Successful Treatment of Acne Vulgaris Using a New Method

Results of a Randomized Vehicle-Controlled Trial of Short-Contact Therapy With 0.1% Tazarotene Gel

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Context: Short-contact application of 0.1% tazarotene gel for acne was devised to minimize local adverse effects. Its efficacy and safety are unknown.

Objectives: To assess acne improvement and tolerability during 12 weeks of short-contact treatment with 0.1% tazarotene gel vs a nonmedicated gel control.

Design: A randomized, masked, vehicle-controlled trial.

Setting: Outpatient facilities at an urban medical school and an affiliated suburban office practice.

Participants: Ninety-nine volunteers with facial acne were enrolled; 81 completed the study.

Intervention: Thirty-three patients were randomly assigned to each of 3 groups: T+T applied 0.1% tazarotene gel twice daily, T+V applied 0.1% tazarotene gel once daily and vehicle gel once daily, and V+V applied vehicle gel twice daily. Patients adjusted the contact period as tolerated, between 30 seconds and 5 minutes per application.

Main Outcome Measures: Acne efficacy by reduction in acne lesions, treatment success (50%-100% improvement in global response to treatment) and improvement in overall disease severity. Local adverse effects, scored from none to severe.

Results: By week 12, T+T and T+V achieved significantly greater improvement in acne than V+V based on mean percentage reduction in noninflammatory lesions (46% and 41% vs 2%; \( P = .002 \)) and inflammatory lesions (38% and 34% vs 9%; \( P = .01 \)), percentage of treatment successes (64% and 61% vs 15%; \( P < .001 \)), and reduction in overall disease severity (30% and 29% vs 3%; \( P < .001 \)). Local adverse effects did not differ significantly among the 3 groups after week 4.

Conclusion: Short-contact 0.1% tazarotene gel therapy is a safe and effective new method of acne treatment.

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Acne treatment with topical retinoids originated in 1969 with the discovery by Kligman et al\(^1\) of vitamin A acid for this disorder. Tazarotene, which was introduced in 1997, is the newest retinoid agent for treating acne and the sole member of this class approved by the Food and Drug Administration for topical psoriasis therapy.\(^2\) It is available in both gel and cream vehicles containing either 0.05% or 0.1% tazarotene, but only the 0.1% formulations are Food and Drug Administration approved for acne. Tazarotene has also been used successfully for basal cell carcinoma,\(^3\) chronic sun damage,\(^4\) and congenital ichthyosis.\(^5\)

Retinoids as a group exert their effects after activation of 2 families of nuclear receptors, retinoic acid receptors (RARs) and retinoid X receptors, each having alpha, beta, and gamma subclasses.\(^6,7\) Whereas tretinoin is a flexible molecule that binds to all RAR subclasses, tazarotene and adapalene are rigid, receptor-selective retinoids.\(^10,11\) Tazarotene is converted in the skin to its active metabolite tazarotenic acid, which has a high affinity for RAR-beta and RAR-gamma.\(^12\) It does not activate the RAR-alpha subclass or retinoid X receptors. Retinoic acid receptor–gamma is the most ubiquitous RAR in mature keratinocytes.\(^13\) This subclass has been shown to mediate desirable and adverse retinoid effects in animal models.\(^14\) The mechanisms of action of tazarotene, most extensively studied in psoriatic skin, are normalization of keratinocyte proliferation and differentiation as well as reduction in keratinocyte-expressed markers that attract inflammatory cells.\(^15-17\)

Local adverse effects, including skin peeling, dryness, redness, burning, and itching, often limit topical retinoid use.\(^18\) During one author’s (S.B.) early experience with tazarotene for facial acne, several patients noted skin discomfort within 10 minutes of...
PATIENTS AND METHODS

PARTICIPANTS AND SETTING

A total of 99 patients aged 12 to 39 years with facial acne were enrolled at 2 study sites affiliated with the Department of Dermatology of the Mount Sinai School of Medicine. Forty patients were enrolled at a suburban office practice (site 1) and 59 were enrolled at an urban medical center outpatient facility (site 2). All patients were volunteers recruited via local advertisements or posters exhibited on site.

