

The Use of Azelaic Acid 15% Gel, Topical Retinoids, and Photoprotection in the Management of Rosacea and Comorbid Dermatologic Disorders

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Rosacea is a common chronic, inflammatory disease of the skin that can significantly affect quality of life. Although the pathophysiology of rosacea remains unclear, most researchers and clinicians agree that it is a photoaggravated disorder and that the signs of rosacea often parallel those of photoaging and photodamage. The cases presented in this article underscore the relationship that may exist between UV light damage and rosacea. Fortunately, there is an array of topical medications that can help manage this photoaggravated disorder. Azelaic acid is a naturally occurring component of grains that has demonstrated efficacy in the treatment of rosacea and acne vulgaris. Although its mechanism of action is unknown, azelaic acid probably has anti-inflammatory and antioxidant effects. It also has been used successfully as monotherapy and in combination with tretinoin to treat dyschromias such as melasma and postinflammatory hyperpigmentation. The topical application of all-*trans*-retinoic acid has been shown to provide photoprotection and, with prolonged use, to repair UVA- and UVB-mediated skin damage. The unique combination of azelaic acid, topical tretinoin (off label), and a physical sunblock can provide long-term management of rosacea.

Rosacea is a common chronic, inflammatory disease of the skin. Frequent facial flushing and sun damage, especially solar elastosis, are consistent characteristics of rosacea.¹ Other signs include inflammatory lesions (papules and pustules). In addition, some patients develop phyma, or tissue overgrowth. This constellation of symptoms can significantly impact the quality of life of individuals with rosacea. Fortunately,

we can empower our patients to gain control of their disease (Table).

Although the pathophysiology of rosacea remains unclear, most researchers and clinicians agree that it is a photoaggravated disorder.^{2,3} A study conducted by Kosmadaki et al⁴ found that exposure to UV radiation appears to trigger the release of vascular endothelial growth factor, leading to new but distorted blood vessels that often become visible signs of rosacea (telangiectasias). Evidence suggests that prolonged exposure to UV light can lead to a detrimental inflammatory process, including the production of damaging oxygen free radicals.⁵⁻¹⁰ UV radiation stimulates angiogenesis (ie, telangiectasias), vascular leakage, and a subsequent inflammatory cascade that alters the integument, contributing to signs and symptoms of rosacea.^{1,2,8-10} Signs of rosacea

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Initial and Continuous Education for the Patient With Rosacea

- Recognize that rosacea is a chronic, progressive, inflammatory disease of the skin
- Identify and minimize triggers that induce flushing
- Use a daily maintenance regimen to keep rosacea at bay
- Listen to your skin and call your dermatologist if you have any problems or concerns
- Follow up with an ophthalmologist to screen for or treat ocular rosacea
- Request written educational material from your dermatologist as reinforcement
- Practice daily sun-smart behavior
- Use physical sunblock containing zinc oxide or titanium dioxide as daily moisturizer (sun protection factor of 30 or above)
- Reapply sunblock every 2 hours when exposed to UV radiation
- Seek shade when feasible
- Wear protective clothing, eyewear, wide-brimmed hat

often parallel those of photoaging and photodamage.^{3,11} The classic histopathologic signs of rosacea include damage to the dermal matrix (elastosis) and damage to the dermal collagen (collagenolysis).^{2,3,11} Indeed, according to Kligman,¹² separating rosacea from advanced photodamage is difficult, “because the two may come together.”

Excessive sun damage may perhaps correspond to an increased severity of rosacea, particularly the erythematotelangiectatic subtype. This correlation is seen within our large university-based practice. Unfortunately, there are no large studies that associate the amount of photodamage with severity of disease in patients with rosacea.

TOPICAL THERAPEUTIC OPTIONS

Azelaic Acid

Azelaic acid is a naturally occurring component of grains that is available in a hydrogel formulation.^{13,14} It has an acceptable safety and efficacy profile and is generally well tolerated in the treatment of rosacea.¹⁵⁻¹⁷ Its proposed anti-inflammatory and antioxidant mechanisms also make it a reasonable option for treating acne lesions.^{18,19} Additionally, various topical formulations of azelaic acid have been used successfully as monotherapy and in combination

with tretinoin in the treatment of dyschromias such as melasma and postinflammatory hyperpigmentation.^{20,21} The inflammatory lesions of perioral dermatitis have also responded favorably to azelaic acid.²²

