

Rosacea: An Update on Medical Therapies

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ABSTRACT

Rosacea is a common, chronic cutaneous condition that affects the face. Two topicals and one oral medication are currently approved for the treatment of rosacea, including azelaic acid, metronidazole, and sub-antimicrobial dose of doxycycline. Identification of subtypes can help guide treatment strategies. It is essential for psychosocial implications of rosacea to be considered and conservative management, such as nonpharmacologic routine skin care, must form an important part of the overall care. Recently, new insights into the pathophysiology of rosacea have led to the emergence of etiologically oriented treatments. Ivermectin, an acaricidal agent that has been shown to be effective against rosacea refractory to other therapies, is currently in Phase 3 trials. Brimonidine, which was US FDA approved last year and recently sanctioned by Health Canada, has filled an essential therapeutic void in the targeted treatment of diffuse facial erythema.

Key words: alpha-2 adrenergic receptor agonists, anti-bacterial agents, antiparasitic agent, erythema, inflammation, rosacea, telangiectasia

Introduction

Rosacea is a common chronic cutaneous condition that primarily affects the central facial area, including the cheeks, nose, eyes, chin, and forehead.¹ Primary cutaneous manifestations include sensitive skin, flushing, persistent erythema, papules, pustules, and telangiectases. Although symptoms may wax and wane in the short-term, rosacea is slowly progressive in the long-term for many patients.²

The National Rosacea Society has classified rosacea into four main subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular.³ Progression from one subtype to another is possible.⁴ Proper identification of subtypes may help guide therapeutic strategies.

Rosacea affects up to 10% of the general population and onset is typically between the ages of 30 and 50 years.⁵ It is especially common in light-skinned individuals of Northern European descent,⁶ with women more frequently affected,⁵ but men are more prone to develop thickening and distorting phymatous skin changes, especially of the nose. Although infrequent, some cases have been diagnosed in darker skin types; however, underdiagnosis and low reported incidence may be attributable to sampling bias and decreased visibility of clinical signs (e.g., erythema and telangiectasias).⁷

The pathophysiology is multifactorial and currently not fully understood. Multiple factors have been proposed to play a role, including vascular abnormalities, gastrointestinal disorders, matrix degeneration, pilosebaceous gland abnormalities,

microbial activity, and altered innate immune response.^{8,9} A new understanding of rosacea pathogenesis is emerging and alongside it the development of novel agents that target specific pathogenic factors and the symptoms they induce.

Rosacea can create psychosocial burdens, such as embarrassment, anxiety, and low self-esteem that adversely affect quality of life. These negative impacts should be taken into consideration when treating rosacea patients.^{10,11} Conservative measures, such as trigger avoidance, proper skin care, and the use of camouflaging cosmetics and photoprotection should also be incorporated in the management plan.¹²

Conventional Therapies

Topical Metronidazole

Metronidazole was first shown to be an effective treatment against rosacea in the 1980s.¹³ Despite being an antibacterial and antiprotozoal agent, metronidazole's therapeutic benefits in rosacea are mostly derived through its anti-inflammatory and antioxidant effects.¹⁴ Multiple trials have demonstrated that topical metronidazole significantly decreases the number of inflammatory lesions and reduces erythema compared to placebo, is generally well tolerated, has a low incidence of adverse effects, and is effective in maintaining remission.¹⁵⁻¹⁸ Importantly, different formulations of metronidazole have been demonstrated to have similar efficacy, regardless of vehicle type (cream, gel, or lotion) or concentration (0.75% or 1%).¹⁹⁻²¹ Once-daily dosing was also confirmed to be similarly effective as twice-daily application.^{19,22} In addition, when combined with a sun protection

factor 15 sunscreen, metronidazole may reduce the development of facial telangiectasia.²³ Of note, topical metronidazole is a pregnancy category B medication.

Topical Azelaic Acid

Azelaic acid is a naturally occurring dicarboxylic acid approved in the last decade for the treatment of mild to moderate rosacea.²⁴ Mostly applied as a 15% gel or a 20% cream, azelaic acid can attribute its efficacy to anti-inflammatory, anti-keratinizing, and antibacterial effects.²⁴ Multiple trials have demonstrated that azelaic acid is more effective than placebo at reducing the number of inflammatory lesions and degree of erythema.²⁵⁻²⁷ The pooled rates of patients showing marked improvements with azelaic acid treatment were 70-80%, compared with 50-55% in the placebo group.²⁸ Azelaic acid also has a relatively low incidence of adverse effects, with burning, stinging, and irritation being the most commonly reported.²⁶ The incidence of side effects is greater with azelaic acid compared with metronidazole, but these effects are generally mild and transient.²⁹ Although the conventional regimen is twice-daily application of azelaic acid, once-daily dosing has been found to be equally effective.³⁰ Further studies are needed to support the use of azelaic acid as a maintenance therapy.²⁸ It is listed as a pregnancy B category medication.

