BEST PRACTICES IN:
Treating Rosacea – A Focus on Azelaic Acid

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Rosacea: A Common, Chronic Condition

Skin disease is commonly seen in the primary care setting. A 2-year chart review conducted at the University of Miami reported that 36.5% of patients who visited their primary care physician had ≥1 skin problem; for 58.7%, a skin condition was the primary reason for their visit.[1] Rosacea is a chronic skin disorder that primary care physicians see with some frequency; it is estimated that close to 1 in 20 Americans is affected by rosacea.[2] Therefore, primary care providers should be prepared to accurately diagnose and effectively treat this condition.

Although its etiology is not fully understood, rosacea may be an inflammatory condition in which free radical formation plays a central role.[3] Individuals with rosacea have been shown to have high levels of cathelicidin (a peptide that acts as the skin's endogenous antimicrobial barrier) in their facial skin.[4] Overexpression of cathelicidin leads to the production of abnormal peptides that can induce inflammatory changes characteristic of rosacea.[4]

Rosacea is characterized by facial flushing, erythema, telangiectasia, inflammatory episodes with papules and pustules, and, sometimes, rhinophyma.[5] Diagnosis depends on identifying these clinical features, although individual presentation can vary greatly. Four subtypes of rosacea have been defined: erythematotelangiectatic, papulopustular (inflammatory), phymatous, and ocular.[6]

Treatment Essentials

Rosacea often "flares" in response to triggers, which are patient-specific and may be difficult to avoid.[7] Common triggers include sun exposure, emotional stress, hot or cold weather, and exercise.[6] Helping patients identify their triggers is the foundation of preventative care.[6,7]

Although there is no cure, rosacea can be successfully managed, and topical therapy is often used first-line for mild to moderate disease. Only three of the available topical therapies have demonstrated effectiveness in clinical studies and are approved for the treatment of rosacea: azelaic acid (AzA) 15% gel; metronidazole (0.75% and 1.0%) cream, lotion, and gel; and sodium sulfacetamide 10%/sulfur 5% lotions, creams, and cleansers.[7] This column focuses on the efficacy and safety of AzA.

Azelaic Acid

AzA (1,7-heptanedicarboxylic acid) is indicated for the topical treatment of inflammatory papules and pustules of mild to moderate rosacea.[8] AzA 15% was one of the first agents reformulated from a cream to a gel, which greatly increased skin absorption and bioavailability of the active ingredient.[9] There is now increasing evidence that AzA has multiple mechanisms of action that may be beneficial in the treatment of rosacea,[3,10] including:

- Anti-inflammatory and antioxidant activity mediated by inhibition of reactive oxygen species and lipoxygenase
- Antikeratinizing effects, including interference with the terminal phase of epidermal differentiation and cytostatic effects on proliferating keratinocytes
- Antimicrobial activity against cutaneous microorganisms, without induction of bacterial resistance.

Efficacy

The following Table provides an overview of the clinical studies verifying the effectiveness of AzA.

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Two vehicle-controlled studies demonstrated that twice-daily AzA was effective in patients with moderate papulopustular rosacea.[11] Significantly greater reductions in inflammatory lesion count and erythema scores were seen in patients treated with AzA, compared with vehicle (**Table**).[11] Investigator global assessment of success (sum of "clear," "minimal," and "mild" rating) was also significantly higher in patients receiving active treatment (**Table**).[11] AzA demonstrated a rapid onset of action; differences between treatment groups in mean inflammatory lesion count were seen as early as 4 weeks after starting treatment.[11]

A double-blind, randomized study found that AzA had statistically significant efficacy over metronidazole 0.75% gel in most efficacy variables ($P<0.05$ for all comparisons) (**Table**).[5] The differences in lesion count and erythema score between treatment groups at the end of treatment could possibly be attributed to a leveling off of improvement in the metronidazole group after week 8.[5]

Another comparative study concluded that AzA and metronidazole 1.0% gel were similarly effective in terms of lesion count, erythema, and investigator global severity scores.[12]

A systematic (Cochrane) review of controlled trials of rosacea therapies concluded that topical AzA and metronidazole are both effective, but firm conclusions regarding other therapies could not be drawn from the current evidence base.[13]

