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Next-Generation Retinoids: Selectivity Implications

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Selectivity Implications

CME Recognition

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Target Audience

This activity has been developed for dermatologists and other health care professionals who manage patients with topical or systemic retinoids

Educational Needs

Both acne vulgaris and plaque psoriasis depend on retinoids among other therapies. Although topical retinoids are very effective and internationally recommended as first-line therapy for acne, they are significantly underprescribed and concomitant skin irritation remains problematic. Currently available oral retinoids are effective against psoriasis but are associated with serious long-term side effects. Clinicians should be aware that these concerns have been addressed with improved topical formulations and new oral agents, respectively.

Learning Objectives

By reading and studying this supplement, participants should be able to:

- Differentiate rationally designed tazarotene from nonselective retinoids.
- Discuss acne pathogenesis and corresponding retinoid mechanisms of action.
- Explain the influences that affect cutaneous tolerability.
- Appreciate the impact of patient satisfaction with acne or psoriasis therapy.
- Itemize psoriasis treatments and accompanying safety issues.

Faculty Disclosures

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

Dr Abramovits has received funding for clinical grants and is a consultant to Allergan, Inc. and Galderma. **Dr Anderson** is a consultant to Allergan. **Dr Leonardi** discusses the investigational use of oral tazarotene for the treatment of psoriasis. **Dr Leyden** has received funding for clinical grants from and is a consultant to Allergan, CollaGenex Pharmaceuticals, Inc., Dermik Laboratories, Inc., Fujisawa Healthcare, Inc., Galderma, Medicis Pharmaceutical Corporation, Novartis Pharmaceuticals Corporation, Ortho-Neutrogena, Roche Pharmaceuticals, and Warner Chilcott. **Dr Tanghetti** is a consultant to Allergan.

Introduction

Emil A.Tanghetti, MD

The new synthetic retinoids have become an essential component of our therapeutic armamentarium. Unlike nonspecific retinoids, tazarotene, which is approved for the treatment of acne, photodamage, and psoriasis, is a rationally designed selective prodrug. The beneficial consequences of tazarotene selectivity are explained by Craig L. Leonardi, MD.

Although international guidelines recommend topical retinoids as first-line therapy in acne vulgaris, physicians do not necessarily implement these guidelines. Retinoid physiologic and molecular mechanisms of action are updated with respect to acne pathogenesis by William Abramovits, MD, who then presents the promising results of a double-blind trial with adapalene and tazarotene creams in mild to moderate acne.

One problem facing dermatologists is dermatitis with erythema, peeling, dryness, or pruritus induced by topical application of retinoids, effects that peak within the first 4 to 6 weeks of treatment and diminish thereafter. Retinoid choice, vehicle, and concentration, as well as skin sensitivity, are evaluated with respect to their influence on degree of cutaneous irritation by James J. Leyden, MD.

Dina N. Anderson, MD, presents the results of an observational study with nearly 1,200 patients dissatisfied with their acne therapies. Following addition of tazarotene cream to former acne therapies, including benzoyl peroxide and/or clindamycin, patient satisfaction was evaluated systematically along with efficacy and tolerability.

Two groups of patients require systemic treatment for psoriasis. Patients with chronic unremitting psoriasis require ongoing systemic therapy to control their disease. More commonly encountered are patients with seasonal flares, most notably in winter, whose disease can be managed with intermittent systemic therapy. Both these groups benefit from a drug such as oral tazarotene. Craig L. Leonardi, MD, presents findings from double-blind trials in nearly 700 patients with moderate to severe psoriasis.

Rational Drug Design

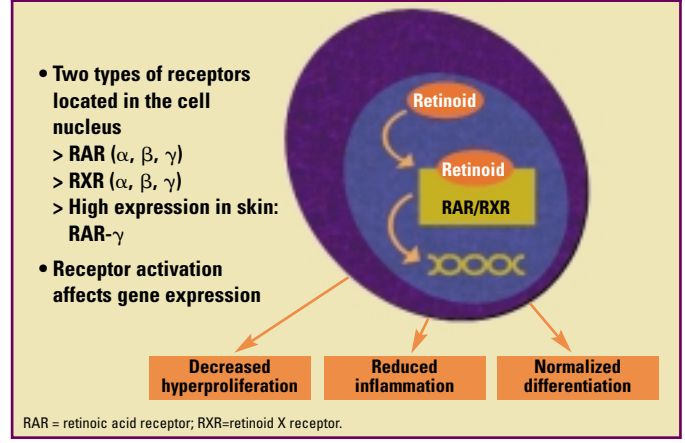
Craig L. Leonardi, MD

Retinoids are small hormone molecules that control gene expression in a variety of fascinating ways by interacting with nuclear receptors. A retinoid, such as tazarotene, binds to an intracellular receptor and is transported into the cell nucleus where it interacts with genetic elements to influence cell function. Retinoid receptors are members of a steroid/thyroid hormone receptor superfamily that includes a diversity of receptors, such as adrenal steroids, sex steroids, vitamin D_3 receptors, thyroid hormones, and peroxisome proliferator-activated receptors (PPARs).

Biologic effects of retinoids are mediated by two distinct families of nuclear receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs) present in the skin (**Figure 1**). RARs and RXRs each come in three varieties: α, β, and γ, which conform to heterodimers and homodimers within the nucleus where they act as coactivators or corepressors, depending on which genes are bound. Retinoids downregulate lipid synthesis, inhibit hyperproliferation, reduce inflammation, and normalize sebocyte differentiation.

There is a multiplicity of retinoid pathways. A heterodimer, RAR/RXR, affects the RAR hormone pathway but also can interact with several other pathways such as thyroid, vitamin D_3, PPAR-γ, and RXR hormone pathways. By way of these receptors and their binding pairs, retinoids affect a wide variety of systems within the cell and tissues, yielding multiple benefits as well as side effects. With respect to retinoid mechanisms of action, a

Figure 1. Retinoid Mechanisms of Action



RAR = retinoic acid receptor; RXR=retinoid X receptor.

variety of pathways implicates a variety of potential therapeutic targets. For example, tazarotene is effective not only in acne and photodamage but also in psoriasis. On the other hand, this large number of pathways may also lead to unwanted side effects. Therefore, one important drug development goal is to design retinoids with improved receptor specificity.

Nonspecific Retinoids

Acitretin and isotretinoin are two nonspecific retinoids that convert to active isomers and metabolites with a wide range of side effects. Whereas acitretin binds to RAR-α, RAR-β, and RAR-γ, isotretinoin metabolites bind not only to these three RARs but also, to a lesser extent, to all three RXRs. These diverse, nonspecific binding patterns can explain some of their side effects, such as hyperostosis, hypercholesterolemia, hypertriglyceridemia, teratogenicity, and alopecia.