Patients were required to understand and follow the study protocol, which was approved by the medical school institutional review board. Patients and parents or legal guardians of those younger than 18 years gave written informed consent. Inclusion criteria required patients to be 12 years or older and to have mild to moderate facial acne, defined as 10 to 200 noninflammatory lesions (open and closed comedones), 10 to 60 inflammatory lesions (papules and pustules), and fewer than 3 nodulocystic lesions. Medication-free periods were required before study entry, as follows: systemic retinoids, 24 months; oral antibiotics, 4 weeks; and topical acne medications, 2 weeks. Female patients were permitted to take oral contraceptives if initiated at least 3 months before study entry and continued throughout the study. Female patients were excluded if they were pregnant, breastfeeding, or sexually active without using reliable contraception.

STUDY PROTOCOL

This study was randomized, investigator-masked, and controlled by using a nonmedicated (vehicle) gel identical to the base of tazarotene gel. The gels were distributed in identical boxed pairs of 30-g tubes labeled “morning application” and “evening application.” 0.1% tazarotene gel and vehicle gel are odorless and colorless. Because of possible irritation from tazarotene, patient blinding was assumed to be potentially compromised. To maintain investigator masking, clinical assistants collected and recorded data regarding facial skin signs and symptoms, and physician-investigators assessed efficacy measures.

application. In some cases, typical retinoid-induced skin irritation occurred, even when tazarotene was removed after such limited exposure. The possibility of avoiding adverse effects by shortening the period of skin contact with tazarotene was intriguing. Preliminary exploration suggested that acne improvement and good tolerability might result from exposure times shorter than 5 minutes repeated regularly for 12 weeks. The goal of this study was to assess acne progress and local skin irritation, using a novel short-contact method of applying 0.1% tazarotene gel (Tazorac; Allergan Inc, Irvine, Calif), in patients with mild to moderate facial acne. Comparisons of these measures were made among 3 groups: those using 0.1% tazarotene gel twice daily (T+T), those using 0.1% tazarotene gel once daily and nonmedicated (vehicle) gel once daily (T+V), and a control group using vehicle gel twice daily (V+V).

Patients were randomly assigned to 1 of 3 treatment groups, each having 33 enrollees: (1) patients in the T+T group received 0.1% tazarotene gel as the morning and evening application; (2) patients in group T+V received 0.1% tazarotene gel as the evening application and vehicle gel as the morning application; and (3) patients in group V+V received vehicle gel as the morning and evening application.

All patients received instruction cards detailing the short-contact method, which required twice-daily (morning and evening) application of the study gel, spread thinly to facial skin after washing with a nonsoap liquid cleanser (Cetaphil; Galderma Laboratories, LP, Fort Worth, Tex) and rinsing with lukewarm water. The dosage of gel per application was approximately 0.6 g, described and demonstrated to patients as a pea-sized amount. Patients rinsed with lukewarm water after contact periods starting with 2 minutes per application (timed using digital timers [Big-Digit Timer, RadioShack, Fort Worth] that were provided to monitor all applications). All patients were instructed to increase the contact period, if tolerated without local effects, in 1-minute increments at intervals of at least 3 days to a maximum of 5 minutes. The written instructions directed patients to reduce the contact period to 30 seconds if peeling, erythema, dryness, burning, or itching occurred. In such cases, patients were to increase the contact period in 30-second increments at intervals of at least 3 days, if tolerated, to the 5-minute maximum. Patients were requested to maintain diary records in which they recorded contact periods of all applications. Clinical assistants collected these records at each visit.

CLINICAL ASSESSMENTS

Patients were seen at baseline, defined as the visit when treatment was initiated, and again at 2, 4, 8, and 12 weeks of treatment. At each visit, physicians used 3 methods to assess efficacy for acne. First, facial lesion counts were performed of individual acne lesions, divided into noninflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules), and nodules (lesions ≥4 mm). Second, global response to treatment scores were assessed by comparing the patient’s condition with baseline photographs and then were graded from 0 to 6 as follows:

RESULTS

PATIENT CHARACTERISTICS

Of 99 patients enrolled, 64 were female and 35 were male. The median age was 25 years (range, 12-39 years). There were no significant differences in demographic characteristics among the 3 treatment groups (Table 1). Eighteen (18%) of 99 patients did not complete the study: 6 in the T+T group, 4 in the T+V group, and 8 in the V+V group (Figure 1). The differences in discontinuation rates in the 3 treatment groups were not significant (P=.44).

