

Consensus Recommendations From the American Acne & Rosacea Society on the Management of Rosacea, Part 2: A Status Report on Topical Agents

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A variety of topical therapies have been utilized in the treatment of rosacea. In part 2 of this 5-part series, topical agents that have been utilized in the treatment of the common clinical presentations of rosacea, including those that have been approved by the US Food and Drug Administration (FDA) as well as alternative agents, are reviewed. It is important to note that adjunctive skin care and photoprotection are integral components of rosacea treatment that may assist in optimizing therapeutic outcomes.

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Guidelines on the management of rosacea have been previously published by the American Acne & Rosacea Society (AARS); however, these guidelines were limited to medical management and were developed prior to the emergence and/or consolidation of more recent data on pathophysiologic mechanisms associated with rosacea.¹ A variety of topical therapies have been utilized in the treatment of rosacea. Studies primarily have been conducted in patients with inflammatory lesions (classic papulopustular rosacea [PPR]).²⁻⁵ Part 2 of this series reviews topical agents approved by the US Food and

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Drug Administration (FDA) for the treatment of rosacea as well as other non-FDA-approved agents that have been discussed in the literature.

FDA-APPROVED TOPICAL AGENTS

Metronidazole (MTZ) 0.75% gel, cream, and lotion (twice-daily application); MTZ 1% gel and cream (once-daily application); and azelaic acid (AzA) 15% gel (twice-daily application) are FDA approved for the treatment of inflammatory lesions of rosacea based on pivotal phase 2 and phase 3 studies conducted in patients with PPR.^{1,3-17} The efficacy and safety of both agents also are supported by several well-controlled randomized studies conducted in patients with PPR.^{1,3-7,10-17} Although sodium sulfacetamide 10%–sulfur 5% (SS) cleansers and leave-on formulations (ie, cream, gel, foam, lotion) have not been approved by the FDA according to its formal submission process that includes mandatory large-scale pivotal studies, an approved product monograph was grandfathered by the FDA under the Drug Efficacy Study Implementation program that was developed for evaluation of pre-1962 drugs.^{5,7} The indications for SS formulations include acne vulgaris, seborrheic dermatitis, and rosacea, with a few small clinical studies supporting the efficacy of leave-on SS formulations for the treatment of PPR.^{2,3,5,7,18,19}

Although the mechanisms of action for MTZ, AzA, and SS in treating the signs and symptoms of rosacea are not fully known, they previously have been discussed in detail in the literature.^{2-7,10,18-20}

Outcomes

In the clinical studies with MTZ, AzA, and SS, all of the enrolled patients had PPR, usually moderate in severity.^{1,4-19} Following treatment with all 3 topical agents, reductions in inflammatory lesions were statistically superior to vehicle ($P < .05$).^{4,5,8-19,21,22} Some reduction in the magnitude of overall facial erythema scores also was noted, which primarily reflects the decrease in perilesional and inflammatory erythema, though persistence of diffuse background erythema was commonly observed, as these agents do not alter fixed dilation and proliferation of superficial cutaneous vasculature.^{1-19,21-23} Although the product label for AzA states that reduction in erythema was present in rosacea patients with papulopustular lesions,⁹ it is important to note that these topical agents do not have an FDA-approved indication for facial erythema associated with rosacea.^{4,5,8-14,21} A few well-controlled studies comparing MTZ and AzA in participants with PPR demonstrate comparable efficacy in the reduction of inflammatory lesions, with one study of AzA gel 15% twice daily versus MTZ gel 0.75% twice daily noting superior reduction in

facial erythema in the AzA treatment group beyond 8 weeks of use.^{11,22}

Tolerability Profiles

The overall safety and tolerability profiles of MTZ, AzA, and SS have been favorable, with most adverse events related to local tolerability reactions; no major safety signals have been noted.^{1-3,5-19,22,24-34} Although any of these agents can cause cutaneous irritation, they generally are well-tolerated among most rosacea patients. Azelaic acid is unique in its ability to induce a distinctive nociceptive response in the skin with some patients experiencing neurosensory symptoms (eg, stinging, tingling, burning) after application that are not related to worsening of the stratum corneum permeability barrier and are not associated with visible skin changes suggestive of contact dermatitis.^{4,11,21,22} These neurosensory symptoms usually are transient, are tolerable in most patients, and commonly remit after 1 to 2 weeks; they also can be mitigated by concomitant use of a gentle cleanser and moisturizer.^{4,5,7,11,21}