Topical Retinoids

Topical all-*trans*-retinoic acid has demonstrated photoprotective effects.^{23,24} The mechanisms responsible for this photoprotection could involve anti-inflammatory and antioxidant effects.^{25,26} These mechanisms, in addition to the known ability of retinoids to normalize hyperkeratinization, may be at least partially responsible for the efficacy of topical retinoids in dyschromias and inflammatory and keratotic dermatoses.²⁷⁻²⁹ Multiple studies, dating back to 1962, have proven tretinoin capable of achieving complete regression of actinic keratoses (AKs) and basal cell carcinomas.³⁰⁻³⁶ Its efficacy, however, is not comparable to that of other treatment modalities, and it is generally used adjunctively for this reason. It would be prudent, however, to use topical retinoids for chemoprevention of precancerous lesions.³⁷⁻⁴¹

The following cases illustrate the use of topical azelaic acid and topical tretinoin for the treatment of various comorbid dermatologic conditions.

CASE REPORTS

Case 1

This first case involved a 53-year-old woman who presented with a 4-year duration of progressive facial redness that had become more pronounced in the previous 2 years. The patient's medical history was significant for basal cell carcinoma, but negative for malignant melanoma or squamous cell carcinoma. She had an “itchy spot” on the left cheek (mildly scaly, atrophic plaque) that had been present for the previous 6 months. Also evident were signs of solar lentigines, elastosis, and generalized dermatoheliosis. Additionally, she showed signs of moderate, centralized, nonconfluent facial erythema, telangiectasias, and multiple pink plaques (some with minimal scale) on her forehead (Figure 1A). The patient was diagnosed with AKs, dermatoheliosis, and moderate rosacea. Known triggers for her rosacea flares included alcohol, stress, weather and temperature changes, heat, and exercise. At baseline she had not been treated previously for rosacea and did not use daily sunblock. Treatment for the AKs included fluorouracil 0.5% cream once daily for 6 weeks, applied sparingly to the cheeks and forehead. The patient was advised to discontinue therapy for 1 to 2 days if the areas became tender, scabbed, or blister-like, to apply petroleum jelly or Aquaphor®, and then resume therapy when these adverse events resolved. She was also advised to engage in a monthly cutaneous self-examination and to present for an annual full cutaneous

