BEST PRACTICES IN: TREATING ROSACEA

Background: Rosacea is a chronic disorder that primarily affects the cheeks, chin, nose, or central forehead and is often characterized by flare-ups and remissions. Although few epidemiologic data are available, the National Rosacea Society (NRS) estimates that rosacea affects approximately 14 million Americans.[1]

Onset of rosacea usually occurs between 30 and 50 years of age, and is more common in women than men.[2,3] Rosacea may occur in any race or ethnic group, and often affects multiple members of the same family.[2,4,5] The pathophysiology of rosacea is unknown, but dermal inflammation appears to be a common factor.[6,7] Overexpression and dysregulation of cathelicidins, the skin's endogenous antibacterial barrier, also contribute to a proinflammatory environment.[8] Therapeutic regimens addressing these aspects of inflammation that contribute to rosacea may help to clear symptoms and minimize recurrences.

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Diagnosis and Differential Diagnosis: Rosacea is characterized by inflammatory papules and pustules on a background of erythema and dilated superficial blood vessels (telangiectases).[3] An expert committee convened by the NRS developed a standardized diagnostic and classification system for rosacea in which the clinical signs of rosacea are divided into primary and secondary features.[9] The presence of 1 or more primary features affecting the central face is indicative of a diagnosis of rosacea; the prominence of primary or secondary features refines the diagnosis into 1 of 4 main subtypes: erythematotelangiectatic, papulopustular, phymatous, or ocular.[9]

Rosacea may be confused with, or coexist with, a number of other dermatologic conditions affecting the face, ie, perioral dermatitis, seborrheic dermatitis, corticosteroid-induced acneiform eruption, systemic lupus erythematosus, photodermatitis, irritant or allergic contact dermatitis, and sarcoidosis, among others.[2,3,10-12] Rarely, acne can coexist with rosacea, further complicating the diagnosis.[3]

Treating Rosacea: An important component of rosacea control is identification of triggers. These can include stress, hot/cold weather, spicy foods, alcohol, hot drinks, exercise, cosmetics, medications (eg, vasodilators, amiodarone, topical corticosteroids), and medical conditions (eg, menopause, chronic cough, caffeine withdrawal syndrome).[13,14] Avoidance of triggers may improve disease control. Patients with rosacea should limit sun exposure and regularly use sunscreens.[10,15] Pharmacologic treatments for rosacea include topical or oral medications.[16]

Topical Therapy: Approved topical treatments for rosacea include metronidazole 0.75% and 1% gel, azelaic acid 15% gel, and sulfur 5%/sodium sulfacetamide 10%.[15,16]

A number of patients with rosacea have a sensitive skin phenotype, and many may be classified as "stingers": They experience irritation with application of a weak lactic acid solution.[17,18] These patients experience a stinging sensation with application of topical products that do not evoke a response in the general population.[18] In addition, patients with rosacea may have concomitant allergic or irritant contact dermatitis, and the presence of these conditions and/or sensitive skin can complicate the choice of topical therapy. For these patients, the vehicle of the topical therapy is important.[19]

Metronidazole 1% gel has been shown to be as effective as azelaic acid 15% gel in patients with rosacea, with less burning or stinging during the early treatment stage (around 3 weeks).[20] In a randomized, single-blind, controlled trial in 160 rosacea patients, 50.0% of patients in the group receiving metronidazole 1% gel once daily experienced adverse events (AEs) compared with 37.2% in the group receiving azelaic acid 15% gel twice daily, but a greater proportion of patients using metronidazole reported not being bothered by the side effects (74.0% vs 52.7%, respectively; $P=.009$).[20] Moderate to severe stinging and burning were more common with azelaic acid, and at least moderate scaling was reported with metronidazole. At week 3, the stinging and burning score was significantly higher in the azelaic acid than the metronidazole group (0.57 vs 0.23; $P<.001$), but was no different by week 12. The difference in the incidence of moderate to severe dryness or itching did not reach statistical significance.[20] These results are consistent with irritancy assessments in healthy volunteers, showing metronidazole 1% gel had a lower potential for irritation than azelaic acid 15% gel or metronidazole 0.75% gel.[21]

Oral Therapy: The only oral therapy approved by the FDA to treat papulopustular rosacea is subantimicrobial-dose (40 mg controlled release) doxycycline. At this dose, doxycycline has an anti-inflammatory but not an antimicrobial effect.[22] Though not indicated for rosacea, antibiotic-dose tetracyclines are also still used.[4] At antibiotic doses, these agents carry a risk of bacterial resistance development, as well as significant gastrointestinal symptoms and Candida vaginitis.[4,22]

