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CLINICAL UPDATE

Topical Retinoids in Acne:
Emerging Strategies for Tolerability, Maintenance, and Skin of Color

Topical retinoids are a mainstay for the treatment of acne vulgaris, and several agents are currently available; however, key issues remain concerning the use of these agents. These issues include tolerability, optimal regimens for maintenance treatment, and use in skin of color. In addition, employment of antimicrobials for the management of acne has come under fire as a result of increasing rates of bacterial resistance. Each of these clinical considerations will be discussed in this supplement through a review of the literature, and practical tips to enhance patient outcomes will be provided.

ACCREDITATION
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Elsevier Office of Continuing Medical Education (EOCME) and Skin & Allergy News. The EOCME is accredited by the ACCME to provide continuing medical education (CME) for physicians.

CME CREDIT STATEMENT
The EOCME designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should claim only those credits commensurate with the extent of their participation in the activity.

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TARGET AUDIENCE
This activity has been developed for dermatologists who are involved in the diagnosis and management of acne.

EDUCATIONAL NEEDS
Although topical retinoids have been a mainstay in the treatment of acne, the strategies for their utilization continue to evolve. Emerging therapies and regimens offer dermatologists a broader range of options to improve tolerability, sustain positive clinical outcomes, and effectively treat a diverse patient population. This supplement provides an assessment of the current trends in topical retinoid therapy and discusses strategies for achieving the best results for patients with acne. Dermatologists reading this supplement can benefit from the practical tips and perspectives offered by the recognized program faculty and can apply this new knowledge in their daily practice to improve clinical outcomes for their patients.

LEARNING OBJECTIVES
By reading and studying this supplement, participants should be able to:
- Identify practical and effective ways to improve tolerability of retinoids for the treatment of acne
- Understand and implement acne maintenance regimes for optimal clinical results
- Compare and contrast acne in patients with skin of color.

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Dr Baldwin serves on the Speaker's Bureau for Allergan Inc., Galderma Laboratories, OrthoNeutrogena, and Stiefel Laboratories and is also a consultant for CollaGenex, Inc. Dr Tanghetti has received funding for clinical grants from, is a consultant for, and serves on the Speaker's Bureau for Allergan Inc. and Stiefel Laboratories. Dr Taylor has received funding for clinical grants from, is a consultant for, and serves on the Speaker's Bureau for Allergan Inc., Galderma Laboratories, and Johnson & Johnson Family of Companies. She intends to reference unlabeled/unapproved uses of tazarotene and tretinoin.

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Improving Tolerability While Maintaining Efficacy: Practical Tips

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The tolerability as well as efficacy of topical retinoids affect their clinical utility in acne vulgaris. The efficacy of topical retinoids is best judged one to another against comedonal acne. In data from a number of studies (N=630), reduction in comedonal lesion count after 12 weeks of therapy ranged from 55% to 71% for tazarotene 0.1% cream or gel and 36% to 48% for adapalene 0.1% cream or gel, tretinoin 0.025% gel, and tretinoin microsphere 0.1% (*P* values for tazarotene versus other agents ranged from $P<0.001$ to $P=0.042$) [*Cutis*. 2002;69(2 suppl): 12-19; *J Drugs Dermatol*. 2005;4(2): 153-158; *Cutis*. 2002;69(2 suppl): 4-11; *Cutis*. 2001;67(6 suppl):4-9]. Thus, for comedonal acne, it is evident that more potent retinoids are more effective than less potent agents. Other clinical parameters, such as total lesion count and inflammatory lesions, may not adequately differentiate one retinoid from another, as all retinoids directly or indirectly reduce inflammatory lesion count. In the studies mentioned above, the reduction in inflammatory lesion count showed less of a difference between agents and ranged from 54% to 70% for tazarotene preparations and 44% to 55% for tretinoin and adapalene (*P* values for tazarotene versus other agents significant only versus adapalene gel, where $P=0.0002$).