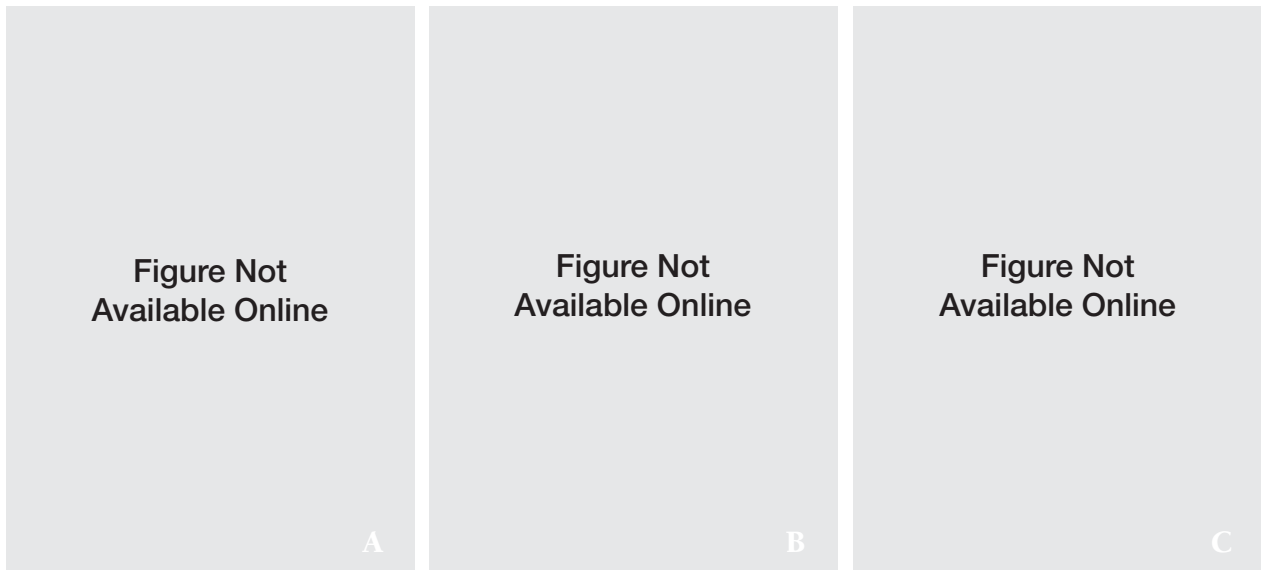


Figure 1. A 53-year-old woman with actinic keratoses, dermatoheliosis, and moderate rosacea prior to topical therapy (A), 1 month after using azelaic acid 15% gel twice daily and tretinoin 0.05% cream every night (B), and 2 months after using azelaic acid 15% gel twice daily and tretinoin 0.05% cream every night (C). The actinic keratoses resolved, and dermatoheliosis and rosacea improved significantly. The actinic keratoses were treated with fluorouracil 0.5% cream daily for 6 weeks before topical therapy for rosacea was prescribed.

examination with her dermatology health care provider. Clinical findings following fluorouracil therapy resulted in resolution of the AKs. She was then prescribed azelaic acid 15% gel twice daily and tretinoin 0.05% cream every night as maintenance therapy for rosacea. She was also counseled about daily photoprotection and avoidance of rosacea triggers. The erythema and overall dermatoheliosis showed significant improvement after utilizing this treatment regimen for 1 month (Figure 1B), and progressive enhancement was appreciated after 2 months (Figure 1C). The subsequent treatment plan involved use of a pulsed dye laser (PDL) for recalcitrant erythema and telangiectasias, and the patient was instructed to return for follow-up in 6 to 8 weeks.

Comment—This case underscores the relationship that may exist between UV damage and rosacea. Topical tretinoin (off label) coupled with a daily physical sunblock will serve as chemoprevention for further AKs while adding an anti-inflammatory and antioxidant benefit. Azelaic acid provides adjunctive anti-inflammatory and antioxidant protection. This unique combination should provide long-term management of rosacea.

Case 2

This patient was a 47-year-old woman who reported acnelike breakouts for more than 10 years prior to being referred to our facility. She also was frustrated with her progressive facial redness and was unsure of her triggers. Prior treatment regimens for these conditions included oral isotretinoin for approximately 5 months, sodium

sulfacetamide 10% lotion for 4 years, tretinoin 0.05% cream for 6 years, and metronidazole 0.75% in both gel and cream formulations for 6 years. She initially presented with moderate, confluent facial erythema and telangiectasias that were greatest in the malar region. Enlarged pores were present without inflammatory papules or pustules, and she did not complain of facial itching. This patient was diagnosed with moderate rosacea, including telangiectasias. Two treatments with PDL were initiated 2 months apart to treat the erythema and telangiectasias. She was advised to continue using photoprotection adjunctively with metronidazole 0.75% cream once or twice daily and tretinoin 0.05% cream every night. The PDL, coupled with pharmacologic interventions, resulted in clearing of her symptoms. She was counseled regarding the imperative aspects of rosacea prevention. Approximately 6 months later, her condition had worsened, and she evidenced multiple itchy, red lesions. Physical examination revealed greasy-looking patches of skin with marked confluent erythema as well as inflammatory papules above her medial forehead, cheeks, and nose. The patient was diagnosed with acute seborrheic dermatitis and rosacea exacerbation (Figure 2A). She was advised to continue use of her physical sunblock, but to discontinue topical metronidazole and tretinoin. She was prescribed ketoconazole 2% cream twice daily to be used on her entire face for 3 weeks. The patient was restarted on tretinoin 0.05% cream every night after the ketoconazole course was completed. She was instructed to use azelaic acid 15% gel twice daily in addition to treatment



Figure 2. A 47-year-old woman with seborrheic dermatitis and rosacea exacerbation using metronidazole 0.75% cream once or twice daily and tretinoin 0.05% cream every night (A) and 5 months after using ketoconazole 2% cream twice daily for 3 weeks followed by azelaic acid 15% gel twice daily and tretinoin 0.05% cream every night (B). Seborrheic dermatitis resolved and rosacea improved.

with topical tretinoin. This regimen was able to resolve her seborrheic dermatitis and improve her rosacea. (Figure 2B; no PDL between photos). The patient then was scheduled for PDL treatments at 6- to 8-week intervals to address recalcitrant erythema and telangiectasias. She was advised to continue using azelaic acid 15% gel twice daily and tretinoin 0.05% cream every night as a maintenance regimen, along with routine use of a physical sunblock.

