The Treatment of Rosacea

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Rosacea is a chronic condition affecting the facial and frequently ocular tissues. It is historically underdiagnosed and affects people of all ethnicities, with higher overall prevalence in people of Celtic descent. The exact pathophysiology of rosacea is poorly understood. A variety of medical therapies, depending on the subtype, are available to treat the various signs and symptoms of rosacea.

Rosacea is a common, chronic skin disorder that frequently affects light-skinned white population. Overall prevalence of rosacea ranges from less than 1% up to 10%. The nose, cheeks, chin, forehead, and glabella are the most frequently affected sites. The disease has a variety of clinical manifestations ranging from flushing, persistent erythema, telangiectasias, papules, pustules, and sebaceous gland hyperplasia. Significant psychological stress and perceived diminished quality of life often accompany this condition.[1] The pathogenesis is likely multifactorial and includes genetic and vascular elements, climatic exposures, pilosebaceous unit abnormalities, and possibly microbial organisms and antimicrobial antibodies.[2]

Diagnosis of rosacea is based primarily on clinically recognizable morphologic characteristics. An expert committee assembled by the National Rosacea Society on the classification and staging of rosacea defined and classified rosacea in April 2002 into 4 clinical subtypes based primarily on morphologic characteristics. The subtypes include erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PR), phymatous rosacea, and ocular rosacea.

In order to design appropriate treatment regimen it is essential to correctly identify the subtype of rosacea. In addition, rosacea has to be distinguished from its clinical mimickers. Erythematotelangiectatic rosacea must be differentiated from chronic sun damage and photodermatitis. Papulopustular rosacea must be distinguished from acne vulgaris, seborrheic dermatitis, lupus miliaris disseminates faciei, collagen vascular diseases, perioral dermatitis, and *Demodex* folliculitis. Differential diagnosis of ocular rosacea includes allergic conjunctivitis and blepharitis.

Therapy of rosacea is centered on symptomatic improvement, including reduction of facial erythema and number of inflammatory lesions; decrease in the number, duration and intensity of flares; and reduction of concomitant symptoms of itching, burning, and facial tenderness.

In addition to medical therapy, sun protection and appropriate skin care regimen need to be chosen because rosacea patients often exhibit marked skin sensitivity and suffer from intolerance to skin products and cosmetics.[3] In a National Rosacea Society survey of 1066 patients, 41% reported that certain skin care products aggravated their condition and 27% said certain cosmetics also caused rosacea flare-ups. Ingredients frequently quoted as triggers for irritation include alcohol (66%), witch hazel (30%), fragrance (30%), menthol (21%), peppermint (14%), and eucalyptus oil (13%). Most respondents said they avoided astringents, exfoliating agents, and other types of products that may be too harsh for sensitive skin.[4] Triggers for cutaneous flushing should be identified and eliminated. Commonly identifiable triggers include topical cosmetics and corticosteroids, alcohol, tobacco, exercise, hormonal changes, sun exposure, hot weather, exercise, ingestion of hot or spicy foods/drink, caffeine, emotional stress, and medications such as topical and systemic steroids, niacin, and nitroglycerin. A flare of rosacea may be anticipated when steroids are discontinued and may be dramatic.

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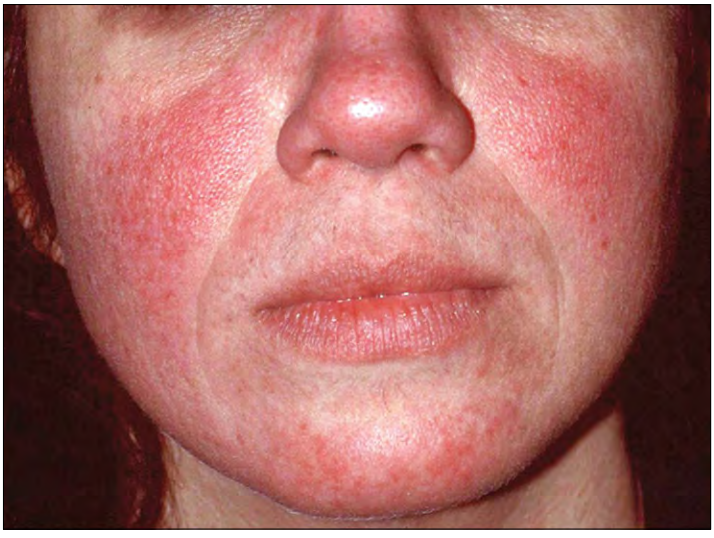

Figure 1. Facial redness associated with the erythematotelangiectatic rosacea subtype. Flushing, persistent redness, and visible blood vessels also may appear.