The clinical efficacy of anti-inflammatory–dose doxycycline was demonstrated in 2 pivotal, randomized, double-blind, placebo-controlled phase 3 studies (Studies 1 and 2) in 537 patients with moderate to severe rosacea.[23] In both studies, anti-inflammatory–dose doxycycline reduced the total inflammatory lesion count compared with placebo, and the between-group differences were statistically significant from the first assessment at week 3 ($P=.005$).[23]

Overall improvement was measured using the Investigator's Global Assessment (IGA) score, which measured overall disease severity on a 5-point scale from 0 (no signs or symptoms present; skin clear) to 4 (severe; ≥20 papules or pustules present, and nodules).[23] A significantly greater percentage of patients in the active treatment groups had an IGA rating of 0 or 1 (clear or near-clear skin) at week 16: 30.7% of anti-inflammatory–dose doxycycline recipients vs 19.4% of placebo recipients in Study 1 ($P=.036$), and 14.8% vs 6.3%, respectively, in Study 2 ($P=.012$).[23] Assessments 4 weeks after treatment discontinuation in Study 1 demonstrated that overall treatment benefit with anti-inflammatory–dose doxycycline was maintained through week 20.[23] Anti-inflammatory–dose doxycycline was well tolerated, with most AEs (82%-94% of patients; nasopharyngitis, diarrhea, and headache) rated as mild to moderate.

In a randomized, double-blind, noninferiority comparison of anti-inflammatory–dose doxycycline with doxycycline 100 mg, both oral agents showed similar effectiveness in reducing inflammatory lesions of rosacea, with rapid reduction in the number of lesions (mean of –14.3 with doxycycline 40 mg and –13.0 with doxycycline 100 mg at week 16).[24] However, anti-inflammatory–dose doxycycline was better tolerated, with fewer patients experiencing AEs compared with doxycycline 100 mg (6/44 patients [13.6%] vs 26/47 patients [55.3%]).[24] More gastrointestinal events occurred in the doxycycline 100 mg group, with 17% experiencing nausea, 4% diarrhea, 4% esophageal pain, 4% vomiting, and 2% abdominal pain.[24]

Treatment Selection: Treatment choice for rosacea patients depends on disease severity, predominant symptoms, AEs with previous dermatologic therapies, adherence/compliance history, and skin sensitivity. Because rosacea is chronic, long-term treatment is generally required,[10] and patients may need to use topical therapy, oral therapy, or a combination of the 2 to manage symptoms and flares and to provide long-term maintenance of remission.[25]

In a randomized, double-blind, placebo-controlled study, anti-inflammatory–dose doxycycline plus metronidazole 1% gel was more effective than metronidazole gel alone in reducing inflammatory lesions.[26] Doxycycline 40 mg was shown to be well tolerated during long-term therapy, with no increase in AEs relative to placebo in a 9-month study; it did not induce antimicrobial resistance nor affect the constituency of oral microflora.[27] Because of the frequency of irritation from topical therapies, a safe oral maintenance treatment may be preferred by some.[24,27]

Adjunctive therapies can be used to treat specific symptoms (eg, liquid tears for symptomatic relief of ocular rosacea, clonidine to reduce flushing).[10] Patients with concomitant conditions may require other treatment, ie, calcineurin inhibitors in patients with coexistent seborrheic dermatitis, or crotamiton cream if Demodex mites are found or suspected.[16] Ceramide- or colloidal oatmeal-containing moisturizers are generally well tolerated by patients with rosacea. Laser- or light-based options, or electrosurgery or dermabrasion, may be used for prominent telangiectasia, erythema, and phymatous changes, which are unresponsive to topical or oral therapy.[3,15,25]

Summary: Rosacea has a diverse spectrum of manifestations, and care should be taken regarding differential diagnoses. Each patient requires individualized treatment, and therapy should be chosen after taking a full patient history. Topical metronidazole remains a very effective topical option and, along with azelaic acid and sodium sulfacetamide, comprises the most widely prescribed topical therapy for rosacea. Oral anti-inflammatory–dose doxycycline has proven effective and may be a good option in combination with a topical medication for patients with severe disease at initial presentation, as well as for those who might have compliance problems with topical therapies.

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