Complicated and extensive metabolism also characterizes these nonspecific retinoids. Oral acitretin undergoes interconversion by isomerization to its 13-*cis* form. Both parent compound and isomer are further metabolized into chain-shortened breakdown products and conjugates. Because of high lipophilicity, half-lives of acitretin and 13-*cis*-acitretin average 47 and 119 hours, respectively.[1]

In a similarly complex manner, oral isotretinoin converts to at least three metabolites that, in turn, isomerize; all may possess more retinoid activity than the parent compound. Moreover, two of these metabolites are geometric isomers that *reversibly* interconvert. Half-lives of isotretinoin and its major 4-oxo metabolite average 29 and 22 hours, respectively,[2] and the isotretinoin accumulation ratio ranges from 0.9 to 5.43 in patients with cystic acne.[3]

A Rationally Designed Retinoid

Unlike the nonspecific retinoids, oral tazarotene is a rationally designed prodrug that is converted rapidly and specifically to a single active metabolite, tazarotenic acid. Tazarotene is a *locked* molecule so it does not isomerize, thus diminishing the risk of side effects associated with nonspecific retinoid isomers. Furthermore, unlike acitretin and isotretinoin, low lipophilicity limits tazarotene storage in fatty tissue. Thus, its half-life of 7 to 12 hours is a considerable advantage since it clears the body after only 1 week.

Specificity also characterizes tazarotene binding affinities. Unlike nonspecific retinoids, tazarotene does not activate RXRs but transactivates selectively by binding preferentially with RAR-β and RAR-γ.[4] Tazarotene affects keratinocyte hyperproliferation, abnormal differentiation, and immune cell infiltration characteristic of psoriasis by normalizing gene overexpression and antagonizing inflammatory cytokines and growth factors.[5] In addition, novel tazarotene-induced genes (TIGs) may act as growth regulators to suppress hyperproliferation.[6,7]

Topical tazarotene gel was originally approved for plaque psoriasis and facial acne vulgaris in 1997 and, shortly thereafter, development of the molecule for oral administration commenced. Since then, topical tazarotene cream has been approved for plaque psoriasis, acne vulgaris, and photodamage. In November 2003, oral tazarotene was submitted to the Food and Drug Administration for treatment of psoriasis; approval is expected in a matter of months.

"In contrast to nonspecific retinoids, tazarotene is designed to be highly selective for epithelial receptors (RAR-γ) and forms a single metabolite without isomers."

Oral Tazarotene Clinical Data

Clinical studies administered daily oral doses of 4.5 mg tazarotene to all subjects since systemic exposure to tazarotenic acid is independent of body weight. Once-daily dosing with or without food is permitted since tazarotene absorption is independent of food interaction. Oral tazarotene does not interact with drugs or alcohol; unlike other oral retinoids, it has no effect on the pharmacokinetic profile or efficacy of two commonly prescribed contraceptives (**Table 1**).

Side effects are minimal with no evidence of gastrointestinal problems in healthy volunteers. Because of teratogenic risk, women of childbearing potential are required to use appropriate means of contraception during and after retinoid therapy. In contrast to acitretin, which requires contraception for 3 years following a single dose, conception is safe as early as 1 month after tazarotene therapy because of its short half-life and rapid clearance.

Summary

Retinoids control gene expression by interacting with nuclear receptors. In contrast to nonspecific retinoids, tazarotene is designed to be highly selective for epithelial receptors (RAR-γ) and forms a single metabolite without isomers. Tazarotene specificity, pharmacokinet-

Continued on page 14

Table 1. Benefits of Selectivity

> one dose for all body weights
> once-daily dosing
> dosing with or without food
> no drug interactions
> no alcohol interaction
> minimal side effects
> safe conception by 1 month

Clinical Benefits of Topical Retinoid Selectivity

William Abramovits, MD

Acne pathogenesis is complex and entails several critical aspects, all of which provide ideal targets for acne therapy. Generally speaking, modified sebum production, excretion, and composition are paramount to acne, but differential conversion rates of testosterone to dihydrotestosterone also may be crucial. Hyperkeratinization around follicular ducts with abnormal desquamation also plays an important role in acne eruption. Finally, colonization of pilosebaceous units with *Propionibacterium acnes* and monocyte secretion of proinflammatory cytokines result in perifollicular inflammation and destruction. More recently proposed mechanisms of acne pathogenesis include sebaglandular duct obstruction and irritation by pathogenic concentrations of sebum (seboliths) that rupture and inflame follicles.[1,2]

Topical treatment with retinoids addresses many of these issues. Studies by the pioneers who first recognized topical retinoids as useful acne therapy[3,4] demonstrated that topical tretinoin alters the pattern of keratinocyte differentiation by decreasing keratohyalin production, tonofilaments, and desmosomes. In turn, horny cells become thinner, smaller, irregularly shaped, and filled with lipid droplets, thus reducing horny layer coherence. Consequently, tretinoin normalizes desquamation of follicular epithelium, facilitates comedolysis, prevents formation of new comedones, and suppresses inflammation.

Retinoid Biology

As described in the previous presentation of this supplement, retinoid receptors are nuclear receptors that belong to the steroid receptor superfamily, proteins that function as ligand-dependent transcription factors. It is worth remembering that retinoid X receptors (RXRs) are involved with a multiplicity of hormone pathways in addition to the retinoic acid receptor (RAR) pathway. In contrast to tretinoin and isotretinoin that nonselectively bind to all RAR types and, via isomerization to 9-*cis*-retinoic acid, to all RXR types, adapalene and tazarotene exhibit more specific binding, only interacting with RAR-β and RAR-γ.

Tazarotene incorporates into the RAR to yield either of two actions (**Figure 1**). One promotes differentiation and decreased intercellular adhesion whereas the other decreases inflammation and proliferation. The molecular basis of these therapeutic effects involves many pathways and tazarotene-induced genes (TIGs) expressed as a result of selective tazarotene-RAR interactions.