Comment—Rosacea often occurs concomitantly with seborrheic dermatitis.⁴¹ These disorders may result from an inflammatory reaction to yeasts.⁴² Topical corticosteroids have been used to treat seborrheic dermatitis. Unfortunately, they carry a risk of skin atrophy and can, with prolonged use, exacerbate inflammatory rosacea and induce telangiectasias.⁴² Topical metronidazole has shown promise for this indication.⁴³ Interestingly, however, this patient had been using topical metronidazole to treat her rosacea for the previous 6 years and still suffered an outbreak of seborrheic dermatitis. Antifungal agents offer efficacy without risk of corticosteroid-induced rosacea exacerbation.⁴⁴⁻⁴⁶

Case 3

A 46-year-old woman had been diagnosed with rosacea 8 years prior to presenting to our facility. Classified as a Fitzpatrick phototype I, she was highly sensitive to sun exposure and at increased risk for UV-induced skin carcinomas. Prior to seeking treatment at our facility, she had undergone a number of previous treatment interventions: potassium-titanyl-phosphate laser in 1999, cauterization

in 2000, and metronidazole 0.75% gel for 2 months without success.

While under our care, she received a total of 4 PDL sessions, which ended in July 2006. The PDL decreased her erythema and telangiectasias. She was treated with sodium sulfacetamide 10% lotion for 1 year coupled with tretinoin 0.05% cream for 2 years that resulted in decreased breakouts. She was using a zinc oxide-based sunblock as a moisturizer. Upon routine follow-up, this patient had noticed that her skin had suddenly become oilier. She claimed not to have changed any skin care products for the past year. The patient presented with moderate, centralized, nonconfluent facial erythema on her forehead, medial cheeks, and nose. Also evident were oil gland enlargements on her forehead (Figure 3A). She was advised to discontinue the

sodium sulfacetamide 10% lotion and to continue with the tretinoin 0.05% cream every night; azelaic acid 15% gel was added to her pharmacologic regimen. Initially, the patient was advised to titrate the topical azelaic acid from once to twice daily based on her facial tolerance. Additionally, she received education to reinforce photoprotection and other issues related to rosacea prevention. Marked improvements in her erythema and oil gland enlargements (sebaceous hyperplasia) were noted (Figure 3B). For maintenance, she was advised to continue with the tretinoin 0.05% cream every night and the azelaic acid 15% gel twice daily and to use her physical sunblock as her daily moisturizer. PDL therapy for recalcitrant erythema and telangiectasias will follow as deemed necessary at 6- to 8-week intervals.

Comment—Implementing a topical maintenance regimen is often challenging because patients with rosacea generally have sensitive skin. It is important to inform patients that retinoid-induced peeling is a healthy process that occurs during the first 6 to 12 weeks of therapy and subsides thereafter, depending on the amount of photodamage present. The peeling phase can be prolonged if it is counteracted by overmoisturizing or discontinuation of therapy.

Dermatology health care providers can reinforce the fact that retinoids have the ability to reveal and eliminate superficial precancerous lesions. This information is often comforting to patients and enables them to persevere through the temporary irritation phase of treatment.

This patient was encouraged to use a physical sunblock, such as one containing zinc oxide, as her moisturizer and

Figure Not
Available Online

A

Figure Not
Available Online

B

Figure 3. A 46-year-old woman with moderate rosacea using sodium sulfacetamide 10% lotion every day and tretinoin 0.05% cream every night (A) and 2 months after using azelaic acid 15% gel twice daily and tretinoin 0.05% cream every night (B). Rosacea improved with the topical regimen and sun-smart behavior.

to avoid additional moisturizers when possible. In light of the role played by UV exposure in the etiology of rosacea, it is reasonable to use an adjunctive topical agent with antioxidant properties, such as *l*-ascorbic acid.^{47,48}

SUMMARY

Although it is generally thought that sun exposure is one of the most important factors in the etiology of rosacea, observational studies correlating UV light exposure with rosacea severity are lacking. However, anecdotal studies suggest that it is prudent to advise patients to routinely use a physical sunblock, such as one containing zinc oxide or titanium dioxide. Sun-smart behavior may prove to be important in the battle against rosacea, photocarcinogenesis, and photoaging.