Management Caveats

Patients with PPR generally are good candidates for treatment with MTZ, AzA, or SS, either as monotherapy or as part of a combination regimen based on available studies and extensive clinical experience.^{4,5,7} Sodium sulfacetamide–sulfur formulations are not used as extensively now as they were in the past, likely because of the malodor of sulfur and limited efficacy data, especially pertaining to cleanser formulations.^{5,7,18,19}

The recommended application frequency for these topical agents in the treatment of PPR is once or twice daily depending on the formulation. Metronidazole 1% gel and cream are FDA approved for once-daily use.^{4,5,7,8,12} Metronidazole 0.75% gel, cream, and lotion, as well as AzA gel 15%, are FDA approved for twice-daily use; although once-daily use of these agents was not studied in the pivotal clinical trials submitted for FDA approval, some data suggest that results achieved with once-daily application of these formulations is comparable to twice-daily use in patients with PPR.^{4,5,7,8,17,25,26}

In more severely affected cases of PPR or those that do not achieve a satisfactory response with topical monotherapy, MTZ, AzA, or SS can be used in combination with an oral agent based on multiple studies completed primarily with MTZ or AzA in combination with an oral tetracycline agent, most commonly doxycycline.^{4,16,17,27-33} Although more data are needed, the available studies of MTZ or AzA in combination with oral doxycycline suggested faster results, greater reduction of inflammatory lesions, and

greater overall visible improvement of PPR lesions (based mostly on investigator assessments) compared to the topical agents alone, with no untoward or unanticipated safety signals observed.^{16,17,27-34}

Metronidazole gel 0.75% twice daily and AzA gel 15% twice daily also have been evaluated as monotherapy for prolonged control of PPR over a 6-month period.^{29,30} In individual controlled studies, MTZ gel 0.75% twice daily or AzA gel 15% twice daily were first combined with oral tetracycline²⁹ and doxycycline,³⁰ respectively, for up to 12 weeks to control flares of PPR. In participants who achieved an adequate level of improvement of their PPR flare in 12 weeks or less on the initial combination regimen, MTZ or AzA markedly sustained control of PPR compared to vehicle over the ensuing 6 months.^{29,30} Although flares did occur in some participants in both studies, flaring that occurred while using MTZ or AzA usually was less frequent and less severe compared to the vehicle group.^{29,30}

Topical therapy for rosacea is optimized by concomitant use of proper skin care to assist in the repair and maintenance of the stratum corneum permeability barrier function, which includes the use of photoprotection to avoid induction of acute flares and to mitigate the adverse cutaneous effects of chronic photodamage (eg, fixed erythema, telangiectases) that accumulate visibly along with similar clinical manifestations noted in rosacea-affected skin (eg, erythematotelangiectatic [ETR] and PPR-type presentations).^{1-7,10,14,35-40}

ALTERNATIVE TOPICAL THERAPIES (NON-FDA APPROVED)

Although data are limited, a variety of non-FDA-approved topical agents have been reported in the treatment of rosacea, mostly in patients with PPR but also in those with ETR and topical corticosteroid (TCS)-induced rosacea (steroid rosacea).^{1,2,10,14,17,18} These agents include topical calcineurin inhibitors (TCIs) (eg, tacrolimus, pimecrolimus), macrolides and macrolide analogues (eg, erythromycin, clindamycin, azithromycin), benzoyl peroxide (BP), BP-clindamycin, permethrin, and retinoids. Therapeutic benefits have been noted in some cases; however, data are limited to a few studies and collectively only a relatively small number of patients have been treated in publications with these alternative topical agents.^{1,3-7,14,17,41-59} A given alternative agent may prove to be helpful in selected clinical situations based on specific patient-related circumstances and the judgment of the clinician.

Management Caveats

Alternative topical therapies (non-FDA approved) may be helpful in selected cases based on the clinical

history and assessment of the clinician, though data are limited overall on the use of these agents for rosacea.^{4,5,7,10,14,17}

Pimecrolimus cream 1% has been used to treat patients with both PPR and ETR. Reduction in erythema and papulopustular lesions has been demonstrated in some cases, including in patients known to be refractory to other therapies, while other reports showed limited efficacy.^{7,14,17,41-44} Tacrolimus ointment 0.1% has been used to treat patients with PPR and ETR; some patients experienced a reduction in erythema, while negligible effects on papulopustular lesions were observed in others.⁴⁵ In some patients, treatment with topical TCIs has been associated with exacerbation of rosacea signs and symptoms.⁵

Patients with TCS-induced rosacea or TCS-exacerbated rosacea have been successfully treated with both topical pimecrolimus and tacrolimus^{5,14}; coupled with discontinuation of TCS use, reductions in erythema and associated symptoms were observed.^{1,5,14,46-48}