Currently, the following medications are the only drugs that are approved by the US Food and Drug Administration (FDA) for the treatment of rosacea:

- *Topical medications: metronidazole gel, cream, lotion 0.75% and 1%; azelaic acid cream 15% and 20%; sulfacetamide 10% with sulfur 5% gel, cream, topical suspension, wash)*
- *Systemic: Oracea 30 mg immediate release and 10 mg delayed release doxycycline*

Other non–FDA-approved treatments used off-label also have been beneficial and will be discussed below.

ETR

The ETR subtype is clinically characterized by diffuse erythema and telangiectasias on the cheeks, forehead, dorsal nose, or sometimes entire face (Figure 1). Patients frequently complain of intolerance or sensitivity to topical products and cosmetics.

This type of rosacea is best treated with avoidance of triggers leading to flushing, strict photoprotection, electrosurgery, and phototherapy. In recent years phototherapy and laser therapies have been gaining popularity as treatments of rosacea-associated erythema and telangiectasias. Laser therapies include pulsed dye laser (PDL), potassium-titanyl-phosphate (KTP) laser, Nd:YAG laser, or intense pulsed light (IPL).[5,6] In a study of 34 patients with ETR, IPL treatment resulted in overall patient and physician reported over 50% improvement in 73% and 83% of patients, respectively.[6] The results were sustained at 6 months. In a different study 83% of patients had less facial redness, 75% noted less flushing and better skin texture, and 64% noted fewer acneform breakouts.[7]

The use of nonpurpuragenic PDL and IPL treatment to reduce erythema, telangiectasia, and symptoms in patients with moderate facial ETR was evaluated in a case series on 29 patients.[5] Evaluation measures included spectrophotometric erythema scores, blinded investigator grading, and patient assessment of severity and associated symptoms. Both PDL and IPL resulted in reduction in cutaneous erythema, telangiectasia, and patient-reported associated symptoms. No significant difference was noted between PDL and IPL treatment.

A topical selective α-agonist, oxymetazoline, represents a novel approach to management of ETR-associated erythema and flushing. A small study showed notable benefit with the use of oxymetazoline in reducing the flares and the inflammatory symptoms in patients with traditional medication-resistant ETR.[8]

Facial edema may be a prominent clinical feature of rosacea. Recurrent vasodilation results in a feeling of fullness of the cheeks and visible subtle induration of the cheeks, so-called solid facial edema. Solid facial edema of ETR can respond to isotretinoin.

PR

The PR subtype is characterized by papules and pustules often on an erythematous base primarily affecting the nose, cheeks, and forehead. Predilection of the lesions on the central, convex aspect of the face, sometimes with corresponding central facial edema, is frequently noted.

TOPICAL THERAPIES

The major topical antibiotics used to treat PR are metronidazole, clindamycin, and erythromycin. Other topical therapies include azelaic acid, pimecrolimus, antiparasitics, α-adrenergic agonists, and topical sulfacetamide 10% with sulfur 5%.

Metronidazole

Clinical efficacy of topical metronidazole in the treatment of rosacea has been shown in a number of clinical trials.[9-12] The mechanism of action of metronidazole is not yet well established, but appears to be anti-inflammatory. Topical metronidazole is commercially available in a gel, lotion, and cream 0.75% for twice-daily use and a gel 1% for once-daily use. Twice-daily metronidazole 0.75% was shown to be well tolerated and effective in the treatment of 582 patients with mild to moderate PR.[12] Mean erythema severity score was reduced by 50% by week 12 of treatment.[13] In a 12-week, randomized control study, Jorizzo et al[14] showed that once-daily dosing of metronidazole cream 1% is as effective as twice-daily dosing. Metronidazole is generally well tolerated and has a low incidence of adverse side effects. Most commonly reported side effects include mild pruritus, skin irritation, and dryness.