A number of topical agents exist for the treatment of rosacea. Azelaic acid and topical metronidazole are treatments validated by randomized, controlled trials.^{15,17} The use of topical retinoids and *l*-ascorbic acid in rosacea is not validated by the same order of evidence. However, these agents have demonstrated usefulness in anecdotal reports. It is important to tailor a topical regimen for each individual patient with rosacea based on comorbid dermatologic conditions. Health care providers have the ability to empower patients with the knowledge and skills to achieve control of their rosacea and ultimately improve the quality of their lives.

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REFERENCES

1. Millikan L. The proposed inflammatory pathophysiology of rosacea: implications for treatment. *Skinmed*. 2003;2:43-47.
2. Dahl MV. Pathogenesis of rosacea. *Adv Dermatol*. 2001;17:29-45.
3. Murphy G. Ultraviolet light and rosacea. *Cutis*. 2004;74(3 suppl):13-16.
4. Kosmadaki MG, Yaar M, Arble BL, et al. UV induces VEGF through a TNF- α independent pathway. *FASEB J*. 2003;17:446-448.
5. Kawaguchi Y, Tanaka H, Okada T, et al. Effect of reactive oxygen species on the elastin mRNA expression in cultured human dermal fibroblasts. *Free Radic Biol Med*. 1997;23:162-165.
6. Miyachi Y. Potential antioxidant mechanism of action for metronidazole: implications for rosacea management. *Adv Ther*. 2001;18:237-243.
7. Oztas MO, Balk M, Ogos E, et al. The role of free oxygen free radicals in the aetiopathogenesis of rosacea. *Clin Exp Dermatol*. 2003;28:188-192.
8. Baz K, Cimen MY, Kokturk A, et al. Plasma reactive oxygen species activity and antioxidant potential levels in rosacea patients: correlation with seropositivity to *Helicobacter pylori*. *Int J Dermatol*. 2004;43:494-497.
9. Jones D. Reactive oxygen species and rosacea. *Cutis*. 2004;4(3 suppl):17-20.
10. Obagi S, Rolewski S. Rethinking the role of tretinoin in the management of rosacea. *Cosmet Dermatol*. 2004;17:505-511.
11. Katoulis AC, Georgala S, Stavrianeas NG. Poikiloderma of civatte and rosacea: variants in the same nosological spectrum? *Dermatology*. 2005;211:386-387.
12. Kligman AM. A personal critique on the state of knowledge of rosacea. *Dermatology*. 2004;208:191-197.
13. Fleischer AB Jr. The evolution of azelaic acid. *Cutis*. 2006;77(2 suppl):4-6.
14. Elewski B, Thiboutot D. A clinical overview of azelaic acid. *Cutis*. 2006;77(2 suppl):12-16.
15. Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase III studies. *J Am Acad Dermatol*. 2003;48:836-845.
16. Frampton JE, Wagstaff AJ. Azelaic acid 15% gel: in the treatment of papulopustular rosacea. *Am J Clin Dermatol*. 2004;5:57-64.
17. Elewski BE, Fleischer AB Jr, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. *Arch Dermatol*. 2003;139:1444-1450.
18. Passi S, Picardo M, Zompetta C, et al. The oxyradical-scavenging activity of azelaic acid in biological systems. *Free Radic Res Commun*. 1991;15:17-28.
19. Akamatsu H, Komura J, Asada Y, et al. Inhibitory effect of azelaic acid on neutrophil functions: a possible cause for its efficacy in treating pathogenetically unrelated diseases. *Arch Dermatol Res*. 1991;283:162-166.
20. Graupe K, Verillo-Rowell VM, Verillo V, et al. Combined use of 20% azelaic acid and 0.05% tretinoin cream in topical treatment of melasma. *J Dermatol Treat*. 1996;7:235-237.
21. Del Rosso JQ. The use of topical azelaic acid for common skin disorders other than inflammatory rosacea. *Cutis*. 2006;77(2 suppl):22-24.

