Medical Management of Facial Redness in Rosacea

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KEYWORDS

• Erythema • Topical • Management • Erythematotelangiectatic • Papulopustular • Rosacea

KEY POINTS

- Rosacea is a chronic skin condition characterized by central facial erythema and flushing.
- Options for the medical management of facial erythema, telangiectasias, and flushing are limited.
- Medications to reduce erythema and flushing may provide temporary relief but do not alter the chronic nature of the disease.
- The goal of this article is to review the topical and systemic treatments for rosacea-related erythema and flushing to help facilitate decision making in clinical practice.

INTRODUCTION

Rosacea is a chronic skin condition that presents with a broad diversity of cutaneous manifestations. Facial erythema, the most common primary characteristic of all subtypes of rosacea, is a mandatory diagnostic feature.[1,2] Persistent centrofacial erythema is the predominant hallmark of patients with rosacea, especially in the erythematotelangiectatic rosacea (ETR) and the papulopustular rosacea (PPR) subtypes.[3] Treatment has been difficult because, until recently, there were no effective medications for the erythema and flushing associated with rosacea.[4,5]

As with most chronic skin diseases, rosacea management requires long-term treatment with multiple modalities. Management strategies for people with rosacea should be tailored to the specific subtype of rosacea. For patients with mild symptoms, nonpharmacologic measures may be sufficient for reducing facial redness, flushing, skin sensitivity, and skin dryness. Successful rosacea management may be possible through avoidance of triggers that cause flushing, such as spicy foods, alcohol, exercise, sunlight, and some types of cosmetics.[6] When satisfactory improvement is not achieved through these lifestyle modifications, treatment with topical and systemic medications is an option.

New insights into the pathophysiology have led to advances in the management of rosacea. A deeper understanding of rosacea means more opportunities to target specific pathogenic factors and clinical manifestations with novel agents. Although topical metronidazole and azelaic acid and systemic tetracyclines are efficacious for PPR, there are few treatment options for persistent facial erythema.[7]

Novel treatments are on the horizon for the management of facial erythema of rosacea. Although it is unlikely that a single modality will result in complete and permanent resolution, treatment options are available that yield good results when tailored to the right clinical scenario. Topical medications, either as monotherapy or as part of a combination regimen, are the first-line choice and often sufficient for patients with mild to moderate ETR or

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PPR. Topical medications primarily used for PPR (eg, topical antimicrobials and azelaic acid) may also reduce rosacea-associated facial erythema.[8–10] However, telangiectasias are unlikely to improve with topicals and are best managed with light-based treatments. The authors discuss topical and systemic treatments for rosacea-related erythema and aim to facilitate treatment decision making in clinical practice.

METHODS

PubMed, Embase, and Google Scholar databases were used to search for literature published in English pertaining to treatment options for erythema related to rosacea. Keywords included "erythematotelangiectatic rosacea," "erythema," "papulopustular rosacea," "brimonidine," "oxymetazoline," "calcineurin inhibitors," "retinoids," "tetracyclines," and "isotretinoin." Treatment types were combined with the keywords "rosacea" and "erythema." Article abstracts were reviewed for relevance to the subject matter, with an emphasis on ETR. Articles included in the review specifically discussed the medical management of rosacea-related erythema, the clinical trials of these treatments, and/or adverse effects of treatment. Articles that did not discuss the medical management of rosacea-related erythema were excluded.

TOPICAL TREATMENTS

Brimonidine

Brimonidine 0.33% topical gel is a topical agent approved for the treatment of persistent facial erythema of rosacea.[11] Brimonidine tartrate is a vasoconstrictive α2-adrenergic receptor agonist originally used in the treatment of open-angle glaucoma. Brimonidine tartrate is 1000-fold more selective for the α2-adrenergic receptor than the α1-adrenergic receptor.[12] It causes direct vasoconstriction of small arteries and veins, leading to constriction of abnormally dilated facial blood vessels in patients with erythema.[11] To a lesser degree, it exerts anti-inflammatory effects.[13] Brimonidine tartrate is a more specific and potent vasoconstrictor of human subcutaneous vessels less than 200 μm in diameter than oxymetazoline, a selective α1-adrenergic receptor agonist and partial α2-adrenergic receptor agonist. Unlike oxymetazoline, brimonidine tartrate is not active against the 5-hydroxytryptamine 2B receptor, which is related to valvular heart disease after long-term treatment.[13,14]

Multiple studies suggest that brimonidine 0.33% gel is safe and efficacious in the treatment of patients with moderate to severe erythema of rosacea. In these studies, the severity of erythema was measured using the clinician's erythema assessment (CEA) and patient's self-assessment (PSA) scales.[11,15–17] In a dose-response phase 2a study, a single application of brimonidine tartrate gel (0.5% vs 0.18% vs 0.07% vs vehicle) reduced facial erythema in a dose-dependent manner over 12 hours compared with vehicle based on CEA, PSA, and chromameter examinations.[15] Brimonidine tartrate 0.5% gel exhibited the greatest reduction of erythema at all time points over 12 hours, achieving a 2-grade improvement in erythema by both CEA and PSA and by median change in chromameter values ($P<.001$). Reduction in erythema occurred within 30 minutes, with the peak effect lasting 4 to 6 hours after single application. After the peak effect diminished, the erythema did not return to baseline level up to 12 hours after application.[15] A phase 2b dose-response study evaluated brimonidine tartrate gel applied once daily (0.5%, 0.18%, vehicle) and twice daily (0.18%, vehicle) for 4 weeks, followed by a 4-week posttreatment phase.[15] Brimonidine 0.5% gel once daily was the most effective in reducing erythema based on both CEA and PSA. Erythema reduction after 28 days of daily use of brimonidine tartrate 0.5% gel was the same or better than day 1, with results superior to vehicle ($P<.001$). Over the 4-week posttreatment phase, no clinically relevant rebound erythema was noted.[15]

In 2 multicenter, randomized, double-blind, parallel-group, vehicle-controlled phase 3 studies, brimonidine 0.33% gel once daily showed significantly greater efficacy compared with vehicle for all efficacy endpoints, with a faster onset of action and good safety and tolerability profiles.[11] Efficacy, defined as a 2-grade improvement in both CEA and PSA over 12 hours, was significantly greater with brimonidine 0.33% gel in comparison to vehicle. At the end of the study, at least 2-grade reductions in both CEA and PSA were achieved 3 hours after application by 31% and 25% of subjects treated with brimonidine 0.33% gel versus only 11% and 9% of patients treated with vehicle.[11] In a separate open-label, multicenter study, the long-term safety and efficacy of brimonidine 0.33% gel once daily was evaluated over 12 months.[17] Improvement was noted after the first application of brimonidine 0.33% gel with reductions in CEA from 3.1 at baseline to 1.7.

In 2013, the US Food and Drug Administration (FDA) approved brimonidine 0.33% gel for the treatment of persistent facial erythema of rosacea. A meta-analysis in 2015 found that there was high-quality evidence to support the effectiveness of topical brimonidine for rosacea.[7] Long-term