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Status Report on Topical Tazarotene for the Management of Acne Vulgaris

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EDITORIAL

ORIGINAL ARTICLES

The Only Topical Retinoid Without a Generic Alternative: Tazarotene

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Over the past 4 decades, topical retinoids have become standard therapy for the treatment of acne vulgaris. The market has grown to encompass multiple formulations of tretinoin and other next-generation topical retinoids such as adaplene and tazarotene. Tazarotene is unique amongst all other topical retinoids because of its dual role as a US Food and Drug Administration–approved treatment option for both acne vulgaris and psoriasis vulgaris.

A common overall impression often voiced in dermatology circles is that tazarotene is the most effective topical retinoid for acne treatment but carries the greatest risk for cutaneous irritation. Although this may be true based on many studies with the 0.1% gel formulation of tazarotene, the availability of tazarotene cream has improved the adaptability of topical tazarotene for clinicians. Additionally, tazarotene has continued to maintain its established role as a widely used and reliably effective treatment option for a range of patients with acne. As clinicians have gained experience with the product over the years, they have come up with several different ways of using tazarotene for their acne patients. One of the most recent studies demonstrated the benefits of combined use of tazarotene with topical dapsone in acne patients, where dapsone's unique anti-inflammatory properties may help to overcome retinoid irritation. The pages ahead explore the substantial data related to the use of tazarotene in the treatment of acne—data that taken together suggest that dermatology providers continue to rely on the drug, alone or in combination with other treatments, for many of their patients with acne.

As a final and important thought, tazarotene still does not have a generic substitution. This gives us the confidence that our patients will receive what we actually prescribe.

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Disclosures

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A Status Report on Topical Tazarotene in the Management of Acne Vulgaris

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ABSTRACT

Tazarotene is a synthetic retinoid that, depending on the concentration and vehicle, is approved by the US Food and Drug Administration for the topical treatment of acne vulgaris (AV) and plaque psoriasis. Tazarotene is also used as adjunctive treatment for specified clinical manifestations of chronically photodamaged skin (facial fine wrinkling, mottled facial hypopigmentation and hyperpigmentation, and benign facial lentigines), along with comprehensive skin care and photoprotection from sunlight. The gel formulation was released in the United States in 1997, with the cream formulation made available in 2000. Multiple studies are available supporting the effective and safe use of topical tazarotene for each of its indications. This article provides an overview of the pharmacology of topically applied tazarotene, discussing in particular up-to-date information on the efficacy, tolerability, and safety of topical tazarotene for AV, including monotherapy and combination therapy studies. Topical tazarotene 0.1% in both formulations is highly effective in reducing both inflammatory and noninflammatory acne lesions, and can be used in combination with other topical agents, including formulations containing benzoyl peroxide or dapsone 5% gel. Although many patients tolerate the use of topical tazarotene without significant issues or concerns, some patients experience application-site tolerability reactions, which can usually be managed with proper skin care and are less frequent with the cream formulation.

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INTRODUCTION

Overview of Topical Tazarotene

Topical tazarotene is a synthetic topical retinoid that has been available in the United States since 1997. It is formulated in 2 vehicles, a gel and a cream, and in 2 concentrations, 0.1% and 0.05%.[1-4] The US Food and Drug Administration (FDA) approved tazarotene 0.1% gel applied once daily for moderate to severe facial acne vulgaris (AV) in 1997 and tazarotene 0.1% cream applied once daily for AV in 2000. The latter application does not mandate anatomic location or severity in the approved package insert under "Indications and Usage".[2,3] Both concentrations and vehicles of tazarotene are FDA approved for once-daily topical treatment of plaque psoriasis, and the 0.1% cream applied once daily is approved for adjunctive treatment of facial fine wrinkling, mottled facial hypopigmentation and hyperpigmentation, and benign facial lentigines, along with comprehensive skin care and photoprotection from sunlight.[2-4] This article discusses the use of topical tazarotene in the management of AV.