There are few studies addressing the comparative tolerability of retinoids. To address this issue, Leyden and colleagues utilized a split-faced, randomized, investigator-masked design in 253 healthy volunteers. Each subject used one retinoid formulation (tazarotene 0.05% and 0.1% cream, tazarotene 0.1% gel, adapalene 0.1% cream and gel, tretinoin 0.02% and 0.05% emollient cream, tretinoin 0.1% cream, tretinoin microsponge 0.1%) applied on one side of the face and a different formulation on the other side of the face for up to 29 days [*J Drugs Dermatol*. 2004;3(6): 641-651]. Erythema and dryness/peeling varied between formulations and vehicles, and did not appear to be an attribute of any given retinoid. Skin sensitivity proved to be an important factor, with sensitive skin (history of difficulty with detergents or topical products) exhibiting worse tolerability than did normal skin (*P* values for dryness/peeling in those with normal versus sensitive skin ranged from $P<0.001$ to $P=0.059$).

In real-world clinical experience, all retinoids are inherently irritating, and patients with sensitive skin (ie, overreaction to all exogenous stimuli, and in conditions such as atopic dermatitis, rosacea, and psoriasis) typically find retinoids more irritating than do those with normal skin. A key challenge is to control irritation and thereby enhance tolerability. There are a number of factors that can enhance the tolerability of all retinoids. More potent retinoids can then be used to permit the clinician to best address the patient's acne.

Epidermal Barrier Integrity Is Linked to Tolerability

The problem with tolerability sometimes observed in patients with sensitive skin appears to be largely related to the integrity of the epidermal barrier. Epidermal barrier disruption leads to transepidermal water loss from the stratum corneum, with xerosis and peeling occurring when water content decreases below 10% [*Dermatol Clin*. 2000;18(4): 597-607]. There are multiple forces besides skin sensitivity that work against efforts to maintain epidermal barrier integrity. These include products that contain soap and/or surfactants, or retinoids [*Br J Dermatol*. 1996;134(3):424-430], and environmental factors such as sunburn, low temperature, and low humidity.

There are some simple suggestions and solutions that can enhance the integrity of the epidermal barrier (Table 1). Indeed, barrier restoration alone may significantly improve outcomes in dermatologic conditions. Simple emollients play an important role in maintaining barrier function [*Am J Contact Dermat*. 2000;11(3):165-169; *Cutis*. 1998;61(6):344-346], with timing of application and type of product (hydrating versus occluding) being important considerations.

For example, a comparison of betamethasone-17-valerate, hydrocortisone, and petrolatum for the treatment of

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Skin of Color: Evaluating Similarities and Differences

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Clinical practice surveys in skin-of-color populations (individuals of African, Asian, Native American, and/or Latino descent) indicate that acne is among the top cutaneous disorders reported in these individuals, often ranking as the number one complaint. The chief concern among patients is not so much the acne lesion itself, but the resulting dark (hyperpigmented) macule, or postinflammatory hyperpigmentation (PIH) [*J Am Acad Dermatol.* 2002;46(2 suppl):S98-S106].

There are some racial differences in acne lesions. A survey of 1,646 incarcerated males showed the incidence of nodulocystic lesions to be lower in African American (0.5%) than in white (5%) subjects ($P<0.001$) [*Arch Dermatol.* 1970; 102(6):631-634]. (No conclusions were drawn from this study regarding Latino or Asian populations.) Histologic differences in acne have also been reported in African Americans, with biopsies of papular and pustular lesions demonstrating massive inflammatory infiltrates [*J Invest Dermatol.* 1996;106:888]. At least part of the mechanism underlying acne-induced PIH may involve production of the chemical mediators interleukin-1 alpha and prostaglandin E_2 in keratinocytes as demonstrated following oleic acid (a fatty acid involved in acne) stimulation [*Pigment Cell Res.* 2003;16(5):603]. Acne-induced PIH can be long lasting, persisting for months or years, and can have devastating psychological effects.

Ideally, PIH should be prevented. Strategies include prompt treatment and prevention of acne, avoidance of irritating medications, and sunscreen use. Sunscreen impacts the stimulatory effect of the sun on melanocytes as well as the transfer of existing melanosomes from melanocytes into keratinocytes. Patients should be encouraged to use sunscreen with both UVA and UVB protection such as the physical blockers (zinc oxide or titanium dioxide).

