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Rosacea and Its Topical Management

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Abstract and Introduction

Abstract

Many options exist for the treatment of rosacea, including topical and systemic therapies, laser and light-based therapies, and surgical procedures. A classification system for rosacea identifies 4 subtypes (i.e., erythematotelangiectatic, papulopustular, phymatous, and ocular), which may help guide therapeutic decision-making. The goals of therapy include reduction of papules, pustules, erythema, physical discomfort, and an improvement in quality of life. Standard topical treatment agents include metronidazole, azelaic acid, and sodium sulfacetamide-sulfur. Second line therapies include benzoyl peroxide, clindamycin, calcineurin inhibitors, and permethrin.

Introduction

Rosacea is a chronic relapsing skin disorder characterized by facial flushing, persistent erythema, telangiectasia, and inflammatory papules and pustules affecting the central face. The National Rosacea Society has described a classification system based on 4 main subtypes: erythematotelangiectatic, papulopustular, phymatous, ocular, and one variant, i.e., granulomatous.^[1] Rosacea can contribute to lower self-esteem and have significant psychosocial implications, e.g., stress at work and social isolation.^[2] This can have a significant impact on quality of life and should be taken into consideration when treating these patients.

Treatment starts with making a proper diagnosis, including identification of subtype. Following this, conservative measures, such as trigger avoidance, proper skin care, camouflaging cosmetics, and photoprotection should be discussed in detail. Topical pharmacotherapeutic options include: azelaic acid (Finacea[®] Gel, Intendis/Bayer), clindamycin, clindamycin 1%-benzoyl peroxide 5% gel (BenzaClin[®], sanofi-aventis; Duac[®], Stiefel), erythromycin, metronidazole (MetroCream[®], MetroLotion[®], MetroGel[®], Rozex[®] Gel, Galderma; Noritate[®], Dermik), or sodium sulfacetamide 10% + sulfur 5% (Plexion[®], Medicis; Rosac[®] Cream, Stiefel; Rosula[®] Lotion, Doak Dermatologics; Sulfacet-R[®], Novacet[®] Lotion, Perrigo). For patients with moderate-to-severe papulopustular rosacea or those with ocular involvement, systemic therapy is often prescribed and options include doxycycline, erythromycin, metronidazole, minocycline, tetracycline, or in severe cases, low dose isotretinoin. The telangiectatic component does not respond to either oral or topical therapy, and is best treated with laser and light-based therapies. Surgical intervention may be required for the phymatous subtype. Therapeutic choices will depend on patient expectations, tolerance, previous therapies used, rosacea subtype, and severity. This article will focus on topical therapies for rosacea.

Azelaic Acid (AZA)

AZA is a newer therapeutic option for the treatment of rosacea. It was approved by the US FDA in 2002, the European Union in 2003, and in Canada in 2004, although it has only recently become commercially available in Canada. AZA is a naturally occurring dicarboxylic acid that can be found in dietary sources, such as whole grains.^[3] It lacks toxicity, is nonteratogenic and nonmutagenic.^[4] It has multiple biologic effects including anti-inflammatory, antikeratinizing and antibacterial activities. The likely mechanism of action is via inhibition of reactive oxygen species produced by neutrophils.^[4]

A novel 15% gel formulation (Finacea[®], Intendis/Bayer) is available for the treatment of rosacea, in addition to a 20% cream formulation approved for use in acne vulgaris. The 15% gel, although formulated to a lower concentration than the cream, is significantly more bioavailable than the cream because of an optimized aqueous gel vehicle. Multiple reviews have been published examining the use of AZA in rosacea.^[3,5,6] Two pivotal phase III trials have shown that AZA 15% gel, applied twice daily for 12 weeks, was superior when compared with the vehicle for patients with papulopustular rosacea.^[7] A mean reduction in inflammatory lesion counts ranged from 51%–58% in the AZA group, compared with 39%–40% in the vehicle group. Improvement in erythema scores ranged from 44%–46% in patients treated with AZA, compared with 28%–29% in the vehicle group.^[7] In a 15-week study, AZA 15% gel applied twice daily also showed significant benefit over metronidazole 0.75% gel.^[8] In these studies, the use of AZA 15% gel led to a mean reduction in inflammatory lesion counts ranging from 51%–73% and a reduction of erythema severity ranging from 44%–56%. The number of patients achieving success, as defined by the investigator global assessment, ranged from 61%–69%.^[7–9]

A split-face study by Maddin^[10] comparing AZA 20% cream with metronidazole 0.75% cream, showed a reduction in inflammatory lesions of 78.5% and 69.4%, respectively. There was also a reduction in erythema of 25.5% and 18.7% for AZA and metronidazole, respectively. Both treatments led to a significant reduction in inflammatory lesions over 15 weeks, but the difference between treatments was not significant.^[10] Of note, the physician rating of global improvement was significantly higher on the side treated with AZA at both weeks 9 and 15.^[10] In the comparative studies, AZA had a greater potential to cause irritation than the metronidazole, which included facial skin signs and symptoms. However, these events were reported as mild to moderate and transient in nature.^[8] There was no improvement reported in telangiectasia severity in any study of AZA for rosacea.

The dosing recommendation for AZA 15% gel is a twice daily application. However, Thiboutot et al. found once daily dosing to be as effective as twice daily.^[11] Research has shown that AZA when used as a treatment for papulopustular rosacea is a safe and effective and exhibits a favorable tolerability profile.