Treatment groups demonstrated similar baseline distributions of acne lesions (open comedones, closed comedones, papules, pustules, and nodules) and facial
Compared with the V+V group, as demonstrated by the rules, were significantly reduced in the T+T and T+V groups, respectively.

Week 12, reductions of 46.06%±38.31%, 41.19%±39.24%, and 2.48%±35.84% were observed in the T+T, T+V, and V+V groups, respectively.

The treatment score of 0 to 3 (50%-100% improvement). A sample size of 99 patients (33 patients per treatment arm) was required based on the following assumptions: (1) use of a 2-sided test with α=.05 and a power of 0.8; (2) an average difference between the active treatment regimens and the control regimen of 35% (ie, "successes" in the treatment groups=50% and successes in the control group=15%); and (3) a dropout rate of 15%.

Analyses were conducted on an intent-to-treat basis and included all patients randomized to the study treatment. The χ² procedure was used to compare the sex and race of the 3 treatment groups at baseline and to compare nodule counts. Analysis of variance was used to compare all other measures, including other baseline characteristics, lesion counts, global response to treatment scores, overall disease severity scores, and facial skin sign and symptom scores. Comparisons between active treatment and control pairs were computed using the Dunnett 2-tailed test. In the analyses of all outcome measures, including lesion counts, global response to treatment scores, overall disease severity scores, and facial skin signs and symptoms, the last recorded score for each patient was carried forward to all subsequent visits.

The SAS PLAN procedure computer program (SAS Institute Inc, Cary, NC), using 3 treatments in blocks of 6, was used to generate treatment allocation for 102 patients and to obtain randomization. Patients were randomized to treatment through the sequential allocation of patient numbers at the first study visit. Sealed opaque envelopes containing treatment allocation information for each patient number were maintained at a separate location by a contract research organization (Integrated Research Inc, Dollard-des-Ormeaux, Quebec). Treatment allocation was not revealed for any study patient before the completion of statistical analyses.

**PHOTOGRAPHY**

During each visit, front and bilateral 45° side facial views of every patient were taken using a platform-mounted 35-mm SLR camera system (Nikon Corp, Tokyo, Japan) with a fixed-magnification 60-mm lens (f2.8) (Nikkor; Nikon Corp) and a dual-point light system (Twinflash; Canfield Scientific, Inc, Fairfield, NJ). Patients were positioned in a stereotactic device (Canfield Scientific, Inc) designed to capture registered serial photographs using standardized subject angles, framing, lighting, exposure, and reproduction ratio.

**ACNE EFFICACY**

Reductions from baseline in noninflammatory lesions in the T+T and T+V groups, expressed as mean±SD percentage change, were significantly greater than in the V+V group from week 4 to week 12 (P=.002) (Figure 2). At week 12, reductions of 46.06%±38.31%, 41.19%±39.24%, and 2.48%±35.84% were observed in the T+T, T+V, and V+V groups, respectively.

At week 12, inflammatory lesions, excluding nodules, were significantly reduced in the T+T and T+V groups compared with the V+V group, as demonstrated by the mean±SD percentage change from baseline in papules and pustules: 38.06%±36.22%, 33.58%±53.25%, and 8.76%±34.59%, respectively (P=.01) (Figure 3). Nodule counts were insufficient to accommodate statistical comparison. There were no significant differences between the 2 study sites in mean percentage reduction in noninflammatory or inflammatory lesions in any treatment group.

Achievement of treatment success was defined as global response to treatment of 0 to 3 (50%-100% improvement) by week 12. Significantly more treatment successes were observed in the T+T and T+V groups than in the V+V group: 64%, 61%, and 15%, respectively (P<.001).