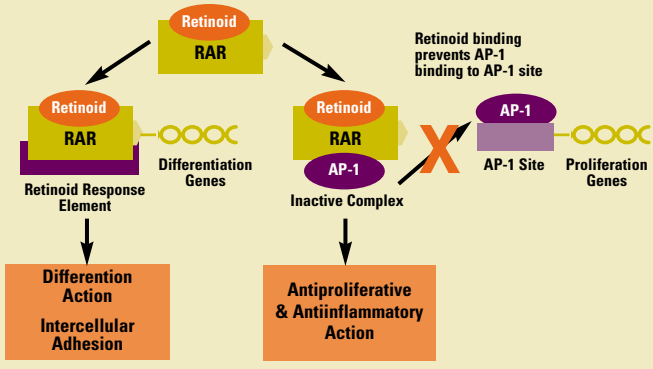
As an ester prodrug, tazarotene metabolizes to active tazarotenic acid only once it is absorbed by skin and blood. In turn, tazarotenic acid promptly catabolizes to less active and toxic (irritating) sulfoxide and sulfone metabolites, metabolites that bind to none of the RAR types and clear from the body within hours. In contrast, tazarotenic acid binds very quickly and strongly to RAR-β and RAR-γ. Therefore, based on its pharmacokinetic profile, tazarotene would be expected to produce minimal systemic adverse effects because (1) systemic exposure is minimized by limited transcutaneous absorption and rapid elimination and (2) accumulation in adipose tissue is minimized by rapid metabolism to hydrophilic metabolites in skin and blood.

Clinical Studies in Acne

In a double-blind, five-center, parallel-group study, 173 subjects who were diagnosed mostly with mild to moderate acne vulgaris and were older than 12 years were randomized to receive either tazarotene 0.1% cream or adapalene 0.1% cream applied topically every evening for 12 weeks.[5] Most subjects completed the study, but 2% and 3% receiving tazarotene and adapalene, respectively, discontinued prematurely because of lack of efficacy and an additional 5% of the tazarotene group discontinued because of adverse events.

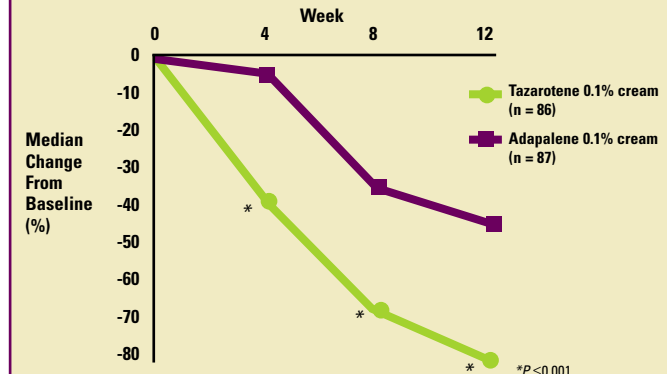
Both creams were effective. Treatment success,

Figure 1. Acne: Mechanisms of Action



RAR = retinoic acid receptor.

Figure 2. Open and Closed Comedones[5]



defined as more than 50% improvement on a 7-point global response scale, was experienced by 77% of study subjects administered tazarotene cream and 55% of those administered adapalene cream. Tazarotene proved more effective in reducing the number of open and closed comedones; this superiority was statistically significant by Week 4 ($P \leq 0.001$) and continued throughout the 12-week treatment period (**Figure 2**).

Although topical tazarotene caused statistically more peeling ($P \leq 0.001$) and dryness ($P \leq 0.05$) than did adapalene at Weeks 4 and 8, both these cutaneous reactions were very mild and the difference between groups disappeared by Week 12. At Week 4 only, tazarotene induced a burning sensation more often than did adapalene ($P \leq 0.05$), but this sensation was very mild and the between-group difference disappeared by Week 8. Very mild erythema and itching were occasionally reported but did not differ statistically between treatment groups at any time point. Perception of oiliness decreased equally at Week 4 for both treatment groups.

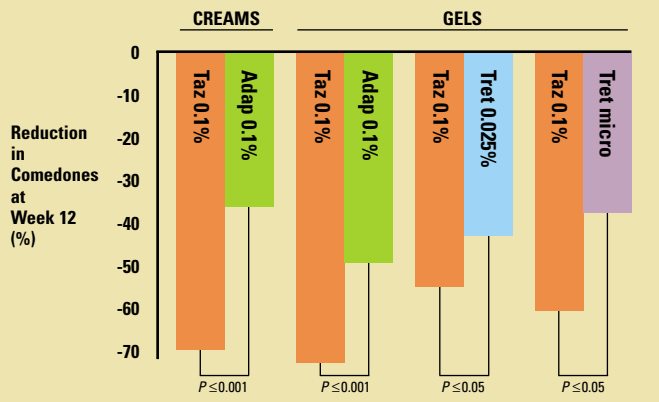
Previous studies have demonstrated the benefits of tazarotene when compared with adapalene[5-8] and tretinoin.[9] After 4 weeks of treatment, tazarotene 0.1% cream was nearly as effective as tazarotene 0.1% gel in reducing comedones, and both formulations were superior to adapalene 0.1% cream ($P \leq 0.001$) and adapalene 0.1% gel ($P \leq 0.01$).[5,7-9] In these same studies, tazarotene efficacy not only endured but was even more robust with time. After 12 weeks of retinoid treatment, adapalene as well as tretinoin proved statistically inferior to tazarotene in reducing comedones (**Figure 3**). Inflammatory lesions were reduced by all retinoids, but statistical superiority was evident for tazarotene 0.1% gel when compared with adapalene 0.1% gel.[9]

Summary

Surprisingly, many dermatologists fail to initiate topical retinoid therapy at the first patient visit, despite evidence of its efficacy in well-conducted clinical studies and the unlikelihood of significant irritation with newer formulations. International guidelines recommend topical retinoids as initial therapy for most forms of acne.[10] Retinoids are effective not only for comedonal acne but for inflammatory acne as well. Take the time to educate patients: be pragmatic, vigilant, and cautious, particularly during the first weeks of acne therapy. Perhaps begin with a gentle retinoid cream rather than a gel formulation or consider alternate-day therapy during the first 4 to 8 weeks, especially during winter months. Recommend moisturizers and mild cleansers. Since tazarotene cream has proved nearly as effective as tazarotene gel and more effective than other retinoids in reducing comedones, it is ideal for starting acne therapy.

> "International guidelines recommend topical retinoids as initial therapy for most forms of acne."

Figure 3. Reduction in Comedones at Week 12[5, 7-9]



Taz = tazarotene; Adap = adapalene; Tret = tretinoin; Micro = microsponge.

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Tolerability of Topical Retinoids

James J. Leyden, MD

Topical retinoids have been prescribed for more than 30 years in the treatment of acne vulgaris[1] because they effectively reduce comedones and papulopustular lesions.[2-4] Their benefit during the inflammatory phase of acne is likely due to their effect on microcomedones, the precursor phase of both inflammatory and noninflammatory lesions.[5] Topical retinoids are now recommended for most forms of acne vulgaris at the initiation of therapy.[6]

One problem occasionally facing dermatologists is dermatitis with erythema, peeling, dryness, or pruritus caused by topical application of retinoids,[7] effects that peak early and diminish thereafter. Clinical study protocols have evolved over the years, such as split-face analysis and various instruments. Additionally, manufacturers are trying to develop skin-friendly detergents. In several studies over the last couple of years, a large number of individuals reported to a laboratory 5 days every week. In this manner, compliance and volume of applied retinoid were standardized although weekend applications were administered unmonitored.