Pharmacologic Properties of Topical Tazarotene

After topical application, tazarotene undergoes rapid deesterification with conversion to the active metabolite, tazarotenic acid.[1-3,5] Due to rapid conversion and a very short half-life (<20 minutes), systemic absorption of tazarotene is negligible.[2,3,5] The early pharmacokinetic data on topical tazarotene were completed using the gel formulation, with data on the cream formulation completed later. Tazarotenic acid is metabolized to inactive metabolites that are excreted in the urine and exhibit an elimination half-life of 1 to 2 hours and a terminal half-life of 18 hours; maximum concentrations in systemic circulation are achieved at 9 hours after application, with less than 5% of systemic absorption after topical application to normal skin, less than 1% absorption within 10 hours of application to unoccluded psoriatic skin, and less than 6% absorption within 10 hours of application to occluded normal skin.[6-11] In females with AV treated over 28 days with tazarotene 0.1% cream to the face, or to 15% of their body surface area (BSA), the mean maximum serum concentration (C_{max}) and area-under-the-curve (AUC) levels of tarazotenic acid were achieved by day 15 in both groups, with 10-fold higher mean C_{max} and AUC levels noted in the group treating 15% of their BSA.[3] In a study comparing C_{max} and AUC values in healthy subjects, these values were 40% in those treated with tazarotene 0.1% gel compared with 0.05% gel.[2]

Importantly, the repeated application of tazarotene 0.1% cream to female patients with facial AV over 28 days demonstrated that continued systemic accumulation of either tazarotenic acid or tazarotene did not occur after peak bloods levels were reached at day 15, with very low blood levels of tazarotenic acid (~0.1 ng/mL) noted in the group applying it only to facial skin.[3,11] Although the overall systemic absorption of both tazarotene and tazarotenic acid appear to be low in both healthy and diseased skin, the use of a higher drug concentration and application to a greater BSA than only the face have been shown to correlate with an increase in systemic absorption, especially of tazarotenic acid, albeit still to levels that are believed to be low and apparently

devoid of systemic toxicity.[1,11] Application of tazarotene to the face for the treatment of AV appears to avoid a potential relevant risk for greater systemic absorption, and there is no suggestive or definitive evidence that the higher blood levels achieved with more widespread application of topical tazarotene beyond just facial skin (ie, 15%-35% BSA) increases the risk of systemic toxicity. Moreover, these systemic absorption levels are substantially lower than those that occur with ingestion of an oral retinoid (ie, oral isotretinoin >1,000 ng/mL).[11,12] In addition, the FDA-approved indication in the product labeling for tazarotene 0.1% cream for AV does not restrict use to a specific body location or to specific ratings of acne severity.[3]

Correlations Between Cellular Mechanisms and Inflammatory Pathways Modulated by Topical Tazarotene and Therapeutic Responses in Acne Vulgaris

Both the systemic and topical retinoids exhibit a variety of biologic effects, and modulate many physiologic pathways and cellular mechanisms within the epidermis and dermis. In disease states where specific cellular processes become aberrant, application of a topical retinoid may provide therapeutic benefit if countering the aberrant process falls under the umbrella of its modulating effects on ketatinocyte differentiation, cellular proliferation, and/or specific pathways of inflammation.[1,5,6,11,13,14] As topical retinoids achieve their access to target sites in skin only through percutaneous absorption, some of the effects achieved may differ from those that occur with the use of an oral retinoid such as isotretinoin.[15] For example, topical retinoids do not exert the sebosuppressive effect that occurs with oral administration of isotretinoin, nor do they typically produce long-term remission of AV after their discontinuation. Nevertheless, topical retinoids modulate several biologic activities in human skin that appear to correlate with their ability to reduce both comedonal and inflammatory acne lesions, and may therapeutically modify dermal matrix degradation that, if left unchecked, could otherwise lead to worsening of skin contour and possibly scarring in some patients.[1,2,3,6,11,16]

Tazarotenic acid (the active metabolite of topically applied tazarotene) binds to and has relative differences in affinity to all 3 retinoic acid receptors (RARα, RARβ, and RARγ), and its effects on skin are believed to be due to its high-affinity binding to RARγ, the predominant RAR receptor in skin.[1,5,11,17] The RAR receptor binding by tarazotenic acid directly modifies the activity of specific retinoid-responsive genes and/or indirectly modulates signal transduction pathways, culminating in the regulation of cell differentiation, cell proliferation, and certain inflammatory cascades.[1,5,11,14,17-20]

Tazarotene downregulates markers of keratinocyte differentiation, keratinocyte proliferation, and inflammation, and upregulates 3 specific tazarotene-induced genes (transforming growth factor 1 [TGF1], tazarotene-induced gene 2 [TIG2], and tazarotene-induced gene 3 [TIG3]). These cellular mechanisms may correlate with antiproliferative effects, and block induction of ornithine decarboxylase activity with decreasing cell proliferation and hyperplasia.[1,11,13] Topical retinoids, including tazarotene, have exhibited diverse effects on the skin, and some are likely to be operative in the pathogenesis of AV.[1,5,6,11,13,14,15,17-27] These diverse effects that appear to correlate with the therapeutic benefits of topical tazarotene are described in Table 1 and depicted in Figure 1.