Studies indicate that topical retinoids may offer a way to address both acne and PIH in those with skin of color.

Hydroquinone (HQ)—which inhibits tyrosinase activity and the conversion of tyrosine to melanin—is currently the gold standard for treating PIH in the United States. However, it has no anti-acne activity, necessitating separate medications for the treatment of acne and PIH. In addition, possible regulatory changes (including a proposed US Food and Drug Administration ban on over-the-counter HQ products and a New Drug Application requirement for all HQ-containing products) have the potential to severely limit HQ availability. Thus, there is a need for either new therapeutic options or a reassessment of existing options for the treatment of acne-related PIH.

Topical Retinoids May Be Effective for PIH

Topical retinoids are currently a mainstay of acne therapy, and recent studies suggest they may be effective for the treatment of PIH as well. Topical retinoids are hormones that interact with nuclear retinoid receptors and regulate gene transcription. Their efficacy in acne derives from their ability to normalize desquamation of the follicular epithelium, promote drainage of comedones, and inhibit formation of new comedones [*Clin Ther.* 1992; 14(6):773-780; *J Am Acad Dermatol.* 1986;15(4, pt 2):907-915]. In addition, they appear to down-regulate gene expression dependent on AP-1 (a transcription factor associated with cell proliferation and inflammation), resulting in anti-inflammatory action.

The effectiveness of retinoids in the treatment of PIH is postulated to be related to inhibition of tyrosinase induction in melanocytes, enhancement of desquamation (which speeds up the sloughing of melanin in keratinocytes), inhibition of melanosome transfer from melanocytes to keratinocytes, and enhancement of the absorption of other ingredients.

The first study to demonstrate the efficacy of a retinoid in the treatment of PIH was reported by Bulengo-Ransby and colleagues in 1993 [*N Engl J Med.* 1993;328(20): 1438-1443]. In a randomized, double-blind study, 54 black patients with PIH received either vehicle or tretinoin 0.1% cream QD (along with daily sunscreen SPF 15 use) for 40 weeks. PIH was significantly lighter (as determined by investigator assessment) in tretinoin-treated than vehicle-treated subjects ($P<0.001$), with 91% of tretinoin patients judged as lighter or much lighter after treatment versus 57%

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irritant contact dermatitis showed petrolatum to be just as effective as betamethasone-17-valerate [*Exog Dermatol.* 2002;1(2):97-101].

Improvements in Tolerability Are Seen With Combination Therapy

Combination therapy is increasingly being used for acne treatment. Two recent studies have examined the additive effects of an antibiotic/benzoyl peroxide (BP) product plus a topical retinoid and found that, contrary to an expected increase in irritation, the combinations were better tolerated than retinoid monotherapy.

A double-blind, randomized, parallel-group combination therapy study observed 121 subjects with moderate to severe acne treated with (1) a clindamycin 1%/BP 5% gel with humectants and occlusive agents QD AM plus tazarotene 0.1% cream QD PM or (2) vehicle gel QD AM plus tazarotene 0.1% cream QD PM [*J Drugs Dermatol.* 2006;5(3): 256-261]. Median percent change in open and closed comedo count was significantly better at all time points with the combination than with tazarotene alone (median reductions of 34% versus 18%, respectively, at week 4 and 70% versus 60%, respectively, at week 12; $P\leq0.01$ for both comparisons). Median percent change in papule and pustule count was also greater with combination therapy than with tazarotene alone at weeks 8 and 12; this trend was most striking in those more severely affected at baseline (eg, with a median baseline papule/pustule count of ≥25), with median reductions of 63% (combination therapy) versus 52% (tazarotene alone) seen at week 12 in this subpopulation ($P\leq0.01$). Additionally, there was a lower overall incidence of peeling and dryness with the combination than with the single-agent regimen (10% versus 18% and 8% versus 12%, respectively). Of particular interest, significant improvement in tolerability occurred during the first 4-week period of retinization.