Study Design

Tolerability of topical retinoids was evaluated in 262 healthy volunteers in randomized, investigator-blinded studies using the split-face technique. For each study subject, one retinoid formulation was applied to one side of the face and another was applied to the opposite side in an identical fashion. Medications were put on the face once daily for 29 days and irritation was graded Monday through Friday by the same expert clinician throughout the study.

Erythema and dryness were assessed by comparing area under the curve (AUC) to determine statistically significant between-group differences. For the purpose of these evaluations, AUC was estimated by plotting mean erythema or dryness score against time. Four variables were evaluated to determine if they influenced degree of irritation following topical application: retinoid vehicle (gel or cream), retinoid concentration, skin sensitivity (normal or sensitive), and inherent retinoid properties per se.

Retinoid Vehicle

Although creams may be less effective than their gel counterparts, they are often better tolerated. In these studies, however, the 0.1% microsponge gel formulation of tretinoin was clearly better tolerated than its 0.1% cream formulation, especially during the first week ($P \leq 0.01$). Likewise, adapalene 0.1% gel was also better tolerated than adapalene 0.1% cream ($P \leq 0.01$). However, tazarotene 0.1% cream was much better tolerated than the same concentration in a gel formulation. In general terms, irritation was marked during the first week of treatment but then diminished.

Retinoid Concentration

As one would expect, retinoid concentration significantly affected tolerability; without exception, lower concentrations were better tolerated. In the case of tazarotene, its 0.05% cream caused less irritation than did its 0.1% cream ($P \leq 0.01$). Again, most of the irritation occurred in the first 7 to 10 days. Over time, fewer and fewer visible signs of irritation were evident after application of either cream formulation, but clearly the lower concentration was better tolerated.

With three different concentrations of tretinoin, ranging from 0.02% to 0.1%, the same pattern was obvious (**Figure 1**). The tretinoin cream formulations, particularly the higher concentration (0.1%), were consistently different from lower concentrations and from the microsponge formulation. However, this finding may be confounded by the preservative. With the exception of Renova®, the cream preservative is sorbic, not ascorbic, acid, which can induce erythema, particularly in individuals who tend to flush and blush easily. Nevertheless, the lowest concentration was clearly superior to the 0.05% and 0.1% ($P \leq 0.01$ and 0.001, respectively) with respect to tolerability, and the 0.1% concentration caused the most erythema and dryness.

Skin Sensitivity

What constitutes sensitive skin? The integrity of the stratum corneum is primarily responsible, but a genetically predisposed inflammatory response may be an important secondary factor. The common link among individuals with sensitive skin is a rough and cracked stratum corneum that provides opportunity for topically applied agents to find their way through this otherwise protective layer into the more vulnerable, viable epithelium. Individuals who qualified for our sensitive skin

Figure 1. Topical Retinoid Concentration

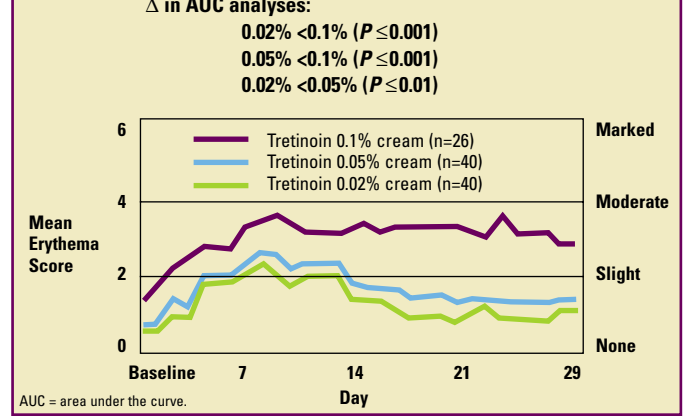


Figure 2. Retinoids: Creams on Normal Skin

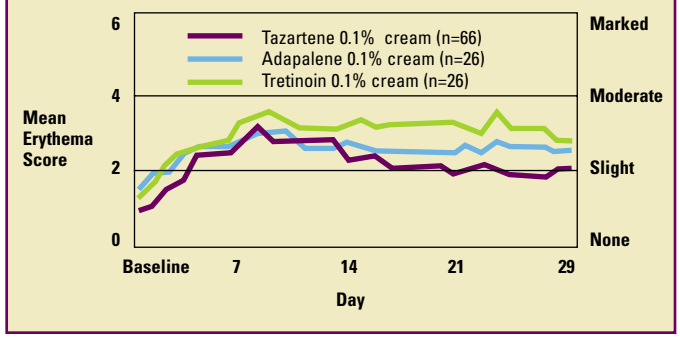
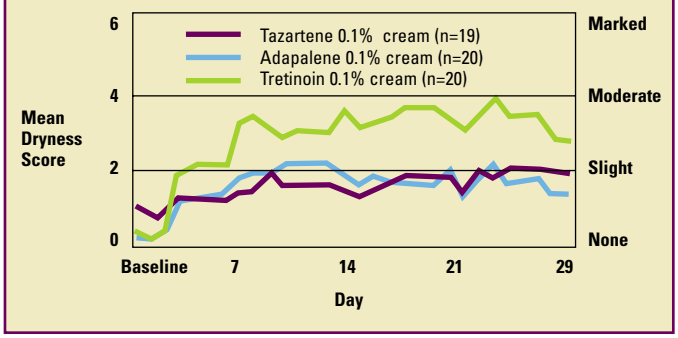


Figure 3. Retinoids: Creams on Sensitive Skin



treatment group either have had or had had atopic dermatitis or have had rosacea and a history of reacting to facial products. A rough, thickened, cracked stratum corneum characterizes both these conditions.

Regardless of formulation, all three topical retinoids were better tolerated by normal skin than by sensitive skin. Erythema and dryness were significantly lower on normal skin than on sensitive skin. With regard to tazarotene gel, individuals with sensitive skin clearly experienced more difficulty. Consistent with the earlier finding that tazarotene 0.1% gel was more irritating than other retinoid gels, tazarotene 0.1% cream was much better tolerated by sensitive skin. Although adapalene was better tolerated than tazarotene, adapalene 0.1% gel caused more irritation on sensitive skin than on normal skin. Similarly, adapalene 0.1% cream was better tolerated by normal skin when compared with sensitive skin. In accordance with these findings, tretinoin 0.1% microsponge and cream also irritated sensitive skin more than normal skin, partly because of the sorbic acid preservative.

