 Clinical studies and case reports

| Study reference | Patient characteristics | Number of participants | Medication regimen | Study design | Study duration | Findings |
|-----------------|-------------------------|------------------------|--------------------|--------------|----------------|----------|
| Stein et al<sup>3</sup> | Subjects >18-year-old males and females; moderate to severe PPR based on IGA; 15–70 facial inflammatory lesions | Study 1 – 683 Study 2 – 688 | IVM 1% cream once daily vs vehicle cream once daily | Two multicenter studies of identical design (study 1 and study 2), randomized, double-blinded, parallel, vehicle controlled | 12 weeks | IGA success rate ivM 1% cream Study 1 – 38.4% Study 2 – 40.1% VC Study 1 – 11.6% Study 2 – 18.8% Adverse events incidence ivM 1% cream Study 1 – 40.5% Study 2 – 36.5% VC Study 1 – 39.4% Study 2 – 36.5% ivM 1% cream showed increased efficacy in study 1 and study 2 IGA success rate ivM 1% cream Study 1 – increased from 38.4% to 71.1% during study duration Study 2 – increased from 40.1% to 76.0% during study duration Adverse events ivM 1% cream Majority who received this treatment in both study 1 and study 2 denied treatment-associated stinging, burning, dryness, or itching AzA 15% gel More patients who received this treatment in both study 1 and study 2 reported treatment-associated stinging, burning, dryness, or itching |
| Stein Gold et al<sup>31</sup> | Subjects >18-year-old males and females; moderate to severe PPR based on IGA; 15–70 facial inflammatory lesions | Study 1 – 622 Study 2 – 636 | IVM 1% cream once daily vs AzA 15% gel BID | Extension of the above study; initial IVM 1% cream groups continued IVM regimen; initial vehicle cream control group switched to AzA 15% gel twice daily | 40 weeks | Percentage reduction of inflammatory lesions IVM 1% cream 83.0% MTZ 0.75% cream 73.7% IGA success rates IVM 1% cream 84.9% MTZ 0.75% cream 75.4% Safety profile Comparable between IVM 1% cream and MTZ 0.75% cream. Skin irritation was the most common adverse event |
| Taieb et al<sup>32</sup> | Subjects >18-year-old males and females; moderate to severe PPR | 960 | IVM 1% cream once daily vs MTZ 0.75% cream twice daily | Investigator-blinded, randomized, parallel group study | 16 weeks | Clinical improvement observed at 1-month follow-up |
| de Macedo et al<sup>35</sup> | 41-year-old female; gnatophyma (phymatous rosacea affecting chin) × 2 years | 1 | Single dose, oral IVM 12 mg, TCN 1 g/d, MTZ 1% cream | Case report | N/A | (Continued) |
Table 1 (Continued)

| Study reference | Patient characteristics | Number of participants | Medication regimen | Study design | Study duration | Findings |
|-----------------|-------------------------|------------------------|--------------------|--------------|----------------|---------|
| Brown et al13    | 12-year-old female; Demodex folliculorum–associated severe recalcitrant oculocutaneous rosacea | I | Single dose, oral IVM 12 mg (250 μg/kg) | Case report | N/A | Marked improvement in cutaneous symptoms at 1-month follow-up with progressive resolution without additional treatments. Ocular symptom resolution. No recurrence at 2-year follow-up |
| Allen et al14    | 68-year-old male; recalcitrant PPR × 6 years, rosacea-like demodicosis | I | Oral IVM 3mg daily × 8 days, permethrin cream 3 times weekly × 2 weeks (continued for 3 months for maintenance) | Case report | N/A | Marked clinical improvement |
| Forstinger et al19 | 32-year-old male; rosacea-like demodicidosis × 4 years, refractory to conventional treatment | I | Single dose, oral IVM 200 μg/kg, subsequent weekly topical permethrin cream | Case report | N/A | Reduction of pruritus within 2 weeks, reduction of inflammation within 4 weeks |
| Guerrero-Gonzalez et al10 | 7-year-old female; crusted, rosacea-like demodicosis | I | Oral IVM 200 μg/kg weekly for 10 doses, permethrin 5% lotion, 30 mg/kg oral erythromycin divided into three doses (then continued for 2 months), metronidazole cream | Case report | N/A | Clinical resolution after 3 months of treatment |

Abbreviations: AzA, azelaic acid; IVM, ivermectin; vC, vehicle control; MTZ, metronidazole; TCN, tetracycline; IGA, Investigator’s Global Assessment of Rosacea Severity; PPR, papulopustular rosacea; BiD, twice daily; N/A, not applicable.

Ivermectin, both oral and topical, has been effective in treating rosacea of various subtypes. In particular, a case of recalcitrant oculocutaneous rosacea in an immunocompetent patient with Demodex folliculorum colonization...
achieved resolution with a single dose of oral ivermectin. An individual with recalcitrant papulopustular rosacea and evidence of numerous Demodex organisms on histologic examination benefited from oral ivermectin and topical permethrin cream. Gnatophyma, a rare variant of phymatous rosacea involving the chin, was treated with oral ivermectin, oral tetracycline, and metronidazole cream with satisfactory results (Table 1).

Patient-focused perspectives
Stein et al reported that in studies 1 and 2 after treatment with ivermectin 1% cream, 34% and 32.0% of subjects, respectively, rated their improvement as “excellent”. Only 9.5% and 7.3% of the subjects treated with the vehicle control in studies 1 and 2, respectively, reported “excellent” improvement. Taieb et al showed that 85.5% of subjects in the ivermectin 1% treatment arm versus 74.8% of subjects in the metronidazole 0.75% treatment arm reported “excellent” or “good” global improvement in their rosacea. Patients in the ivermectin 1% cream group had a higher reduction in their Dermatology Quality of Life Index (DLQI) score than the metronidazole 0.75% cream group, meaning subjects in the ivermectin 1% cream group had a greater improvement in quality of life.

Conclusion
Rosacea poses a therapeutic challenge owing to its likely multifactorial pathogenesis. Rosacea patients tend to be more sensitive to topical treatments and may experience skin irritation with use; noncompliance with the treatment regimen may occur as a result. Despite being a topical treatment, ivermectin cream has a relatively low side effect profile. In comparing ivermectin cream and metronidazole cream, ivermectin was more effective; this treatment modality boasted more improved quality of life, reduced lesion counts, and more favorable participant and physician assessment of disease severity.

Disclosure
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