The multiple biologic activities associated with topical retinoid application against both follicular hyperkeratinization associated with comedogenesis and several inflammatory mechanisms shown to be operative in the pathogenesis of AV support the early and continued use of topical retinoid therapy in the management of AV.[1,6,11,14,28-34] This concept is further supported by the more recent evidence demonstrating that specific inflammatory processes that are subclinical precede or occur concomitantly with follicular hyperkeratosis (microcomedo formation) and persist after resolution of palpable acne lesions.[22,24,35-37] In addition to the basic science implications discussed above, multiple monotherapy and combination therapy studies in patients with AV support topical retinoid therapy as an important component of a topical regimen during both initiation of therapy and to sustain control of facial AV over time. This is based on the chronic nature of the disease, and the ability of topical retinoids to reduce microcomedo formation and to decrease the emergence of both comedonal and inflammatory lesions with continued application over time without loss of efficacy.[1,6,11,14,28,31-34,38-41]

Clinical Implications of Cellular Mechanisms of Action and Correlation With Therapeutic Outcomes in Clinical Trials

During discussions of topical therapy for AV, it has been commonplace to differentiate between agents directed to treat comedonal lesions and those directed to treat inflammatory lesions.[1,28-31] However, there is crossover among different topically applied compounds used to treat facial AV, and therapeutic benefit has been noted against both comedones and inflammatory lesions during clinical trials with topical retinoids, benzoyl peroxide, and clindamycin. The physiochemical qualities of the vehicle formulation may alter the magnitude of therapeutic effect based on release characteristics of the active ingredient from the vehicle and its ability to penetrate through the stratum corneum (SC) and into the epidermis and dermis to gain access to its target sites.[42] Importantly, the ability of topical retinoids to inhibit comedogenesis and modify inflammatory pathways that appear to be operative in AV correlates directly with the results achieved in clinical trials evaluating both monotherapy and combination regimens. The more recent research discussed above supports the early role of subclinical inflammation prior to visible emergence of an acne lesion, the persistent inflammation after palpable lesion resolution, and the potential role of dermal matrix degradation in acne scarring. The dermal matrix degradation occurs via retinoid-induced activation of the AP-1 signal transduction

TABLE 1.

Cellular Mechanisms and Inflammatory Cascades Modulated by Topical Tazarotene That Appear to Correlate With Therapeutic Benefits in the Management of Acne Vulgaris[1,5,6,11,13,14,15,17-27]
Reduced expression of hyperproliferative keratins (K6, K16) that are increased during early comedogenesis.[a]
Suppression of activation of the activator protein 1 (AP-1) signal transduction pathway.[a]
This results in reduced expression of several matrix metalloproteinases (MMPs) from keratinocytes and fibroblasts that have been shown to be increased in acne vulgaris (AV), cause degradation of the dermal matrix, and may play a role in acne scar formation.
Suppression of the AP-1 signal transduction pathway, which normally suppresses procollagen promoters in fibroblasts.[a]
This results in reversal of the altered collagen expression associated with AV (and also chronic photodamage) and allows for more physiologic collagen deposition and dermal matrix remodeling.
Decreased expression of Toll-like receptor-2 (TLR2) which is expressed on many cell types (ie, monocytes, sebocytes, keratinocytes) with a decrease in ligand binding with *Propionibacterium acnes*[a]
This results in a reduction in proinflammatory cytokines, a potential decrease in *P acnes*–induced upregulation of some MMPs, and inhibition of the TLR2-induced innate immune response that triggers inflammation in AV.
Inhibition of the ligand binding between *P acnes* and TLR by decreasing TLR2 expression which is normally upregulated in acne lesions.[a]
Decreasing *P acnes*–TLR2 binding then blocks the activation of keratinocytes and sebocytes to increase production of proinflammatory cytokines such as interleukin (IL)-12 (regulator of adaptive immune response) and IL-8 (a neutrophil chemoattractant), and also inhibits the production of MMP-1 and MMP-9 by monocytes.
Increased epidermal turnover with reduction in postinflammatory hyperpigmentation.[a]
Normalization of epidermal cellular diferentiation and decreased hyperkeratinization[a]
Downregulation of aberrant expression of keratinocyte transglutaminase I (Tgase I).[b]
Downregulated expression of epidermal growth factor receptor (EGFR).[b]