Retinoid Effects

Comparison of one topical retinoid with another by both sensitive and normal skin reveals the relative influence of skin sensitivity and choice of retinoid. Although infeasible, equimolar concentrations in exactly the same vehicle would be ideal when making these comparisons.

Tazarotene 0.1% gel was more irritating than either adapalene 0.1% gel or tretinoin 0.1% gel whether skin was normal ($P \leq 0.001$) or sensitive ($P \leq 0.01$). However, tazarotene 0.1% cream caused statistically less erythema than did adapalene 0.1% cream or tretinoin 0.1% cream on normal skin ($P \leq 0.05$) (**Figure 2**) and was statistically less drying than was tretinoin cream on sensitive skin ($P \leq 0.01$) (**Figure 3**). So tazarotene cream, surprisingly, was much better tolerated by sensitive skin.

Is tolerability affected by retinoid choice? It can be. However, the sensitivity of an individual's skin can affect tolerability at least as much as the choice of retinoid. On both normal and sensitive skin, tazarotene is the best tolerated cream and adapalene is the best tolerated gel.

Summary

In general, skin sensitivity is probably the most influential factor with respect to topical retinoid tolerability. It is at least as important as choice of retinoid and is more important than retinoid formulation or concentration. Therefore, actually feeling a patient's skin can help predict tolerability issues. Even a teenager whose skin has never been treated may possess a rough skin texture, which indicates a cracked and defective stratum corneum that fails to protect inner skin layers. Thus, these individuals are more likely to experience difficulties with any topical skin product, particularly retinoids, and should be encouraged to use moisturizers that fortify lipids essential to normal stratum corneum function. Furthermore, difficulties with irritation can be minimized by simplifying the basic skin care regimen, such as using skin-friendly detergents in a gentle nonabrasive fashion.

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Improved Efficacy and Patient Satisfaction in Acne Vulgaris

Dina N. Anderson, MD

To analyze clinical data with some degree of statistical power, clinical trials often are double-blind and controlled with rigid subject and medication exclusions. Although these criteria facilitate unambiguous interpretation of results, they seldom resemble real-world clinical practice.[1]

One outstanding feature of the Balancing Efficacy, Speed, and Tolerability trial was that it mirrored clinical practice without artificially altering patient behavior. It was an open-label, observational trial with 243 dermatologists at study centers all over the country. Each clinical investigator recruited subjects with facial acne vulgaris who were unhappy with their acne treatment.

As in everyday practice, neither washout periods nor medication discontinuations were necessary; concomitant topical or systemic agents were allowed. Also as in everyday practice, when a patient's treatment regimen is unsatisfactory, often the addition of a topical retinoid is recommended; for this trial, tazarotene 0.1% cream was prescribed. Study subjects were instructed to apply tazarotene cream once daily each evening for 12 weeks.

Assessments

As with other clinical studies of acne, efficacy and tolerability were evaluated systematically. Subjects were observed during two office visits following study entry and tazarotene initiation. The first of these was scheduled 4 to 6 weeks after study entry and the second, after 10 to 12 weeks. At each visit, open and closed comedones, papules, and pustules were counted, overall improvement in inflammation was assessed, and cutaneous irritation was monitored.

This trial was also interested in appraising subject satisfaction. In everyday practice, patients with acne commonly complain about their treatment regimens.[2] Despite apparent improvement, patients often perceive no improvement at all. Could this be consequential? Toward this end, study subjects and physicians were asked to consider their satisfaction with the study treatment regimen.

Patients often try all sorts of over-the-counter products, see more than one dermatologist, or experiment on their own. This study asked subjects to rate the efficacy of study medications relative to other treatments they had tried. Study dermatologists also rated tazarotene relative to other acne therapies.

Population

Most study subjects were young (mean age, 21 years) and Caucasian (Fitzpatrick type II or III),[3] with normal to oily skin who had had facial acne for 1 to 5 years. In other words, these study subjects generally were not adolescents seeing a dermatologist for the first time. They were young adults who had suffered with acne for some time, had tried other treatments, and were motivated to try something new. Of the 1,118 evaluable patients, 56% were female and most completed the trial. Virtually all (96%) returned for the second study visit and nearly all (87%) returned for the third and final study visit.

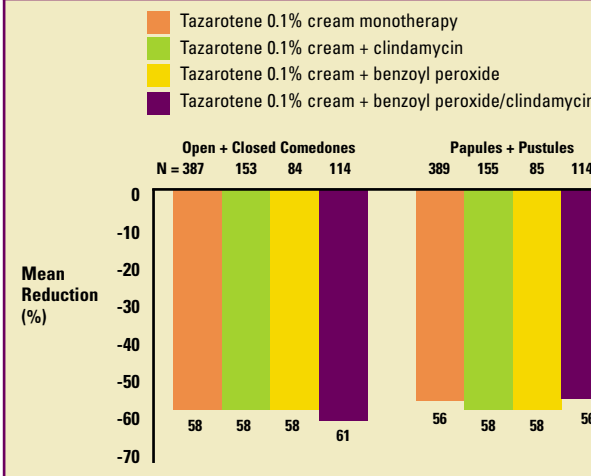
Efficacy

Tazarotene cream was very effective in improving both comedo and inflammatory acne. Comedo and inflammatory lesion counts were reduced 60% and 58%, respectively. Even more impressive was that the onset of this therapeutic response was remarkably rapid, occurring during the first 4 to 6 weeks of treatment.

Topical retinoids have long been recognized to be effective against noninflammatory comedo acne, but these results also support efficacy against inflammatory acne.[4] In this study, monotherapy tazarotene cream reduced comedones and papules/pustules as effectively as did combination therapy (**Figure 1**). Moreover, more than a 50% improvement in inflammatory acne was evident for 81% of the study subjects. Therefore, whether subjects were using a topical antibiotic or benzoyl peroxide, addition of topical tazarotene 0.1% cream substantially improved their condition.

What about other therapies? Among the study population, 60% of study subjects concomitantly used another acne medication, typically either clindamycin, benzoyl peroxide, or a combination of the two.[5] Nevertheless, addition of topical tazarotene cream further improved efficacy. Counts of open and closed comedones as well as of papules and pustules, on average, were reduced more than 50% by any combination of treatments (**Figure 1**).

Figure 1. Lesion Reduction Following Addition of Topical Retinoid*



*Over and above any reductions achieved with prestudy regimens.