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22. Jansen T. Azelaic acid as a new treatment for perioral dermatitis: results from an open study. *Br J Dermatol*. 2004;151:933-934.
23. Bhawan J, Olsen E, Lufrano L, et al. Histologic evaluation of the long-term effects of tretinoin on photodamaged skin. *J Dermatol Sci*. 1996;11:177-182.
24. Gilchrist BA. Retinoids and photodamage. *Br J Dermatol*. 1992;127(suppl 41):14-20.
25. Francz PI, Conrad J, Biesalski HK. Modulation of UVA-induced lipid peroxidation and suppression of UVB-induced ornithine decarboxylase response by all-*trans*-retinoic acid in human skin fibroblasts in vitro. *Biol Chem*. 1998;379:1263-1269.
26. Chouinard N, Rouabhia M. Effects of all-*trans* retinoic acid on UVB-irradiated human skin substitute. *J Cell Physiol*. 1999;181:14-23.
27. Yoshioka A, Miyachi Y, Imamura S, et al. Anti-oxidant effects of retinoids on inflammatory skin diseases. *Arch Dermatol Res*. 1986;278:177-183.
28. Rolewski SL. Clinical review: topical retinoids. *Dermatol Nurs*. 2003;15:447-450, 459-465.
29. Orfanos CE, Zouboulis CC, Almond-Roesler B, et al. Current use and future potential role of retinoids in dermatology. *Drugs*. 1997;53:358-388.
30. Stüttgen G. Historical perspectives of tretinoin. *J Am Acad Dermatol*. 1986;15:735-740.
31. Stüttgen G. Zur Lokalbehandlung von Keratosen mit Vitamin A-Säure. *Dermatologica*. 1962;124:65-80.
32. Klein E, Stoll HI, Milgrom H, et al. Tumors of the skin, VI: study on effects of local administration of 5-fluorouracil in basal cell carcinoma. *J Invest Dermatol*. 1966;47:22-26.
33. Bollag W, Ott F. Retinoic acid: topical treatment of senile or actinic keratoses and basal cell carcinoma. *Agents Actions*. 1970;1:172-175.
34. Robinson TA, Kligman AM. Treatment of solar keratoses of the extremities with retinoic acid and 5-fluorouracil. *Br J Dermatol*. 1975;92:703-706.
35. Gold MH, Nestor MS. Current treatments of actinic keratosis. *J Drugs Dermatol*. 2006;5(2 suppl):17-25.
36. Peck GL. Topical tretinoin in actinic keratosis and basal cell carcinoma. *J Am Acad Dermatol*. 1986;15:829-835.
37. Purcell SM, Pierce DK, Dixon SL, et al. Chemoprevention of actinic keratosis with topical all-*trans*-retinoic acid [abstract]. *J Invest Dermatol*. 1986;86:501.
38. Papa CM. Tretinoin therapy for precancerous skin. *N J Med*. 1989;86:361-365.
39. Lever L, Marks R. Topical retinoid treatment for skin cancer: a review. *Skin Pharmacol*. 1991;4:125-131.
40. Noble S, Wagstaff AJ. Tretinoin: a review of its pharmacological properties and clinical efficacy in the topical treatment of photodamaged skin. *Drugs Aging*. 1995;6:479-496.
41. Stockfleth E, Ulrich C, Meyer T, et al. Epithelial malignancies in organ transplant patients: clinical presentation and new methods of treatment. *Recent Results Cancer Res*. 2002;160:251-258.
42. Powell FC. Clinical practice: rosacea. *N Engl J Med*. 2005;352:793-803.
43. Gupta AK, Bluhm R, Cooper EA, et al. Seborrheic dermatitis. *Dermatol Clin*. 2003;21:401-412.
44. Parsad D, Pandhi R, Negi KS, et al. Topical metronidazole in seborrheic dermatitis—a double-blind study. *Dermatology*. 2001;202:35-37.
45. Skinner RB Jr, Noah PW, Taylor RM, et al. Double-blind treatment of seborrheic dermatitis with 2% ketoconazole cream. *J Am Acad Dermatol*. 1985;12:852-856.
46. Green CA, Farr PM, Shuster S. Treatment of seborrheic dermatitis with ketoconazole, II: response of seborrheic dermatitis of the face, scalp and trunk to topical ketoconazole. *Br J Dermatol*. 1987;116:217-221.
47. Farris PK. Topical vitamin C: a useful agent for treating photoaging and other dermatologic conditions. *Dermatol Surg*. 2005;31:814-817.
48. Lin JY, Selim MA, Shea CR, et al. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. *J Am Acad Dermatol*. 2003;48:866-874. ■