In a recent Cochrane review, topical metronidazole was shown to be more effective than a vehicle in 174 patients with marked reduction of number of inflammatory lesions and erythema scores with an odds ratio of 5.96.[9] Metronidazole plays a role in maintenance therapy, either with or without prior concomitant systemic antibiotic therapy. Effect of metronidazole on rosacea-associated telangiectasias is minimal.

Sodium Sulphacetamide With Sulphur

Despite the lack of randomized, controlled studies, sodium sulphacetamide 10% with sulfur 5% vehicles have been used as a safe, well-tolerated, and effective treatment option for rosacea for over 50 years. Eight-week therapy with sodium sulphacetamide 10% with sulfur 5% resulted in a reduction in inflammatory lesions and facial erythema 80% and 69%, respectively. Adverse effects of topical application were generally mild and included pruritus, contact dermatitis, irritation, erythema, scale, and xerosis. A newer, emollient foam formulation of sodium sulphacetamide 10% with sulfur 5% offers similar benefits with less lingering odor.[15] Anecdotal evidence suggests synergistic benefit of concurrent sodium sulphacetamide 10% with sulfur 5% and metronidazole application.[15]

Azelaic Acid

Azelaic acid, commercially available as gel 15% or cream 20%, is a naturally occurring, saturated 9-carbon dicarboxylic acid derived from *Pityrosporum ovale*. Azelaic acid is FDA-approved for the treatment of mild to moderate rosacea. Its biologic effects encompass anti-inflammatory, antikeratinizing, and antibacterial properties. Recently, peroxisome proliferator activated receptor-γ activation was shown as a main modulator of the inflammatory response modulated by azelaic acid in normal human keratinocytes.[16]

Clinical safety and efficacy of azelaic acid gel 15% applied twice daily for 12 weeks has been demonstrated in 2 phase 3, vehicle-controlled, randomized trials of 664 patients with PR. On average, improvement of erythema ranged from 44% to 46% in patients treated with azelaic acid, compared with 28% to 29% in the vehicle group. A mean reduction in inflammatory papules and pustules ranged from 51% to 58% in the azelaic acid group, compared with 39% to 40% in the vehicle group.

Data from 3 clinical trials analyzed by Cochrane review showed rates of improvement in azelaic acid group of 70% to 80% compared with 50% to 55% in the placebo group.[9] In a randomized trial comparing topical metronidazole with azelaic acid, the efficacy of azelaic acid 20% was greater than metronidazole in improving erythema and inflammation in physician rating of global improvement.[17] Application of azelaic acid was associated with a greater irritation. Wolf et al[18] found the efficacy of once-daily application of metronidazole gel 1% and twice-daily azelaic acid gel 15% to be similar. Both medications were well tolerated, with the number of adverse effects slightly higher in azelaic acid group. All reported adverse effects were mild to moderate.[18]

Anecdotal evidence suggests beneficial effects of topical clindamycin, erythromycin, and combination benzoyl peroxide with clindamycin in the treatment of rosacea, but efficacy of these modalities have not yet been evaluated in well-designed clinical trials. In a double-blind, randomized controlled trial of once-daily clindamycin 1% with benzoyl peroxide 5% gel, a reduction in inflammatory lesion count and erythema was noted. The treatment was generally well tolerated.[19]

Tacrolimus and Pimecrolimus

Topical tacrolimus ointment 0.03% or 0.1% and pimecrolimus cream 1% are macrolide nonsteroidal immunomodulators. Their mechanism of action is inhibition of T-cell activation and inhibition of subsequent cytokine release. In a pilot study, topical pimecrolimus 1% showed clinical benefit with decreased erythema and number of inflammatory lesions after 12 to 18 weeks of therapy.[20] Another randomized trial, nonetheless, demonstrated that pimecrolimus was no more effective than the vehicle when used for 4 to 6 weeks.[21]

In a recent single-center, randomized, open-label study of 48 patients with PR comparing pimecrolimus with metronidazole, both treatments were very effective in the treatment of PR.[22] There were no differences between the treatments in inflammatory lesion counts, overall erythema

severity scores, and physician global assessment scores evaluated from baseline to week 12. Neither treatment produced any clinically relevant improvement in telangiectasia.