Figure 2. Patient Satisfaction

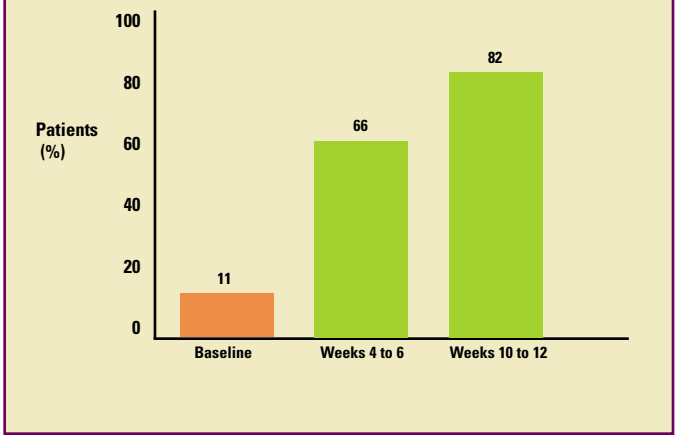
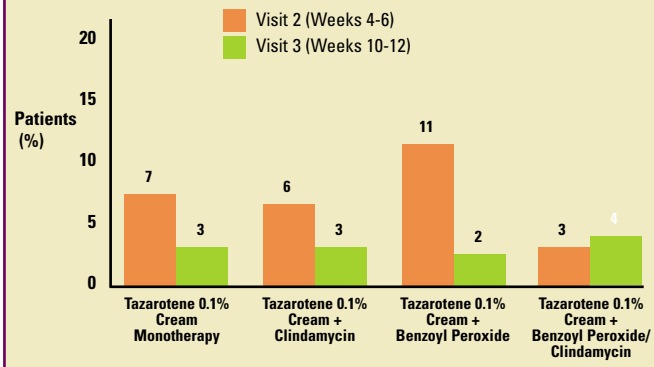


Figure 3. Adverse Events



Satisfaction

At study entry, only 11% of study subjects were satisfied with their acne therapy, but this proportion dramatically increased to 82% only 10 to 12 weeks later (**Figure 2**). Perhaps even more remarkable was that 66% of the study subjects were *satisfied* or *very satisfied* as early as Week 4.

Tazarotene 0.1% cream was perceived by 69% of subjects to be more effective than other acne medications used in the past. Tazarotene was regarded at least as effective as other medications by 94% of study subjects.

Nearly all clinical investigators (96%) considered tazarotene cream good or excellent when compared with other acne medications, and most (73%) regarded its onset of action faster than other topical retinoids.

Tolerability

Because tazarotene gel was introduced as a treatment for plaque psoriasis, its reputation for irritating sensitive skin evolved with its use by individuals whose skin was damaged by psoriatic skin fissures.[6,7] When the gentler cream formulation was applied to intact skin in this study, however, tolerability was excellent. Adverse events were very rare, and mean levels of peeling, erythema, dryness, or burning never exceeded minimal levels. Now that more tolerable retinoid formulations are available, first-line acne treatment no longer requires inordinate hand-holding for the first couple of months.

Since benzoyl peroxide is more irritating than clindamycin,[5,8] it is not surprising in this study that the combination of tazarotene with benzoyl peroxide was the least tolerated therapy; nevertheless, this irritability profile was apparent only during the second study visit, 4 to 6 weeks after tazarotene initiation, when retinization was ongoing (**Figure 3**). At the third and final study visit, after 10 to 12 weeks of tazarotene treatment, the retinization period was over and so were the majority of cutaneous side effects.

Moreover, if study subjects experienced a bit of peeling or dryness, they simply reduced the volume or number of medications or frequency of application. Only in an uncontrolled trial such as this one could such real-life remedial measures be explored. Perhaps open studies like this with other retinoids in a broad spectrum of patients and investigators in various climates and different circumstances would be enlightening.

"Now that more tolerable retinoid formulations are available, first-line acne treatment no longer requires inordinate hand-holding for the first couple of months."

Summary

Topical retinoids are the mainstay of acne therapy. This trial demonstrated that tazarotene 0.1% cream was highly and rapidly effective in the treatment of both inflammatory and noninflammatory acne vulgaris, and it was very well tolerated. These success factors were confirmed by a very high degree of patient satisfaction, an important element in the treatment of this disorder.

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Retinoid Selectivity in Psoriasis

Craig L. Leonardi, MD

Psoriasis is a recurrent inflammatory skin condition that affects approximately 2% of the world's population, including 1.5 million Americans seen annually with associated outpatient costs amounting to $1.6 to 3.2 billion.[1] A 26-year-old individual with psoriasis will need decades of therapy but the available therapies fall short, especially if systemic treatment is required. More reasonable and effective treatment options are needed.

Topical treatments for psoriasis include emollients, corticosteroids, topical retinoids, salicylic acid, tars, anthralin, keratolytic agents, and vitamin D_3 analogs, each with their own set of disadvantages, but many are cosmetically unacceptable and only weakly effective.[2] Phototherapy such as PUVA (psoralen with ultraviolet A) may cause nausea, pruritus, and sunburn acutely, but more worrisome are longer-term effects such as lentigines, ocular complications, and skin cancer.[3]

Until tazarotene, there were four available systemic treatments: methotrexate, acitretin, cyclosporine, and biologics, but all of these are associated with serious adverse effects. Concerns about long-term side effects, such as skin cancer, hepatotoxicity, nephrotoxicity, or pulmonary toxicity, compel one third of patients treated with systemic agents to discontinue treatment; another third stops treatment because of inadequate therapeutic effect.[4]

Methotrexate

Methotrexate, an immunosuppressant, has been available for some time and its limitations are well documented. Hepatic fibrosis and cirrhosis, not always evident on liver function tests, are among its more notable side effects and require monitoring and liver biopsy in chronically treated patients. Other rarer, life-threatening effects include pancytopenia, lymphoproliferative disorders, and acute pneumonitis.[3] Concomitant folic acid can reduce hematologic side effects as well as acute gastrointestinal symptoms.[5]

Acitretin

Acitretin, a nonspecific retinoid that spontaneously isomerizes to 13-*cis*-acitretin, replaced etretinate primarily because of its considerably shorter half-life (50 to 60 hours versus 120 days).[6] The most common adverse effects include elevated serum lipids, generalized xerosis, and alopecia. Furthermore, acitretin as well as methotrexate are teratogens and should never be used when pregnancy is possibile. Following acitretin discontinuation, therefore, 3 years are required before conception is considered safe, mostly because of its accumulation in body fat and alcohol-induced conversion to etretinate.[7]

Cyclosporine

The efficacy against plaque psoriasis of cyclosporine, an immunosuppressant that targets T cells, is rivaled only by the biologic, infliximab,[8] yet its use has never been accepted by American dermatologists. It is a challenging drug to use and has many drug interactions with a bewildering set of consequences. Nephrotoxicity, hypertension, infection, and cutaneous and internal malignancies are observed among chronically treated patients.[3] Cyclosporine is not recommended for patients with weakened immune systems, substantial phototherapy exposure, hypertension, or renal disease, and the Food and Drug Administration (FDA) has approved its use for only 1 year in psoriasis.