Tetracyclines

Off-label use of oral antibiotics has been recognized for more than 50 years as an effective treatment for rosacea. Therapeutic benefits of tetracyclines in rosacea are primarily a consequence of their anti-inflammatory rather than antibacterial mechanisms, as there is insufficient evidence to support a bacterial infection in disease pathogenesis.³¹ Tetracycline-family antibiotics should particularly be considered in the presence of ocular rosacea, which typically affects greater than 50% of patients with rosacea. Tetracyclines, which are contraindicated in pregnant women, are the most frequently used class of antibiotics and are most effective against inflammatory papules and pustules.

Second-generation tetracyclines, including minocycline and in particular doxycycline, are especially safe and effective oral therapies for rosacea. Unlike the parent tetracycline, they have greater bioavailability,³² rapid onset of action, and can be taken with food, which minimizes gastrointestinal side effects. Additionally, second-generation tetracyclines only require once-daily dosing, which may improve compliance. Most importantly, they are effective at a sub-antimicrobial dose, thereby avoiding disruption of the endogenous flora and, of global importance, the propagation of antibacterial resistance.³³

Recently, two Phase 3, multicenter, randomized, double-blinded, placebo-controlled clinical trials³³ demonstrated that a sub-antimicrobial dose of 40 mg doxycycline administered daily to patients with moderate to severe rosacea significantly reduced total inflammatory papule and pustule counts compared with placebo after 16 weeks of treatment, with significant improvements observed at 3 weeks. Prevalence of adverse effects was low and only marginally higher than placebo, with nasopharyngitis (4.8%), diarrhea (4.4%), and headaches (4.4%) being the most commonly reported. There were no cases of photosensitivity or vaginal candidiasis. A separate study demonstrated that the efficacy of 40 mg doxycycline is comparable to that of 100 mg doxycycline in rosacea.³⁴ Sub-

antimicrobial dose of 40 mg doxycycline is approved in both US and Canada for the treatment of rosacea. In contrast, minocycline is not approved for this indication and has five times greater rates of adverse effects compared with doxycycline, with the most commonly reported being hyperpigmentation, hepatotoxicity, and drug-induced lupus.³⁵

Further study is needed to investigate the effectiveness of combination therapy with sub-antimicrobial dose of doxycycline and topical metronidazole, which has been shown in a small-scale study to induce a faster onset of action and be more effective at clearing inflammatory lesions compared with metronidazole alone.³⁶

New and Emerging Therapies

Topical Ivermectin

Several topical acaricidal agents (permethrin 5%, crotamiton 10%, and ivermectin 1%) have been studied for the treatment of rosacea, all of which primarily target *Demodex folliculorum* and *Demodex brevis* mites. The potential etiological role of these mites in rosacea has been debated for many years.⁹ There is renewed interest in Demodex mites due to recent studies that demonstrated antigenic proteins produced by a Demodex-isolated bacterium (*Bacillus oleronius*) may aggravate the inflammatory responses in papulopustular and ocular rosacea,³⁷ as well as in erythematotelangiectatic rosacea.³⁸ This pathogenic scenario implicating the bacterium rather than the Demodex mites themselves may explain the efficacy of antibacterial therapies in rosacea.

Numerous case reports³⁹⁻⁴¹ have been published on the successful treatment of rosacea with topical acaricidal agents refractory to other therapies, however, data from controlled, randomized trials are lacking. Phase 3 randomized clinical trials studying the impact of topical ivermectin 1% cream in rosacea are underway, which compare its efficacy and safety with metronidazole 0.75% cream and azelaic acid 15% gel.⁴²⁻⁴⁴ Results are expected to be available in the near future.

Topical Brimonidine and Oxymetazoline

Diffuse and persistent facial erythema has long been a clinical challenge in rosacea therapy.⁵ One contributing factor to diffuse facial erythema is abnormal cutaneous vasomotor responses, which leads to enlarged superficial facial blood vessels.⁴⁵ Importantly, however, these blood vessels remain responsive to vasoactive stimuli, hence, the growing interest in alpha (α)-2 adrenergic receptor agonists as a therapeutic option to manage the nontransient erythema.⁴⁵

Brimonidine tartrate 0.33% gel, approved by the US FDA in August 2013 and by Health Canada in February 2014, is the latest addition to the treatment armamentarium and the first topical agent approved for the treatment of facial erythema of rosacea. Brimonidine (initially available in prescription eye drops for the treatment of glaucoma) is a highly selective α -2 adrenergic receptor agonist with potent vasoconstrictive activity.⁴⁶