Rarely pimecrolimus may produce a syndrome similar to steroid-induced acne.[23]

Anecdotal evidence suggests that topical tacrolimus may be an effective treatment of steroid-induced rosacea, especially when combined with systemic minocycline.[24]

Retinoids

The role of topical retinoids in the management of rosacea remains controversial. The mechanism of action of the retinoids is regulation of the retinoic acid receptor, an important regulator of keratinocyte proliferation, differentiation, and cutaneous inflammation. Use of retinoids carries a theoretical benefit of decreased angiogenesis and decrease in cutaneous vascularity and possible prevention of new telangiectasias.[25] In a few small series, the topical retinoid tretinoin demonstrated benefit for rosacea with a lessening degree of erythema and a partial to complete disappearance of telangiectasias as well as a decrease in the number of inflammatory lesions, although the clinical response was delayed and not evident until 2 or more months of therapy.[26]

A small study demonstrated the efficacy of topical-free radical scavenger vitamin C for rosacea, suggesting the possibility that free radical production may play a substantial role in the inflammatory response seen in rosacea.[27]

Other Agents

Some antiparasitic drugs have been observed to be helpful as both oral and topical agents in the treatment of inflammatory rosacea. Oral ivermectin and lindane have shown some efficacy in the eradication of *Demodex folliculorum*, one possible factor that may lead to the inflammation underlying the condition.[28] Permethrin and crotamiton topically have not shown great usefulness in eradicating *D folliculorum*, but may still lead to the resolution of some of the underlying inflammation.[29] In a small randomized, double-blind, placebo-controlled study, permethrin cream 5% was found superior to the vehicle and similar in efficacy to metronidazole gel 0.75%.[30]

ORAL THERAPY

Antibiotics

Tetracyclines are broad-spectrum antibiotics that remain the mainstay of oral treatment for rosacea. Tetracycline (250–500 mg twice daily) and more recently second generation tetracyclines, doxycycline (100–200 mg per day and extended release 20–40 mg per day) and minocycline (100–200 mg per day), are commonly used oral therapies. Second generation tetracyclines have an improved bioavailability, longer elimination half-life, once-daily dosing, and can be taken with food, which minimizes gastrointestinal side effects. Azithromycin also has been shown to be beneficial for treating rosacea, is better tolerated than first generation tetracyclines, and can be dosed 3 times a week.[31,32]

The precise mechanism of action of tetracyclines remains unknown. More likely their anti-inflammatory rather than antimicrobial actions, such as the inhibition of angiogenesis, neutrophil chemotaxis, release of proinflammatory cytokines, cellular apoptosis, cell proliferation, and matrix metalloproteinases, contribute to clinical benefit in the management of rosacea. A notable benefit of second generation tetracyclines is their clinical effectiveness at subantimicrobial, anti-inflammatory doses limiting undesired side effects (candidal vulvovaginitis, gastrointestinal distress) and possibly bacterial resistance. Systemic tetracycline antibiotics should not be used in children under the age of 8 years because of potential permanent discoloration of teeth.

Anti-inflammatory dose doxycycline, a 40-mg doxycycline monohydrate containing 30 mg immediate-release and 10 mg delayed-release doxycycline, is the only tetracycline approved in the United States for long-term (<12 months) use. Commercially available as Oracea, it has been shown to be effective in treatment of PR with a favorable risk-benefit ratio. Used at subantimicrobial doses, long-term use of anti-inflammatory doxycycline might not exert selective pressure on bacteria, and thus limit development of bacterial resistance.[33]

Two phase 3, controlled studies have demonstrated the safety and efficacy of a 16-week treatment with anti-inflammatory 40 mg doxycycline administered daily in the management of PR.[33] Both studies included patients with inflammatory PR with 10 to 40 papules, moderate to severe erythema, and telangiectasias. At the end of 16 weeks, the mean change in lesion count in doxycycline groups was −11.8 and −9.5 lesions compared with −5.9 and −4.3 lesions in the placebo group. Doxycycline was well tolerated with a low incidence of adverse effects. Most commonly reported side effects included nasopharyngitis, diarrhea, and headaches. Efficacy beyond 16 weeks and safety beyond 9 months has not yet been established in randomized controlled studies.

Current research on a small number of patients suggests that combination therapy of oral anti-inflammatory dose of doxycycline and topical metronidazole leads to quicker and more effective alleviation of inflammatory lesions.[34,35]

Macrolides

Oral erythromycin at 250 to 1000 mg per day is considered an effective drug for the treatment of PR. The use of erythromycin is reserved for those patients that are intolerant, allergic, or refractory to tetracyclines or in cases when tetracycline therapy is contraindicated (eg, pregnancy).