[a]Mechanism believed to correlate with therapeutic activity in acne vulgaris.
[b]Uncertain correlation with acne vulgaris.

pathway that increases "collagenolytic" matrix metalloproteinase (MMP) activity and magnifies even further the diverse therapeutic benefits that a topical retinoid contributes to the management of AV (Figure 1). The available data show that topical retinoids reduce both facial inflammatory and comedonal lesions, but data are very limited for nonfacial AV with essentially all available topical therapies for AV, including all 3 prescription-only topical retinoid compounds.[1,6,11,14,28-31,33]

Several studies, including pivotal trials depicted in the FDA-approved package inserts, have shown the ability of monotherapy with tazarotene 0.1% gel and 0.1% cream to markedly reduce both comedonal and inflammatory facial acne lesions, and also exhibit the potential for augmented efficacy when used in combination with other topical agents (benzoyl peroxide, benzoyl peroxide-clindamycin, benzoyl-erythromycin, dapsone 5% gel).[2,3,11,38,39,41,43-52] Augmented benefit with combination therapy is true in many cases, especially with greater baseline severity of AV (based on inclusion criteria for the minimum number and range of inflammatory and comedonal acne lesion counts at baseline that are required for enrollment).

Interestingly, in a multicenter, randomized, double-blind study, the combination of tazarotene 0.1% cream once daily and benzoyl peroxide 5%/clindamycin phosphate 1.2% gel once daily produced a more rapid reduction overall in comedonal lesions over the first 8 weeks, and a greater reduction in inflammatory lesions over the duration of the study in the subset of subjects with a higher number of inflammatory lesions (papules and pustules) at baseline.

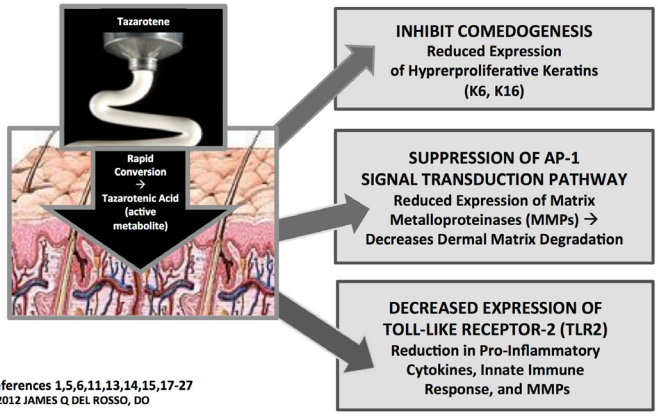
Some of the clinical trials with topical tazarotene were double-blind, randomized, comparative studies completed over 12 to 15 weeks in patients older than 12 years, demonstrating therapeutic superiority in Investigator's Global Assessment (IGA) and reductions in inflammatory and comedonal lesions as compared to other topical retinoid formulations (tretinoin 0.025% gel, tretinoin 0.1% microsphere gel, adapalene 0.1% gel). Most of these studies enrolled patients with mild to moderate severity facial AV.[46-51] Within some parameters, nominal superiority was noted, and within other parameters statistically significant differences were also observed.[11]

A Closer Look at Selected Studies With Topical Retinoids and Topical Tazarotene

Comparative Efficacy Evaluation in Patients With Moderate to Severe Acne Vulgaris

Before drawing definitive conclusions from comparative trials, it is important to analyze several factors that can potentially alter the true meaning or relevance of specific outcomes, such as study methodologies and disposition data, especially baseline severity based on inflammatory and comedonal lesion counts required at enrollment in the protocol inclusion criteria, methods used for data capture and study analysis (intent-to-treat, per-protocol, last

FIGURE 1. Biologic effects of topical tazarotene correlation with potential modes of action in acne vulgaris.