Metronidazole

Metronidazole has been the mainstay of topical rosacea treatment. It is a nitroimidazole antibiotic whose mechanism of action in rosacea is not well established, but appears to work through an anti-inflammatory mechanism.^[12,13] It is the most widely used topical agent for rosacea and is available in a 0.75% gel, lotion, and cream format for twice daily use, and a 1% cream or gel for once daily use. Jorizzo et al.^[14] found that once daily dosing of 1% metronidazole cream was as effective as twice daily dosing. It is generally well tolerated and has a low incidence of adverse effects.^[12,13] A recent review by the Cochrane Collaboration^[15] and a condensed version of this work by van Zuuren et al.,^[5] summarizes 9 "high and intermediate quality" trials, which show clear evidence that topical metronidazole is significantly more effective than vehicle alone. Most of these studies used 0.75% metronidazole and ranged from 8–9 weeks in duration, with 1 trial lasting 6 months. A reduction in inflammatory lesions and erythema scores were noted, as was an improvement in physician's global evaluation, and patient-assessed measures when these were available.^[5,15] No benefits were noted for the telangiectasia in these studies, however, a study by Tan et al. showed improvement in telangiectasiae scores, as well as erythema and inflammatory lesion counts, using a 1% metronidazole cream with SPF 15.^[16]

Although data are limited, 2 studies have shown that topical metronidazole may be as effective as oral tetracycline in reducing the inflammatory component of rosacea.^[17,18] Efficacy of metronidazole is constant regardless of the formulation, strength, and frequency of application.^[12] This drug also plays a role in maintenance therapy, either with or without prior concomitant systemic antibiotic therapy.^[12] Given its high efficacy and tolerability, it will continue to play an important role in the management of rosacea.

Sodium Sulfacetamide 10% + Sulfur 5%

Sodium sulfacetamide 10% + sulfur 5% is an older treatment that has gained new popularity. It is used to treat acne, rosacea, and seborrheic dermatitis,^[13] and is available in multiple formulations as a lotion, cream, gel, or cleanser.^[9,13] The mechanism of action is not well understood, but the sulfacetamide has antibacterial properties, and the sulfur component confers antifungal, antiparasitic, and keratolytic effects.^[19] Two studies, one comparing the sodium sulfacetamide-sulfur combination with the vehicle and another comparing it with metronidazole 0.75% gel, showed a significant reduction in both inflammatory lesion counts and erythema scores in papulopustular rosacea.^[19,20]

Other Therapies

Many other topical treatments for rosacea have been reported. Some are effective, but are not yet approved. Further investigation is needed to determine their potential role in the topical armamentarium of rosacea therapy.

- Topical antibiotics (e.g., clindamycin lotion or cream) have shown benefit, but evidence supporting their use is lacking.
- The calcineurin inhibitors, tacrolimus (Protopic[®], Astellas Pharma) and pimecrolimus (Elidel[®], Novartis), have been investigated for use in papulopustular rosacea because of their anti-inflammatory effects. Early reports suggested benefit from tacrolimus in the treatment of steroid-induced rosacea.^[21] However, while 3 studies have demonstrated a reduction in erythema associated with rosacea, neither tacrolimus nor pimecrolimus had any benefit over vehicle with respect to lesion counts.^[22-24]
- Clindamycin 1%-benzoyl peroxide 5% gel, which is approved for use in acne vulgaris, has shown promise for rosacea therapy. A double-blind, randomized controlled trial using this once daily formulation showed a significant reduction in inflammatory lesion count, erythema severity, and overall rosacea severity. The treatment was well tolerated.^[25]
- Permethrin 5% cream, which is proposed to work because of its anti-parasitic effects, may target *Demodex* mites, a potential cause of rosacea.^[13] This formulation was compared in 1 study with the vehicle and with metronidazole 0.75% gel, and was found to be superior to the vehicle and equal in efficacy to metronidazole.^[26]
- Topical retinoids have been used to treat rosacea, but the true efficacy has not been established. Their use is limited by their irritant potential. Nally and Berson^[13] suggested that better tolerated agents, e.g., adapalene, should be considered.
- Topical steroids are sometimes used on a short-term basis for the severe inflammatory component, but long-term side-effects and exacerbating potential limit their use in this chronic condition.^[13]
- There is anecdotal evidence of 4 patients with erythematotelangiectatic rosacea who were treated successfully with oxymetazoline, a topically applied selective α_1 -adrenergic receptor agonist. The impressive results of this treatment warrant further study.^[27,28]

Conclusions

Because of its chronic, inflammatory nature, rosacea requires continuous management. Treatment can be tailored to the subtype and may involve a combination of therapies. Patients should first be counseled on the triggers of rosacea, proper skin care, photoprotection, and camouflaging cosmetic options. Topical therapy is usually first line, but in moderate-to-severe cases, or those with ocular involvement, systemic therapy may be required. Laser or light-based treatments and surgical procedures can offer added benefit. Many topical agents are available for the treatment of rosacea, and the erythematotelangiectatic and papulopustular variants usually respond most favorably. There is good evidence that topical AZA and metronidazole are both safe and effective treatments. Other treatment options also include sodium sulfacetamide 10%-sulfur 5%, benzoyl peroxide 5%-clindamycin 1%, or clindamycin alone.

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