Of 81 patients completing 12 weeks of treatment, 58 submitted complete diary records. These data show no evidence of a trend correlating treatment success with length of drug contact (Table 2). Statistical comparisons of subgroups, based on contact duration, were precluded by insufficient subgroup size.
By week 12, significant reductions from baseline in mean ± SD overall disease severity scores were observed in the T+T and T+V groups, 30.40% ± 30.96 and 29.09% ± 26.01, respectively, compared with 2.78% ± 17.26 in the V+V group (P < .001) (Figure 4). Significant differences in this variable became apparent by week 8 (T+T and T+V vs V+V; P < .001).

Individuals from the 3 treatment groups demonstrating various global response to treatment scores are shown in Figures 5, 6, and 7.

<table>
<thead>
<tr>
<th>Table 1. Comparability of Demographic Data, Acne Characteristics, and Facial Skin Signs and Symptoms Among Treatment Groups at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
</tr>
<tr>
<td>Sex, No.</td>
</tr>
<tr>
<td>F</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>Ethnic group, No.</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Duration of acne, No. of years</td>
</tr>
<tr>
<td>&lt;1</td>
</tr>
<tr>
<td>1-2</td>
</tr>
<tr>
<td>3-5</td>
</tr>
<tr>
<td>6-10</td>
</tr>
<tr>
<td>&gt;10</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Acne lesions, No.</td>
</tr>
<tr>
<td>Open comedones, mean ± SD</td>
</tr>
<tr>
<td>Closed comedones, mean ± SD</td>
</tr>
<tr>
<td>Subtotal, mean ± SD</td>
</tr>
<tr>
<td>Papules, mean ± SD</td>
</tr>
<tr>
<td>Pustules, mean ± SD</td>
</tr>
<tr>
<td>Subtotal, mean ± SD</td>
</tr>
<tr>
<td>Nodules (1 or 2), No.</td>
</tr>
<tr>
<td>Facial skin sign and symptom scores, mean ± SD</td>
</tr>
<tr>
<td>Peeling</td>
</tr>
<tr>
<td>Erythema</td>
</tr>
<tr>
<td>Dryness</td>
</tr>
<tr>
<td>Burning</td>
</tr>
<tr>
<td>Itching</td>
</tr>
<tr>
<td>Overall disease severity score, mean ± SD</td>
</tr>
</tbody>
</table>

*See the “Study Protocol” subsection of the “Patients and Methods” section for descriptions of the treatment groups.
FACIAL SKIN SIGNS AND SYMPTOMS

The highest mean scores for peeling, erythema, dryness, burning, and itching were observed in the T+T group at week 2 or week 4; the maximum mean ± SD scores achieved for these signs and symptoms were 0.76±0.94, 0.67±0.82, 0.85±0.97, 0.42±0.79, and 0.45±0.79, respectively. Mean scores of signs and symptoms did not exceed 1.0, or trace level, for any group throughout treatment. Increases in these signs and symptoms were significantly greater in the T+T group than in the V+V group at weeks 2 and 4 for peeling and erythema and at week 2 for dryness and burning.

Transient increases in these signs and symptoms were more prominent in the T+V group than in the V+V group at weeks 2 and 4 but did not reach significance. After week 4, the occurrence and severity of these signs and symptoms in the active treatment groups did not differ significantly from those in the control group.

No patient discontinued study medication because of adverse events, but significantly more related adverse events were observed in the T+T and T+V groups than in the V+V group (P=.002). Specifically, 1 or more of the signs and symptoms of local skin irritation was reported by 16 (48%) of 33 patients in the T+T group, 17 (52%) of 33 in the T+V group, and 3 (9%) of 33 in the V+V group.

Local skin irritation tended to be better tolerated by the T+V group than by the T+T group. Of patients completing therapy and submitting full diary records, 10 (50%) of 20 T+T patients reduced the contact period to less than 2 minutes at some time during the study, whereas 1 (4%) of 23 T+V patients reduced the contact period to less than 2 minutes.