Data are limited on the topical treatment of rosacea with macrolides (erythromycin) and macrolide analogues (clindamycin, azithromycin).^{1,4,5,7,14,17,49-51} Some reduction in inflammatory lesions has been noted.⁴⁹⁻⁵¹ However, prolonged use of topical antibiotic therapy generally is not recommended for the following reasons: limited evidence to support treatment; availability of several other viable alternatives; and induction of antibiotic-resistant bacterial strains, which is a predictable consequence of topical antibiotic use. Antibiotic-resistant strains may be induced with short-term application and/or prolonged use of antibiotics that may be used to treat chronic disorders such as rosacea.^{1,4,5,49-53}

Benzoyl peroxide has not been well-studied as monotherapy for rosacea and may be limited by cutaneous irritation, especially with certain vehicles.^{7,14,17} Benzoyl peroxide and antibiotic combinations, including BP-erythromycin and BP-clindamycin, have been shown to reduce papulopustular lesions in patients with PPR; however, a definitive advantage over currently FDA-approved topical agents used to treat PPR has not been established.^{5,7,10,14,17,54-56}

Permethrin cream 5% was shown to be comparable in efficacy to topical MTZ for treatment of PPR in one study (N=63),⁵⁷ and it has been used to treat rosacealike eruptions secondary to demodicosis, also in combination with oral ivermectin.^{14,17,58,59} The anti-parasitic properties of permethrin may potentially be operative in some cases of rosacea with *Demodex* mite proliferation serving as a pathophysiologic trigger that sets in motion innate inflammatory cascades.^{6,14,60,61} Although facial *Demodex* mite proliferation is not currently believed to be mandatory as a cause of

rosacea, it may serve as a trigger in some cases through stimulation of an innate immune response, which is heightened in facial skin affected by rosacea.^{3,6,60-65}

Although topical retinoid therapy has been suggested for rosacea, data are limited and differentiation of the clinical presentations that may benefit from treatment has been poor.^{1,4,5,7,10,14,66-68} In one small study, treatment with topical tretinoin led to reductions in PPR lesions.⁶⁶ In another study that evaluated clindamycin phosphate 1.2%–tretinoin 0.025% gel, a reduction in erythema and telangiectases with a negligible effect on papulopustular lesions was noted,⁶⁷ though further research is needed to confirm the findings observed in this latter study.

Some patients present with rosacea (ETR- or PPR-type presentations) and concurrent characteristic seborrheic dermatitis (SD) or may exhibit rosacea dermatitis due to stratum corneum permeability barrier impairment with marked transepidermal water loss.^{6,69} In all rosacea patients, proper skin care is important in reducing transepidermal water loss and maintaining stratum corneum permeability barrier function.^{4,5,7,14,36-40} In rosacea patients with concurrent SD or atopic skin, a TCI may serve to treat both conditions simultaneously.^{68,70,71} As a general recommendation, use of a TCS is not suggested in cases of concurrent rosacea and SD to avoid the risk for repeated or prolonged application that can exacerbate rosacea.⁷²⁻⁷⁴

NEWLY EMERGING TOPICAL THERAPIES FOR ROSACEA

α -Adrenergic Receptor Agonists

The α -adrenergic receptor agonists (α -agonists), specifically brimonidine tartrate and oxymetazoline, are emerging as an important independent pharmacologic category of topical agents for the management of rosacea.^{3,75,76} Metronidazole, AzA, SS, and some alternative topical therapies can reduce inflammatory lesions and perilesional/inflammatory erythema; however, they exert little to no effect on persistent diffuse centrofacial erythema (DCE), also referred to as background vascular erythema, which intensifies during flares (acute vasodilation) and persists as non-transient erythema between flares (fixed dilation and enlargement of superficial facial vasculature).^{1-7,10,12,14} Based on current data related to the treatment of rosacea-affected skin, these α -agonists specifically affect vasculature within the superficial and deep dermal plexuses that contain a complete, concentric, smooth muscular layer; they have not been shown to exert any beneficial or adverse effects on inflammatory lesions.^{3,75,76} Stimulation of a variety of subtypes of α -adrenergic receptors on peripheral vasculature is how the sympathetic nervous system dynamically

increases vasomotor tone and modulates blood flow physiologically when the central neurological control center signals for vasoconstriction peripherally.^{3,75-80} This function serves to shunt and redistribute blood flow to maintain core body vascularity and proper body temperature.^{3,75-80} After cutaneous application, the α -agonists (ie, brimonidine, oxymetazoline) stimulate α -adrenergic receptors, inducing reversible vasoconstriction that abates once the drug-receptor interaction dissipates.^{3,75,76,81,82}