Biologics

Technically, biologics in development or approved for the treatment of psoriasis are immunosuppressants that will need to be used in chronic or chronic-intermittent dosing schedules. The biologics are very expensive,[9] restricting access to patients with prescription insurance coverage. Because these agents are new and recently approved for treatment of psoriasis, safety data are limited. Associated with tumor necrosis factor antagonists in rheumatoid arthritis are reports of increased infection and, more rarely, congestive heart failure and demyelination.[10-12] Reports of short-term (postwithdrawal rebound) and long-term (chronic T-cell depletion) effects are not fully understood.

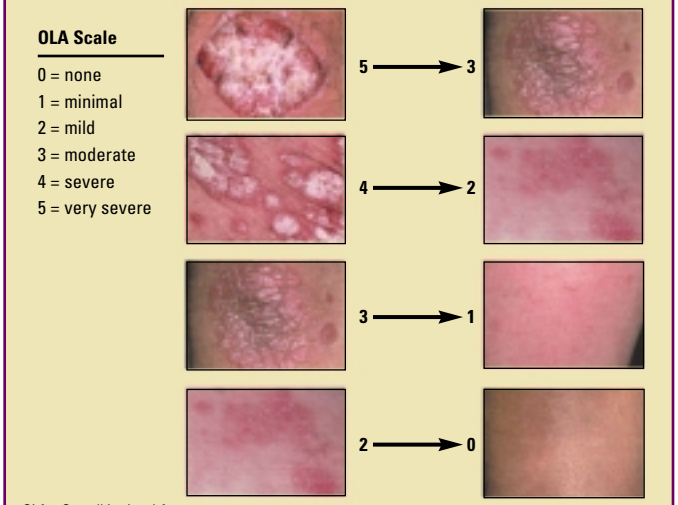
Tazarotene Clinical Studies

Considering its selectivity, lack of isomerization, low lipophilicity, once-daily dosing, no known drug interactions, reduced side effects, negligible levels 1 week after discontinuation, and safe conception as early as 1 month after discontinuation, tazarotene represents a substantial advance in retinoid design. Decreased hyperproliferation, reduced inflammation, and restoration of normal phenotype are among its beneficial effects.

Two large, multicenter, double-blind, randomized, placebo-controlled trials investigated efficacy and tolerability of once-daily tazarotene (4.5 mg) in patients with moderate to very severe psoriasis. Study subjects received oral tazarotene or placebo for 12 weeks followed by a 12-week observational period.

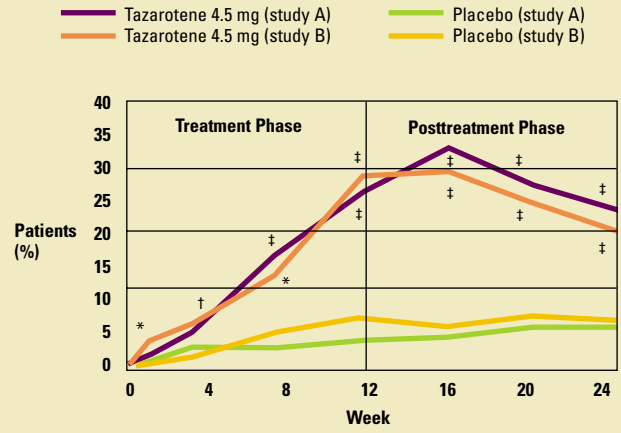
To clarify one point of potential confusion, because of differing preferences of the FDA branches that oversee drug development (Center for Drug Evaluation and Research, CDER) and biologics (Center for Biologics Evaluation and Research, CBER), the primary efficacy variable used in these tazarotene trials was the Overall Lesional Assessment (OLA) rather than the Psoriasis Area and Severity Index (PASI), which is used in studies of biologic agents.

Figure 1. Efficacy Endpoint (OLA)



OLA = Overall Lesional Assessment.

Figure 2. Efficacy: OLA Improvement



*P <0.01; †P <0.05; ‡P <0.001 vs placebo.

The OLA is a 6-point photonumeric scale of psoriasis signs (plaque elevation, scaling, and erythema) ranging from none (0) to very severe (5). One primary efficacy endpoint in these two tazarotene studies was the percentage of study subjects with OLA grades representing no or minimal psoriasis. The second primary efficacy measure was the percentage of study subjects improving at least two OLA grades, a very significant improvement (**Figure 1**). Secondary efficacy variables included physician global response, body surface area affected, and evaluation of target lesions.

Study Population

Of the 690 study subjects, most were white males (80%), and the mean age was 45 to 48 years. This particular study population suffered from substantial psoriasis. The mean OLA was 3.4 (moderate to severe), with approximately one third of the body surface area affected.

Efficacy

After 12 weeks of oral tazarotene therapy, approximately 17% of the study subjects exhibited no or minimal psoriasis according to the OLA, but even more tazarotene-treated subjects (22%) enjoyed this level of improvement by Week 16, 4 weeks after tazarotene was terminated. This prolonged therapeutic effect was sustained throughout the 12-week observation period, thus substantially outlasting the treatment period.

After 12 weeks of oral tazarotene therapy, almost 27% of these seriously afflicted study subjects achieved a two-grade improvement in OLA (**Figure 2**). Furthermore, this therapeutic effect continued to improve until Week 16, 4 weeks posttreatment, and also was maintained throughout the 12-week observation period.

This dramatic and long-lived efficacy was confirmed by the physician global response. More than 75% improvement was achieved by approximately one third of the study subjects after 12 weeks of tazarotene treatment, and even more subjects obtained this endpoint by Week 16.

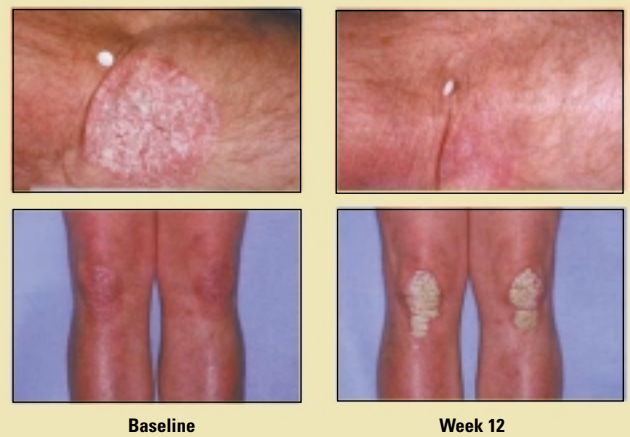
Thus, oral tazarotene was statistically superior to placebo at Week 12 and also at Week 24 (P <0.001), 12 weeks posttreatment, at reducing scaling, erythema, and plaque elevation even among subjects with difficult-to-treat areas such as scalp, elbows, and knees (**Figure 3**). This efficacy was sustained throughout the posttreatment period, and the affected body surface area was significantly reduced by oral tazarotene in both trials (P <0.001).