The benefits achieved by patients in this study compare favorably with those reported in a large, multicenter study of overnight tazarotene therapy for acne. The mean percentage decrease in noninflammatory lesions after 12 weeks of overnight 0.1% tazarotene gel was 55% (vs 35% in the control group) compared with 46% and 41% (vs 2% in the control group) for twice-daily and once-daily short-contact therapy, respectively. Using overnight therapy, the mean percentage decrease in inflammatory lesions was 42% (vs 30% in the control group), whereas results achieved using the short-contact method were 38%, 34%, and 9% for the T+T, T+V, and V+V groups, respectively.

Two differences in study design might account for the relatively better response of the control group in the overnight study. First, patients in the overnight study washed with a soap-based cleanser twice daily, whereas our patients were prohibited from using soap and surfactant-based cleansers on facial skin throughout the study. Second, prolonged application of vehicle gel may have an unexplained palliative effect on acne not seen to the same extent with short-contact use.

Measures of efficacy in the present study showed continuing trends toward improvement at week 12 (Figures 2-4), suggesting that more than 3 months of therapy may be required to achieve the maximum benefit. Gradual improvement over a several-month period is the typical acne response to retinoids.

Comparing overnight tazarotene with other topical retinoids, a recent clinical study showed that nightly 0.1% tazarotene gel is more effective than nightly 0.025% tretinoin gel in the treatment of comedonal acne. Fur-

![Figure 3. Mean percentage change in papules and pustules. See the “Study Protocol” subsection of the “Patients and Methods” section for descriptions of the treatment groups.](attachment:image)

Table 2. Treatment Success by Length of Contact Time per Application at Last Visit in 81 Patients Completing 12 Weeks of Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>T+T (n=27)</th>
<th>T+V (n=29)</th>
<th>V+V (n=25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact time, min</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>2.5-3.5</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>9</td>
<td>13</td>
<td>14</td>
<td>...</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>6</td>
<td>10</td>
<td>...</td>
</tr>
<tr>
<td>Treatment success, by contact time, min</td>
<td>6 (75)</td>
<td>5 (100)</td>
<td>0</td>
<td>.49</td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>3 (100)</td>
<td>4 (80)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>2.5 to 3.5</td>
<td>7 (78)</td>
<td>9 (69)</td>
<td>2 (29)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients. Ellipses indicate not applicable.
†See the “Study Protocol” subsection of the “Patients and Methods” section for descriptions of the treatment groups.
thermore, 0.1% tazarotene gel applied every second night seems to be equivalent therapeutically to 0.1% adapalene gel applied every night.22

The degree of acne improvement demonstrated in the present study is similar to that observed in a large multicenter trial23 comparing 0.025% tretinoin gel with 0.1% adapalene gel. Both agents were applied in the traditional overnight manner. After 12 weeks, the mean percentage reductions in noninflammatory lesions were 33% and 46% for tretinoin and adapalene, respectively. Mean inflammatory lesion counts were reduced by 38% in the tretinoin group and by 48% in the adapalene group. There were significantly fewer incidents of local skin irritation in the adapalene users than in the tretinoin users, but more than 30% of the former group and more than 40% of the latter had erythema and/or scaling of the facial skin persisting at week 12.

Of 446 patients applying tazarotene overnight, 39 (9%) withdrew because of treatment-related adverse effects, particularly local skin irritation.20 In a 12-week acne study24 comparing 0.1% adapalene solution with 0.025% tretinoin gel, 8 of 149 patients using adapalene solution and 4 (3%) of 146 patients using tretinoin gel withdrew because of retinoid-induced effects.

In the present study, signs and symptoms of local skin irritation did not differ significantly between the once-daily tazarotene group and the control group at any visit. There were no withdrawals due to treatment-related adverse effects because the study protocol allowed patients to adjust the contact period within well-defined limits to avoid such effects. In the previous experience of Bershad,19 tazarotene sensitivity differed substantially among individual patients, an observation supported herein. Data from patients’ diary records at week 12 suggest that approximately half of all patients using active treatment had contact times of 3.5 minutes or less, whereas the remainder tolerated longer contact periods (Table 2).