The notion of improved efficacy and tolerability with combination retinoid therapy was repeated in a more recent study comparing adapalene 0.1% gel QD PM for 12 weeks with two other regimens: (1) clindamycin 1%/BP 5% gel (the same formulation used in the above-mentioned study) QD AM and adapalene 0.1% gel QD PM for 12 weeks and (2) clindamycin 1%/BP 5% gel QD AM for 4 weeks, then adapalene 0.1% gel added QD PM for the next 8 weeks [*J Drugs Dermatol.* 2007; in press]. The concurrent clindamycin/BP plus adapalene combination resulted in a significantly better reduction in inflammatory lesions ($P<0.05$) and nonsignificant reductions in noninflammatory and total lesion counts versus adapalene monotherapy. At week 4, dryness was significantly less with either combination than with adapalene monotherapy ($P<0.05$).

It is likely that the humectant and occlusive properties of the excipients in the clindamycin/BP product used in these studies contributed to improved retinoid tolerability. Thus, when considering these types of combinations, consider the vehicle bases (water, alcohol, or emollient). These formulation characteristics can affect the overall tolerability of the regimen.

Practical Strategies Can Enhance Tolerability

There are a number of practical strategies that can help minimize irritation when introducing a topical retinoid (Table 2). Consideration of anatomic variations can also decrease the chance of intolerance. For example, moisture can be a problem in some anatomic areas (eg, the perinasal region, oral commissures, lateral aspects of the chin). Conversely, retinoids are well tolerated periocularly and on the forehead, cheeks, and chin. Being aware of—and making allowances for—these anatomic differences can help patients optimize tolerance to these therapies.

Topical retinoids are a proven, effective option for the treatment of acne. Tolerability issues can be addressed in a number of ways, allowing us to confidently employ even the stronger and more efficacious of these therapies as an important part of our acne armamentarium.

Table 1. Strategies for Maximizing Epidermal Barrier Integrity

Variable	Impact	Solution
Soaps	Harsh soaps, especially alkaline products and products with powerful surfactants, remove protective lipids and damage the stratum corneum, which can result in increased absorption of topical retinoids and/or local irritation.	• Use non-soap cleansers. • Wash gently with nonabrasive product.
Water temperature	In addition to soap, hot water (>104°F) can damage the barrier function of the skin, resulting in permeability changes that also lead to increased absorption of topical retinoids and/or local irritation.	• Use warm (not hot) water for washing.
Bathing	Long, hot showers and tub baths disrupt barrier function.	• Shorten bathing time. • If dryness is an issue, consider applying an emollient immediately after bathing. • Wait 20 to 30 minutes before applying retinoid to allow skin to normalize. Apply emollient to skin if necessary.
Weather and humidity	Low-humidity environments (cold, dry weather; forced air heating; air conditioning; hot, dry weather) increase the sensitivity of the skin to barrier function disruption and can increase irritation from topical medications; high-humidity environments, on the other hand, are ideal for retinoids.	• Use moisturizer if dry. • Use nonsoap cleansers. • Consider retinoid holidays. • Pay close attention to vehicles used.
Emollients	Very important in maintaining and protecting the skin by restoring barrier function and reducing overabsorption of retinoids.	• Utilize an emollient prior to retinoid application where dry skin is/may be an issue; wait 15 to 30 minutes before applying retinoid.
Astringents	Astringents can increase irritation from other topical medications by altering surface lipids and damaging the stratum corneum, causing overabsorption of retinoids.	• Eliminate astringents.

Table 2. Strategies for Minimizing Irritation During Retinization

- Be pragmatic when initiating therapy.
  - Be especially careful during the first 4 to 6 weeks of therapy (retinization period).
- Consider combination therapy with a product that has humectant and occlusive agents.
- Consider using weaker-strength creams or gels during the first 4 to 6 weeks.
- Select retinoid formulation and vehicle best suited to seasonal temperature and humidity conditions.
- Consider alternate-day therapy during the first 1 to 2 months.
- Be open to other application methods (eg, short contact).
- Encourage the use of emollients to enhance barrier function of the skin.
- Educate patients about this period, and allow 1- to 3-day retinoid holidays.
- Consider a 1-month follow-up appointment after initiation of therapy.