Tolerability

There were no treatment-related serious adverse events, and the majority of adverse events were mild. Events statistically more common than those among placebo-treated subjects included cheilitis, xerosis, minor headaches, minor arthralgia, myalgia, and backache, but these generally were very well tolerated; fewer than 5% of study subjects discontinued because of any adverse event.

There were no consistently significant changes in laboratory values or radiographic evaluations, including

Figure 3. Representative Clinical Response (Knees)



"Oral tazarotene produced significant and sustained clinical improvement in moderate to severe psoriasis without causing any serious adverse events."

cholesterol and triglycerides, liver function, hematology, bone density, and thyroid function. Oral tazarotene was not associated with alopecia or neuropsychological changes such as depression. Study subjects were happy with oral tazarotene treatment; 79% of them were very satisfied (P <0.001). Oral tazarotene also improved quality of life, according to the Psoriasis Quality-of-Life Questionnaire; more than half of the study subjects improved by one point, which is equivalent to a decrease from moderate to mild in physician ratings of disease severity,[13] and 40% improved by two points.

Summary

Oral tazarotene produced significant and sustained clinical improvement in moderate to severe psoriasis without causing any serious adverse events. Clinical improvement was evident as early as after 4 weeks of treatment and was significant by 8 weeks. Nearly one third of study subjects achieved more than 75% improvement, compared with 7% treated with placebo. One in five study subjects exhibited no or minimal disease at 16 weeks (after 12 weeks of treatment). Approximately 80% of the therapeutic effect was maintained for at least another 12 weeks posttreatment.

Because oral tazarotene is safe, effective, convenient, interacts with neither alcohol nor oral contraceptives, and has a relatively short half-life, it should replace acitretin in the treatment of psoriasis. Although highly effective as monotherapy, tazarotene may also be combined with ultraviolet light or other therapies such as biologics.

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Rational Drug Design

Continued from page 5

ics, and low lipophilicity focus therapeutic effects and limit unwanted side effects. In contrast to nonspecific retinoids, tazarotene does not accumulate in adipose tissue, clears the body within 1 week, and precludes safe conception for only 1 month.

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INSTRUCTIONS: For each question or incomplete statement, one answer or completion is correct. Seven out of 10 correct responses are required for credit. Circle the most appropriate response.

1. Acitretin and isotretinoin do not:
   a. bind both RARs and RXRs.
   b. require long washout periods before conception is safe.
   c. accumulate in adipose tissue.
   d. convert to metabolites without isomers.

2. Rational drug designs are likely to enable:
   a. selective mechanisms of action.
   b. dosing regimens that complicate compliance.
   c. a nonlinear pharmacokinetic profile.
   d. wide-ranging therapeutic effects.

3. Tazarotene would be expected to produce few systemic adverse effects because:
   a. its free fatty acid, tazarotenic acid, interacts very inefficiently with RAR-α and RXR receptor types.
   b. systemic exposure is maximized by extensive transcutaneous absorption and slow elimination.
   c. it promptly metabolizes to tazarotenic acid, which shows high affinity for RAR-β and RAR-γ receptor types.
   d. accumulation in adipose tissue is curtailed by rapid metabolism to hydrophilic metabolites in skin and blood.

4. Because newer formulations of topical retinoids have a potential for transient irritation:
   a. wait a few visits after starting therapy with other topical treatments.
   b. pre-treat with topical steroids to minimize complaints.
   c. start these retinoids at the first visit for most cases of acne.
   d. do not use these retinoids with topical agents that suppress *P. acnes*.

5. Retinoid-induced dermatitis can be helped by instructing the patient to:
   a. apply no more than the proper volume of retinoid.
   b. incorporate abrasive skin-cleansing methods.
   c. eat foods rich in beta-carotene.
   d. avoid moisturizers that affect the stratum corneum.

6. Skin sensitivity affects facial tolerability:
   a. less than retinoid concentration.
   b. less than retinoid formulation.
   c. at least as much as choice of retinoid.
   d. at least as much as patient age.

7. When tazarotene cream was added to benzoyl peroxide, clindamycin, or a combination of the two, which of the following statements is incorrect?
   a. Patient satisfaction rapidly improved.
   b. Inflammatory acne improved.
   c. Noninflammatory acne improved.
   d. The combination product was superior against inflammatory acne.

8. Patient satisfaction is a key element in the treatment of acne vulgaris because:
   a. patient satisfaction may improve compliance and, therefore, efficacy.
   b. a patient's perceptions of improvement may be inaccurate.
   c. a satisfied patient is likely to discontinue medication prematurely.
   d. acne affects several aspects of daily living.

9. Which of the following treatments for plaque psoriasis is listed with its correct potential disadvantages?
   a. methotrexate (nausea, pruritus, lentigines, ocular problems, skin cancer)
   b. cyclosporine (hepatotoxicity, pancytopenia, acute pneumonitis)
   c. PUVA (nephrotoxicity, hypertension, infection, skin cancer)
   d. biologics (costly, T-cell depletion, congestive heart failure, demyelination)

10. In contrast to current psoriasis treatments, oral tazarotene:
    a. should be used only for mild cases of psoriasis.
    b. is safe and effective.
    c. onset of action is rapid but not sustained.
    d. interferes with the actions of oral contraceptives.

EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for other activities of this type.

1. How would you rate the clarity of the presentation of the material? (Please check.)

	Excellent	Good	Fair	Poor
Text	_____	_____	_____	_____
Photographic Images	_____	_____	_____	_____
Post-Test	_____	_____	_____	_____

2. How would you rate the clinical relevance of the material?

_____ _____ _____ _____

3. How would you rate this material compared with similar independent study presentations in print format?

_____ _____ _____ _____

4. Was this a fair and balanced presentation? Please comment on the scientific rigor, fairness, and balance of the material.

_____
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5. Do you believe such materials, supported by education grants from industry, are appropriate and useful? Please rate from 0 (not appropriate/useful) to 10 (very appropriate/useful). _____

6. What topics would you find useful for future programs?

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