observation carried forward), study power design (superiority study, noninferiority study, underpowered), statistical significance and confidence intervals, study withdrawal rate, and reasons for withdrawal or "dropouts." In one randomized, evaluator-blinded, 12-week study, adapalene 0.3% gel once daily was found to be noninferior to tazarotene 0.1% gel once daily in patients who exhibited AV primarily in the mild to moderate AV severity range.[53] In a more recent randomized, 16-week study comparing tazarotene 0.1% cream once daily and adapelene 0.3% gel once daily in patients with moderate to severe AV, both agents were effective, but the tazarotene-treated group had superior efficacy in lesion count reduction, percentage of subjects reaching a 50% lesion count reduction, overall disease severity rating, and IGA, and also in the reduction in postinflammatory hyperpigmentation (PIH) ($P<.018$). These results may seem contradictory among different studies comparing the same or similar therapies, but looking more closely at several factors, such as inclusion criteria, disease severity, study size, and study power, will often explain, at least partially, the differences among study outcomes.

Efficacy of Alternate-Day Therapy in Selected Cases

In one 15-week, double-blind, randomized trial, tazarotene 0.1% gel applied every other night (total drug applied/subject = 29.9 g) and adapalene 0.1% gel applied every night (total drug applied/subject = 87.2 g) demonstrated equivalent efficacy in more than 50% global improvement and reduction in comedonal and inflammatory lesions.[49] The authors suggested that this alternate-day regimen may be an option for patients who are likely to be less compliant and also to the reduce cost of therapy over time. This may also be used with either the gel or cream vehicle of tazarotene when initiating therapy to allow for easier accommodation of skin tolerability during the first 3 to 4 weeks of topical retinoid therapy, because this is the time period where retinoid dermatitis is most prominent. One can usually progress to once-daily use after the first month if needed.

Concomitant Adjunctive Skin Care

All topical retinoids produce retinoid dermatitis during the first few weeks of application, which can range from barely detect-able to marked erythema, scaling, skin tenderness, burning, stinging, and/or itching. The tendency for topical retinoids to produce a greater severity of retinoid dermatitis appears to be both compound dependent and vehicle dependent. In the case of tazarotene, cutaneous irritation and retinoid dermatitis occur more commonly with the gel vehicle.[11,28,39,43,50] Retinoid dermatitis reflects the inherent epidermal alterations that a topical retinoid induces, and its diverse effects on the epidemis.[15] After application of a topical retinoid to skin, acanthosis, hypergranulosis, and a relative decrease in SC thickness occurs, which is likely related to augmented cell turnover. However, based on data from an animal model, at 2 weeks the acanthosis reverts partially toward baseline, followed by a steady-state equilibrium that persists therafter.[15] Interestingly, this 2- to 3-week course of epidermal alteration prior to stabilization correlates with the time course of retinoid dermatitis, suggesting that the visible changes of retinoid dermatitis that occur early after starting topical retinoid therapy at least partially reflect the therapeutic mechanisms that the topical retinoid initiates within the epidermis. Topical retinoid application also induces desmosomal shedding within the stratum spinosum, a decrease in tonofilaments, and some deposition of nonmucin glycoconjugates, leading to SC loosening and upper epidermal dyshesion.[15] This explains why tape stripping of topical retinoid-treated skin during eyebrow or upper lip hair waxing easily removes a superficial sheet of epidermis and should be avoided.

Retinoid dermatitis may be visible and sufficiently symptomatic to reduce compliance with treatment, and it is recommended to preemptively mitigate retinoid dermatitis with the use of a gentle cleanser and moisturizer.[54,55] This approach reduces the visible signs and symptoms of retinoid dermatitis and decreases the associated increase in transepidermal water loss (TEWL).[54,55] Topical tazarotene has earned recognition for being a very effective topical retinoid for AV, and perhaps the most effective based on some studies. It is also well tolerated by most patients, although skin irritation can limit its usefulness for some patients. Clinical studies and anecdotal clinical experience indicate that tazarotene 0.1% gel or cream do exhibit a greater potential for application-site tolerability reactions than adapalene 0.1% and 0.3% gel and tretinoin 0.1% and 0.04% microsphere gel.[1,6,11,28,30,38-41,43-53] The use of a ceramide-based hydrating skin cleanser and a ceramide-based moisturizer cream that is applied before the application of tazarotene 0.1% cream each day from the start of treatment reduced clinical signs of retinoid dermatitis without reducing efficacy, based on reduction of inflammatory and comedonal lesions.[56]

