CLINICAL VIGNETTE

Topical Management of Rosacea for Primary Care: What's New

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Introduction

Rosacea is a chronic inflammatory disorder affecting the blood vessels and pilosebaceous units of the face, affecting between 1 to 10% of people.[1] Clinical subtypes include erythematotelangectatic, papulopustular, phymatous, and ocular rosacea. The exact pathogenesis of rosacea is still not well understood but is likely multifactorial, triggered by environmental stimuli (such as changes in temperature or sunlight), certain foods and medications, and possibly *Demodex* mites that often reside in sebaceous glands on the face.[2]

Rosacea is considered a treatable, rather than curable condition, and treatment strategies vary depending on subtype. Current therapeutic strategies include behavioral modification, topical and oral medications, and laser treatments.[1] Among the medical treatment options, the most commonly used topicals include metronidazole, azelaic acid, sulfacetamide/sulfur, benzoyl peroxide, and retinoids – often used with oral antibiotics (commonly tetracyclines) for the papulopustular subtype or low-dose isotretinoin for refractory disease.[1] In recent years, four new topical therapeutic options have been approved by the US Food and Drug Administration (FDA), including two therapies for papulopustular rosacea and two for erythematotelangectatic rosacea, detailed below.

Ivermectin 1% Cream

Ivermectin 1% cream functions as an anti-inflammatory and anti-parasitic agent in the treatment of papulopustular rosacea, targeting *Demodex* mites thought to reside in pilosebaceous lesions and cause subsequent local inflammation.[2] Two identical randomized vehicle-control studies (1071 total participants) demonstrated superior efficacy of ivermectin 1% cream over vehicle cream. Successful treatment was defined as "clear" or "almost clear/minimal," based on the Investigator's Global Assessment of Rosacea (IGA).[3] Rates of successful treatment after 12 weeks were 38% and 40% for ivermectin, compared to 12% and 19% for vehicle cream in each respective study.[3] Decrease in mean lesion count and quality of life scores were also superior in participants treated with ivermectin.[3] Both studies showed similar incidence rates of adverse events between ivermectin and the vehicle control, ranging from 36-41%, with the most common reported adverse events being burning, pruritus, and xerosis.[3]

Ivermectin 1% cream once daily and metronidazole 0.75% cream twice daily were compared in a randomized study, finding superior percentage reduction of inflammatory lesions from baseline in ivermectin 83%, versus 74% in metronidazole. Similarly IGA success rates were 85% and 75% for ivermectin versus metronidazole, respectively. Incidence of adverse events was comparable (32–33%), with the most commonly reported adverse event being skin irritation.[3] Additionally, several studies have found lower rates of adverse events with ivermectin 1% cream compared to azelaic acid 15% gel.[3-5]

Azelaic Acid 15% Foam

Azelaic acid is a medium chain dicarboxylic acid produced by *Malassezia furfur*, possessing anti-inflammatory and antioxidant properties in keratinocytes.[6,7] Azelaic acid 15% gel has long been used as treatment for papulopustular rosacea, but recently an azelaic acid 15% foam formulation was FDA-approved in 2015.[6]

A 12-week randomized, double-blinded, vehicle-control study of 401 adults with moderate to severe papulopustular rosacea compared azelaic acid 15% foam to a control vehicle. Therapeutic success rates, defined as IGA scores of "clear" or "almost clear/minimal," were 43% in the azelaic acid foam group and 32% in the vehicle group.[8] Similar results were obtained in a phase 3 study noting decreased inflammatory lesion count and superior efficacy compared to the vehicle control.[6] Adverse events occurred in 31% of participants (compared to 25% in the vehicle group), most commonly pain, pruritus, and dryness at the site of application.[6]

While no head-to-head comparisons of the gel and foam formulations have been conducted, studies evaluating the efficacy of each formulation have used similar protocols with no differences in efficacy.[7] However, the foam formulation has been shown to have lower rates of pain and pruritus compared to the gel formulation, and is often preferred due to improved ease of application as it requires less manipulation of inflamed skin.[6,7]

Brimonidine Gel 0.33%

Brimonidine tartarate, a vasoconstrictive selective alpha-2 adrenergic receptor agonist previously used for open-angle glaucoma, was the first approved topical treatment for rosacea-

associated facial erythema as a 0.33% gel formulation.[9] The efficacy of brimonidine has been supported by phase 2 and 3 clinical trials, including two multicenter randomized vehicle-controlled studies of 0.5% brimonidine gel with 553 total adult participants. A clinically meaningful result was defined as a minimum one-grade improvement in both the clinician's erythema assessment (CEA) and patient's self-assessment (PSA) scales on day 29. Results are shown in Table 1.

		Hour 3	Hour 6	Hour 9	Hour 12
Study A	Brimonidine	70.9%	69.3%	63.8%	56.7%
	Vehicle	32.8%	32.0%	29.7%	30.5%
Study B	Brimonidine	71.1%	64.8%	66.9%	53.5%
	Vehicle	40.1%	43.0%	39.4%	40.1%

Table 1. Percentage of patients with a minimum one-grade improvement in both the clinician's erythema assessment (CEA) and patient's self-assessment (PSA) scales on day 29, measured at 3, 6, 9, and 12 hours.

Studies of long-term safety over 12 months showed brimonidine 0.5% gel was generally well-tolerated. Most adverse events occurred within the first month of treatment, most commonly flushing, paradoxical exacerbation of erythema, burning/irritation, and contact dermatitis.[9,10] However, several post-marketing case reports of worsening erythema in up to 20% of patients have raised concern for significant risk of rebound effect.[3,10] While the efficacy of brimonidine for papulopustular rosacea has not been specifically studied, studies demonstrating a lack of an aggravating effect on pustular lesions suggest brimonidine may not be effective for papulopustular lesions.[11,12]

Oxymetazoline Cream

Oxymetazoline is an alpha-1 adrenergic receptor agonist, commonly used for the treatment of nasal congestion.[9] In 2017, the FDA approved Oxymetazoline 1% cream for the treatment of rosacea-associated facial erythema.[13] Two randomized, vehicle-controlled trials with 885 total participants compared oxymetazoline HCl 1% cream to a control vehicle, with a primary end point of at least a 2-point reduction in both CEA and SSA scores on day 29 of treatment compared to baseline.[13] The percentage of patients who met the primary endpoint in each branch with oxymetazoline ranged from 12-18%, compared to 5-9% for control branches.[13] Adverse events in the oxymetazoline group included treatment-site dermatitis (2%), paradoxical worsening of rosacea symptoms (1%), pruritus (1%), and pain (1%), whereas the control group only had a similar rate of pruritus.[13] However, oxymetazoline appears ineffective for papulopustular rosacea, and studies directly comparing oxymetazoline to other alternatives have not yet been conducted.

Conclusion

The recent FDA approval of topical ivermectin 1% cream and azelaic acid 15% foam for papulopustular rosacea, as well as brimonidine 0.33% gel and oxymetazoline HCl 1% cream for erythematotelangectatic rosacea, increases the number of options available for the treatment of rosacea. However, topical brimonidine and oxymetazoline carry a significant risk of rebound, an important consideration for prescribing physicians. Comparative studies are also still necessary for further characterization of the efficacy of oxymetazoline. While the pathophysiology of rosacea is still poorly understood, ongoing developments in our understanding may lead the way for newer therapies in the future.

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