Unlike agents such as MTZ and AzA, the therapeutic role of topical α -agonists is to reduce the persistent background erythema of rosacea through vasoconstriction of the superficial vasculature of the face.^{3,75,76,81,82} Because telangiectases are not encased by a layer of concentric, vascular, smooth muscle and are devoid of vasomotor tone, the α -agonists do not alter these vessels; however, the decrease in regional blood flow due to vasoconstriction of responsive vasculature may temporarily reduce the visibility of some telangiectases.^{3,82}

Brimonidine tartrate gel has been evaluated in phase 2 and phase 3 clinical trials in rosacea patients with persistent nontransient facial erythema (DCE) with few or no inflammatory lesions (≤ 2 papulopustular lesions). Once-daily application of brimonidine tartrate gel 0.5% (brimonidine gel 0.33%) was determined to be the available concentration and recommended application frequency.^{75,82} Well-designed controlled studies evaluating single and repeated applications of brimonidine tartrate gel 0.5% over 29 days with a posttreatment follow-up phase showed reduction of DCE as early as 30 minutes after application, with peak activity usually noted by 3 hours, and with maximum (peak) erythema reduction lasting 6 to 8 hours with once-daily application.^{3,75,81,82} This effect was followed by a progressive return of facial erythema to scores that were near baseline, with adverse responses of rebound or rapid return of erythema not commonly reported as major adverse responses.^{75,81} Tachyphylaxis was not observed with repeated application of brimonidine tartrate gel 0.5% once daily over the 29-day study period. Tolerability and safety were favorable in both phase 2 and phase 3 studies with brimonidine tartrate gel 0.5% used once daily in patients with facial erythema of rosacea.^{75,81}

To our knowledge, there currently are no pivotal phase 2 (ie, dose-ranging pilot studies evaluating effectiveness and safety) or phase 3 studies in the literature evaluating topical oxymetazoline for the treatment of rosacea. Oxymetazoline nasal solution 0.05% applied to facial skin once daily has been shown to reduce DCE of rosacea over several hours in 2 adult patients with ETR in whom multiple other topical and oral therapies had failed.⁷⁶ Reduction in

facial erythema was observed within 1 to 3 hours after application and lasted several hours in both patients. Efficacy continued with repeated daily use over several months.⁷⁶

Management Caveats—Based on published data to date, topical application of α -agonists is specifically directed at the persistent DCE of rosacea that is present due to fixed dilated and enlarged superficial facial vasculature and should not be considered as an alternative to anti-inflammatory therapies currently available for rosacea (ie, MTZ, AzA, doxycycline) that reduce inflammatory lesions and perilesional/inflammatory erythema.^{3,75,76,81-83}

In patients with rosacea presenting with DCE and inflammatory lesions, a comprehensive medical therapeutic approach would include proper skin care, anti-inflammatory agent(s) used as monotherapy (eg, MTZ, AzA, oral tetracycline agent) or in combination to decrease inflammatory lesions and perilesional/inflammatory erythema, and an α -agonist to treat persistent DCE by inducing vasoconstriction of fixed dilated and enlarged superficial cutaneous vessels. Reduction in telangiectases is not to be expected with any of the currently available FDA-approved and nonapproved topical therapies for rosacea. At the present time, brimonidine tartrate gel 0.5% is the only α -agonist that is approved by the FDA for the indication of persistent nontransient facial erythema of rosacea in patients older than 18 years.⁸⁴

Other Agents

Topical ivermectin currently is under evaluation for treatment of PPR.⁸⁵ Although the mechanism(s) of action of topical ivermectin in rosacea have not been established, the possibility of antiparasitic and anti-inflammatory effects warrant consideration and further evaluation.

CONCLUSION

This article provides an overview of the topical therapies available for the treatment of the common clinical presentations of rosacea with management caveats. Based on outcomes from recent research, selection of therapies for treatment of rosacea can be correlated with clinical manifestations, such as papulopustular lesions and DCE, that relate to specific pathophysiologic mechanisms. To date, all of the FDA-approved therapeutic agents for treatment of PPR have demonstrated effective reduction in papules and pustules, with concomitant reduction in lesional and perilesional erythema; however, the persistence of DCE (background vascular erythema) remains a therapeutic challenge in patients with PPR and in those with ETR. The development of topical α -agonist agents represents a new therapeutic

approach for the major component of the persistent facial erythema of rosacea that is secondary to fixed, dilated, superficial vasculature that is poorly responsive to anti-inflammatory therapies (ie, MTZ, AzA, doxycycline) used to treat papulopustular lesions. It is important to note that adjunctive skin care and photoprotection are integral components of rosacea treatment that may assist in optimizing therapeutic outcomes.

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