Combination Therapy With Dapsone 5% and Tazarotene 0.1% Cream

A randomized, double-blind, 12-week study in patients older than 12 years with AV (n=301) compared the use of dapsone 5% gel twice daily and a moisturizer once daily, dapsone 5% gel twice daily and benzoyl peroxide 4% cream once daily, and dapsone 5% gel twice daily and ada-

palene 0.1% gel once daily. The study showed that the dapsone-adapalene group exhibited a greater reduction in comedonal and total acne lesions than the other 2 study groups.[57] A more recent 12-week study compared the combination of dapsone 5% gel twice daily and tazarotene 0.1% cream once daily (n=86) vs tazarotene 0.1% cream once daily (n=85) in patients with AV.[52] At the end of the study (week 12), the group treated with the dapsone-tazarotene combination exhibited a baseline reduction of 59.7% for comedonal lesions, 63.3% for total lesions, and a treatment success (clear or minimal) rate of 42.2% as compared with 46.5%, 53.6%, and 21.8%, respectively, for the tazarotene monotherapy group. All 3 differences were statistically significant, and reported as *P*=.01, *P*=.02, and *P*=.01, respectively.[52] This study further demonstrated that the combination of topical dapsone with a topical retinoid augments efficacy against comedonal lesions and improves total lesion reduction and overall improvement based on investigator assessment. Both topical regimens were well tolerated.[52]

Pregnancy Considerations and Use of Topical Tazarotene

Although there is no definitive evidence in humans that application of a topical retinoid for AV causes fetal malformations or increases their risk, it is suggested that topical retinoids should not be used during pregnancy and should be discontinued if inadvertent pregnancy occurs.[1,28,58]

Based on animal data that demonstrated teratogenic effects after topical and systemic administration, topical tazarotene is rated as Pregnancy Category X and is contraindicated in pregnancy.[2,3,58-60] It should be avoided in women of child-bearing potential contemplating pregnancy or unwilling to take adequate precautions to avoid pregnancy. Data on outcomes from exposures to topical tazarotene during pregnancy are very limited. Of 9 women who were inadvertently exposed to topical tazarotene during pregnancy throughout clinical studies, one woman elected to terminate her pregnancy and the remaining 8 women delivered healthy infants.[2,3,60] The timing and amount of drug exposure in these cases were unknown.

Although there are no data confirming a true teratogenicity risk with topical tazarotene use, the approved package insert for topical tazarotene cream and gel suggests that a negative pregnancy test performed during the menstrual period, with a sensitivity of at least 50 milli-International Units per milliliter (50 mIU/mL) for human chorionic gonadotropin (hCG), be obtained 2 weeks before starting therapy.[2,3] This can actually be completed by the patient and even be repeated to further substantiate accuracy using a home pregnancy test, as many available in the marketplace demonstrate sensitivity down to 15 mIU to 25 mIU.

CONCLUSION

Topical tazarotene 0.1% gel and cream are highly effective for the treatment of AV, both as monotherapy or in combination with other agents. Despite exhibiting a higher potential for application-site reactions, marked irritation interfering with continued use is infrequent overall and can be mitigated by quality adjunctive skin care which can be recommended preemptively. More recent studies demonstrate that topical tazarotene can be combined effectively with dapsone 5% gel or with a benzoyl peroxide–containing formulation to augment efficacy. In addition, alternate-day therapy may be a good starting point for patients who have sensitive skin. Caution should be exercised in women of childbearing potential, although there are no definitive data demonstrating teratogenicity with topical use for AV.

> "Topical tazarotene 0.1% gel and cream are highly effective for the treatment of acne vulgaris, both as monotherapy or in combination with other agents."

DISCLOSURES

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Dr. Del Rosso has served as a consultant, advisory board participant, clinical investigator, and speaker for Allergan, Bayer, Dermira, Eisai, Galderma, Medicis, Obagi Medical Products, Onset Dermatologics, Pharmaderm, Quinnova, Primus, Promius Pharma, Ranbaxy, Taro, TriaBeauty, Unilever, Valeant, and Warner Chilcott.

Dr. Tanghetti has served as a consultant and speaker for Allergan and Galderma, a speaker for DUSA and Taro, and a consultant for Obagi.

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