Combination With Systemic Therapy

Oral tetracycline antibiotics are often used to treat flares, but long-term treatment at conventional doses has the potential to induce bacterial resistance.[14] In a two-phase study, 172 patients with moderate to severe rosacea received AzA and doxycycline 100 mg twice daily for up to 12 weeks during an initial open-label phase.[14] This led to a ≥75% reduction in inflammatory lesion count in 81.4% of subjects. Patients achieving success during combination therapy were then randomized to double-blind treatment with either AzA or vehicle. AzA provided consistently greater maintenance response than did vehicle at all points up to study end (week 24). The risk of relapse was also reduced by 33% with AzA, compared with vehicle.[14]

Tolerability

AzA has a favorable tolerability profile; the most common adverse events (AEs) are transient and mild cutaneous burning, stinging, and itching.[8,15] Most patients with rosacea have sensitive skin, which poses a serious challenge when selecting topical products.[16] In one 2-week study of 40 women with mild to moderate rosacea, 62.5% had sensitive skin (a positive reaction on the facial sting test), but application of AzA did not significantly increase the occurrence of itching ($P=0.095$) or burning/stinging ($P=0.247$) compared with baseline.[16] The Cochrane analysis confirmed the low discontinuation rate with AzA and the mild and transient nature of local skin reactions.[13] Data from maintenance therapy studies show that long-term treatment with AzA is well tolerated.[14] During 24 weeks of AzA maintenance therapy, the only treatment-related AEs were nonsevere cutaneous reactions, occurring in 9% of patients.[14] No patient developed a treatment-related serious AE or discontinued maintenance therapy because of AEs.

AzA in Practice

From the clinical evidence to date, AzA 15% gel is an effective topical therapy for mild to moderate papulopustular rosacea.[5,11,12] Metronidazole 1% gel and AzA 15% gel have a similar rate of AEs; cutaneous irritation occurs more often with AzA, but scaling is more common with metronidazole.[12] However, the side effects of AzA are generally mild/transient and do not affect patients' overall perception of tolerability or their desire to continue treatment.[5,12,15] As with topical metronidazole, telangiectasia is the sign least likely to respond to topical therapy with AzA.[5]

AzA is effective for inducing rapid remission when used with oral doxycycline for moderate papulopustular rosacea.[14] Moreover, AzA also provides maintenance therapy against relapse,[14] and is safe and well tolerated up to 36 weeks.

The papulopustular subtype of rosacea is considered the easiest to treat,[6] whereas the most common erythematotelangiectatic subtype poses the greatest treatment challenge. Although some improvement in erythema has been noted in patients with the papulopustular subtype treated with AzA, this treatment has not specifically been evaluated for treating erythema in the absence of papules and pustules,[7] and no current treatment is considered effective for flushing.[6]

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Table. Overview of Key Randomized, Double-Blind, Controlled Clinical Studies of Azelaic Acid 15% Gel[5,11,12]

Treatment	Study	Patients (N)	Duration (weeks)	Parameter	Results* AzA	Comparator	*P* value
15% AzA vs vehicle	Thiboutot, 2003 (Study 1)[11]	AzA 164 Vehicle 165	12	Mean ILC reduction (%)	58	40	0.0001
				Improvement in ES (%)	44	29	0.0017
				"Success" by IGA (% of patients)	61	40	<0.0001
15% AzA vs vehicle	Thiboutot, 2003 (Study 2)[11]	AzA 169 Vehicle 166	12	Mean ILC reduction (%)	51	39	0.0208
				Improvement in ES (%)	46	28	0.0005
				"Success" by IGA (% of patients)	62	48	0.0127
15% AzA vs 0.75% metronidazole gel	Elewski, 2003[5]	AzA 124 Met 127	15	Mean ILC reduction (%)	73	56	<0.001
				Improvement in ES (%)	56	42	0.02
				"Success" by IGA (% of patients)	69	55	0.02
15% AzA vs 1.0% metronidazole gel	Wolf, 2006[12]	AzA 78 Met 82	15	Median ILC reduction (%)	80	77	0.264
				ES score of 0–1 (% of patients)	42.3	42.7	>0.1
				"Success" by IGA (% of patients)	56.4	53.7	>0.4

Key: *Intent-to-treat population with last observation carried forward; AzA=azelaic acid; ES=erythema severity; IGA=investigator global assessment; ILC=inflammatory lesion count; Met=metronidazole.

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