Second generation macrolides clarithromycin and azithromycin were found to be effective and tolerable drugs in short-term therapy of rosacea. At the end of a 12-week treatment with azithromycin, a 75% decrease in total scores and an 89% decrease in inflammatory lesion scores was noted compared with baseline values.[36]

A substantial amount of circumstantial evidence links the eradication of *Helicobacter pylori* and treatment of rosacea with a "triple therapy," consisting of omeprazole and 2 of the following antibiotics: clarithromycin, amoxicillin, or metronidazole.[29]

Metronidazole

In a randomized study of oral metronidazole (200 mg twice daily) versus oxytetracycline (250 mg twice daily) both drugs produced an improvement after 6 and 12 weeks of therapy, respectively, with no notable differences between the 2 treatments.[37] In rare instances, treatment with oral metronidazole might be associated with epileptiform seizures, encephalopathy, and sensory neuropathy. Oral metronidazole also requires abstinence from alcohol.

Isotretinoin

In a small number of clinical trials, isotretinoin was found to be effective in the treatment of both ETR and PR. Isotretinoin, although not an antibiotic, may have antibacterial effects.[38] A small study of 22 patients showed the effectiveness of 4-month low-dose (10 mg) isotretinoin therapy in patients with therapy-resistant rosacea. The treatment led to a reduction of number of inflammatory lesions, erythema, and telangiectasia.[39] The overall effect of isotretinoin therapy was delayed in comparison to therapy with oral antibiotics.

Gollnick et al[40] compared efficacy of isotretinoin (0.1 mg/kg, 0.3 mg/kg, or 0.5 mg/kg) with doxycycline (100 mg daily for 14 days, followed by 50 mg daily) in the treatment of grade 2 and 3 rosacea in a double-blinded, randomized 12-week study. Isotretinoin 0.3 mg/kg proved to be the most effective dose compared with placebo. Isotretinoin 0.3 mg/kg treatment resulted in 90% reduction of number of lesions compared with 83% reduction with doxycycline. The dose of isotretinoin was generally well tolerated.

Other Therapies

Other oral therapies that have shown benefit are medications that reduce flushing: β-blockers, clonidine, naloxone, ondansetron, and selective serotonin reuptake inhibitors.[41] Oral contraceptive therapy has been helpful in patients who experience worsening rosacea with their hormonal cycle. Dapsone has been used in severe, refractory rosacea, and has been particularly beneficial for patients who cannot take isotretinoin.[42] Number of anti-inflammatory botanical cosmeceuticals, including licochalcone A (licorice extract), chamomile, feverfew, oatmeal, pycnogenol, lycopene, silymarin, quercetin, and allantoin, have been reported to reduce inflammation associated with rosacea. These compounds, however, are not FDA-approved.

As previously mentioned, both laser and light sources proved to be successful in the management of rosacea-associated erythema. In a study, patients treated for telangiectasia and erythema with a flashlamp PDL, good or excellent reduction of telangiectasia and erythema and overall appearance was achieved in 24 of 27 patients with 1 and 3 treatments.[43] In addition, papule and pustule activity was decreased in 59.2% of the patients, with those with the most severe pretreatment activity having the most improvement.

More recently, photodynamic therapy with either 5-aminolevulinic acid or methylaminolevulate acid was shown to provide benefit in the management of inflammatory PR.[44] In a case series of 17 patients, routine photodynamic therapy with methylaminolevulate acid and red light administered 1 to 4 times resulted in "good" clinical outcome in 10 of 17 patients, and "fair" results in 4 patients.[45] The majority of patients treated could stop or substantially reduce other rosacea therapy for a period lasting from about 3 months and up to 2 years.