A problem inherent in most topical retinoid studies is that noticeable skin irritation may interfere with investigator blinding. In the present study, the risk of ob-
vious retinoid dermatitis was virtually eliminated by the patient’s ability to shorten the contact period at the earliest sign or symptom of irritation. Adverse effects were generally subjective, minor, and transient, mostly occurring during intervals between visits. In no case was the degree of local skin irritation so apparent as to be inconsistent with the control regimen.

To our knowledge, this is the first randomized study showing that a topical retinoid medication can produce pharmacological effects and clinical improvement after exceedingly short periods of skin contact.

A possible explanation for the efficacy of short-contact therapy may be found in the percutaneous absorption studies of Rougier and colleagues. Their work demonstrated that some topically applied substances achieve a reservoir effect in the stratum corneum after contact periods as short as 30 minutes.

Percutaneous absorption of tazarotene is a critical issue, as evidenced by its Food and Drug Administration designation of Pregnancy Category X, prohibiting its use during pregnancy and breastfeeding. Females of childbearing potential must use reliable birth control during tazarotene treatment. Although birth defects have not been reported in humans or laboratory animals after topical exposure to tazarotene, oral administration of high doses is teratogenic in animals. Another retinoid, isotretinoin, is well-known to cause birth defects in humans. Absorption studies in patients with facial acne using tazarotene gel overnight showed detectable plasma concentrations of tazarotene ranging from 0.06 to 0.22 ng/mL in 3 patients, and the active metabolite tazarotenic acid was detected in samples from 4 patients, ranging from 0.06 to 0.13 ng/mL. These levels are considerably lower than levels of endogenous retinoids in normal plasma.

Two of the studies by Rougier and coauthors are particularly relevant to the issue of systemic absorption. In one study, after application of various topical agents to hairless rats, the total doses absorbed were directly proportional to the duration of application, suggesting lower systemic levels with shorter contact periods. Another investigation found that facial skin, compared with other anatomical sites, exhibited the most rapid rate of percutaneous absorption, which may partially offset the theoretical benefit of shorter contact.

Neither the rate of tazarotene absorption into epidermal cells nor the plasma levels achieved after short-contact therapy have been studied to date, to our knowledge. The dose absorbed after 5 minutes is likely to be minuscule, since a previous study showed that total systemic absorption of tazarotene was less than 6% of the applied dose after 10 hours under occlusion. If future investigations confirm that the short-contact method limits tazarotene absorption, it may have an important safety advantage for premenopausal females.

Another benefit of short-contact therapy is the lack of medication residue on the skin. Users of short-contact therapy can apply cosmetics, sunblocks, moisturizers, and other topical preparations without concerns about dilu-

**Figure 6.** A 13-year-old girl in the group receiving 0.1% tazarotene gel once daily and vehicle gel once daily shown at baseline (A) and at 12 weeks (B), with a global response to treatment score of 1, indicating approximately 90% global improvement.
tion or noncompatibility caused by layering of 2 products. This property also facilitates combination antiacne regimens.

Drawbacks of short-contact therapy are the need for careful timing of the application and individualized adjustment of the contact period. Some patients consider overnight therapy simpler for these reasons.

Finally, once-daily short-contact tazarotene therapy offers clear advantages over the twice-daily regimen. In the present study, the former was about as effective but less irritating than the latter. Comparing the two, the less frequent regimen is also more convenient and cost-effective.

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From the Department of Dermatology, Mount Sinai School of Medicine, New York, NY (Drs Bershad, Tan, Sherer, Persaud, and Lebwohl and Ms Kranjac Singer); and Integrated Research Inc, Dollard-des-Ormeaux, Quebec (Dr Parente). Dr Bershad holds US patents and reserves all rights to international patents for the short-contact method of topical retinoid therapy to treat acne, photoaging, and psoriasis (patents 6017938, 6048902, 6083963, and 6096765). She has received compensation for speaking engagements from Allergan Inc, Irvine, Calif. Dr Parente is a co-owner and managing director of Integrated Research Inc, which has received compensation for clinical research consulting services from Allergan Inc. Dr Lebwohl has received research grants and compensation for speaking engagements from Allergan Inc.

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REFERENCES