In two Phase 3 randomized, double-blind pivotal trials, topical brimonidine tartrate (BT) gel 0.5% once-daily was found to be significantly more effective than vehicle over a 4 week treatment period.⁴⁷ In the two trials, approximately 24.82% of the patients using BT gel 0.5% (vs. 9.76%; $p < 0.05$) were assessed on

day 29 to have at least a two-grade improvement by both clinicians and patients over 12 hours after drug application, with peak improvements observed at 3 and 6 hours. Noticeable improvement (one-grade based on Clinician's Erythema Assessment and Patient's Self-Assessment) was observed (28.2% vs. 5.9%; $p < 0.01$) as early as 30 minutes after the first application on day 1. Adverse events were mildly elevated in the active treatment group, but events were mostly skin-related, transient, and mild, with the most commonly reported being worsening of erythema (5.1%), pruritus (5.0%), skin irritation (1.2%), and worsening of rosacea (1.1%). There was no evidence of tachyphylaxis, rebound, or aggravation of telangiectasia or inflammatory lesions. Additionally, recently published data from a 12-month, multicenter, open-label study reported sustained efficacy with no incidence of tachyphylaxis in the long-term treatment of moderate to severe erythema of rosacea.⁴⁸

Phase 2 clinical trial for another promising α -adrenergic receptor agonist, called oxymetazoline, has recently been completed.⁴⁹ Results should be available in the near future.

Other Therapies

Topical sodium sulfacetamide 10% with sulfur 5% has been used for more than 50 years for its clinical efficacy and safety in the treatment of rosacea, although its mechanism of action is not well understood. In an 8-week study, sulfacetamide 10% with sulfur 5% has been shown to significantly reduce inflammatory lesions (78% vs. 36%; $p < 0.001$) and facial erythema (83% vs. 31%; $p < 0.001$) compared to vehicle.⁵⁰ However, studies evaluating this therapy are limited and generally of poor quality.²⁸

Oral isotretinoin can be used off-label for the treatment of more severe or persistent cases of papulopustular rosacea and may help slow or halt the progression of rhinophyma. In a large scale, randomized, double-blind, 12-week study comparing different doses of isotretinoin to doxycycline and placebo in the treatment of rosacea, isotretinoin 0.3 mg/kg demonstrated non-inferiority to doxycycline ($p = 0.00001$) and was well tolerated.⁵¹ However, isotretinoin should only be prescribed with close monitoring and, particularly in women with childbearing potential, an appropriate contraception strategy is essential due to its teratogenic potential.

Laser and light therapies have been used successfully for many years to treat the vascular manifestations of rosacea. In a randomized, controlled, single-blind, split-face trial, both pulsed dye laser and intense pulse light modalities were found to be effective, with similar efficacy, in reducing erythema and telangiectasia in patients with erythematotelangiectatic rosacea.⁵²

In a double-blind, randomized, vehicle-controlled, 12-week clinical trial,⁵³ off-label use of topical benzoyl peroxide 5% with clindamycin 1% once-daily was shown to be effective in reducing papule and pustule count in patients with rosacea compared to vehicle alone (71.3% vs. 19.3%; $p = 0.0056$). Adverse events were only mildly elevated in the treatment group, with localized burning and itching being the most commonly reported.

Pimecrolimus 1% cream was demonstrated in an open-labeled, uncontrolled, 4-week trial to be effective and well tolerated in the treatment of rosacea.⁵⁴ Adverse events were transient and mild, which included local burning, itching, dryness, and stinging.

Conclusion

There are numerous treatment options available for rosacea, however, only a handful of agents are substantiated with quality research. If available, therapeutic decision-making should be guided by high-level evidence and patient-specific factors, such as rosacea subtype, severity, treatment expectations, tolerance, cost, and previous response to therapy. Topical azelaic acid and metronidazole are considered safe and efficacious first-line therapies. Sub-antimicrobial dose of doxycycline is the best research-supported oral therapeutic option and can be used to treat moderate to severe forms of papulopustular or ocular rosacea, or in patients who may be more adherent on a systemic regimen. Low-dose isotretinoin or surgical interventions may be indicated for the phymatous type. Light and laser-based therapies can play a major clinical role in the treatment of the telangiectatic component. The novel therapy, brimonidine, provides targeted treatment of facial diffuse erythema of rosacea. A comprehensive treatment plan must also incorporate non-drug strategies aimed at quality of life improvements and include trigger avoidance, proper daily skin care, camouflaging and photoprotection. Further research is needed on the effectiveness of combination treatments, isotretinoin, sulfacetamide, light-based options, and newly emergent agents compared with conventional therapies.

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