PHYMATOUS ROSACEA

Phymatous rosacea is characterized by thickening of the skin, irregular skin texture, edema, hypertrophy, and hyperplasia of sebaceous glands, connective tissue, and vascular bed. Phymatous rosacea commonly involves the nose (rhinophyma), but changes also can be seen on the chin (gnathophyma), ears (otophyma), forehead (metophyma), and eyelids (blepharophyma).[24] This severe form of rosacea requires aggressive medical therapy with systemic antibiotics, and sometimes warrants use of isotretinoin. Once the medical regimen has been maximized, the patient may be a good candidate for surgery or laser treatment. Electrosurgical sculpturing of the phymatous skin gives excellent results, is fast, and is almost bloodless.[46] A carbon dioxide laser or erbium:YAG laser also may be used for the treatment of rhinophyma, although it is more costly and time-consuming than electrosurgical treatment. Electrosurgical treatment is more likely than laser to scar.

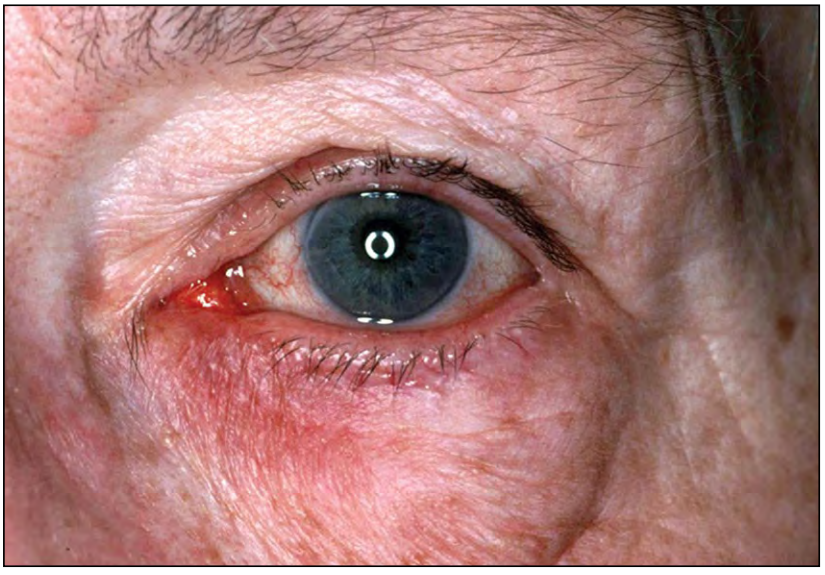

Figure 2. Eye irritation associated with the ocular rosacea subtype. Eyes may have a watery or bloodshot appearance, and individuals may experience irritation, burning, or stinging around the eyes.

Standard surgery and dermabrasion also are effective, but they are more difficult to perform due to the vascularity of the nose.

OCULAR ROSACEA

Ocular rosacea can be seen in the presence or absence of skin manifestations of rosacea (Figure 2). Clinically, ocular rosacea is characterized by conjunctival erythema and injection (sometimes accompanied by eyelid edema), foreign body sensation, inflammation of the lids (blepharitis) and meibomian glands, interpalpebral conjunctival hyperemia, conjunctival telangiectasias and/or glandular inflammation (chalazion) along the eyelid margin.[47] Patients report subjective symptoms such as foreign body sensations, dry eyes, stinging, itching, burning, and photosensitivity. The vision is rarely affected. Ocular rosacea is treated with systemic antibiotics. Oral tetracyclines, including low dose doxycycline, are an excellent first-line therapy for this form of rosacea. Topical corticosteroid eyedrops also may be beneficial.

OTHER ROSACEA SUBTYPES

Granulomatous rosacea is a variant of rosacea clinically presenting with noninflammatory erythematous to brownish papules with peripheral erythema on the malar and perioral region. Treatment of the granulomatous variant is difficult. In a case report, granulomatous rosacea refractory to traditional treatments was treated with IPL with satisfactory improvement.[48] The authors postulated that IPL with nonfixed wavelengths, ranging from visible to infrared, might provide an added benefit of treating telangiectasias at different depths leading to subsequent improvement.[48]

Rosacea fulminans (sudden onset of coalescent papules, pustules, and nodules) may occur with pregnancy, thyroid diseases, depression, emotional stress, or with intake of some medications.[49,50] This exacerbation may require use of systemic corticosteroids (prednisone 0.5 to 1 mg/kg per day) and/or isotretinoin.

CONCLUSION

Rosacea is a complex disease process with unclear etiology. The mainstay of rosacea therapy remains topical treatment with metronidazole, azelaic acid, and oral tetracyclines. As this disease process causes increased skin sensitivity, trigger avoidance and sun protection are crucial.

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