Tazarotene Cream for the Treatment of Facial Photodamage

A Multicenter, Investigator-Masked, Randomized, Vehicle-Controlled, Parallel Comparison of 0.01%, 0.025%, 0.05%, and 0.1% Tazarotene Creams With 0.05% Tretinoin Emollient Cream Applied Once Daily for 24 Weeks

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Objective: To assess the safety and efficacy of 4 concentrations of tazarotene cream in the treatment of facial photodamage.

Design: Prospective weekly multicenter, investigator-masked, randomized, parallel-group study.

Setting: University hospitals and clinical research centers.

Patients: Three hundred forty-nine subjects with facial photodamage.

Intervention: Daily topical application of tazarotene cream (0.01%, 0.025%, 0.05%, and 0.1%) compared with its vehicle and with 0.05% tretinoin emollient cream.

Results: Tazarotene cream and tretinoin cream significantly improved mottled hyperpigmentation and fine wrinkles. At week 24, treatment success rates based on global responses were 67% (39 of 58 subjects) with 0.1% tazarotene, 52% (30 of 58 subjects) with 0.05% tazarotene, 36% (21 of 58 subjects) with 0.025% tazarotene, 41% (24 of 59 subjects) with 0.01% tazarotene, 55% (32 of 58 subjects) with 0.05% tretinoin, and 22% (13 of 58 subjects) with vehicle. Local adverse events, although more frequent with tazarotene at higher concentrations, were generally mild to moderate.

Conclusions: Tazarotene in a cream formulation is safe and is associated with positive changes in the treatment of photodamaged facial skin.

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UV irradiation from the sun causes premature skin aging, also known as photaging. Photaged skin is characterized by coarse and fine wrinkles, roughness, yellowness, laxity, uneven pigmentation, brown spots, and a leathery appearance. In contrast, chronologically aged skin that has been protected from the sun is thin and has reduced elasticity but is otherwise smooth and unblemished. Histologically, photaged skin demonstrates an alteration in the dermal matrix. Abnormal elastin-containing material and a disorganization of collagen fibrils are the hallmark signs. In addition, the levels of types I and III collagen precursors are reduced in photaged skin compared with sun-protected buttock skin. Changes in the epidermis can include a decrease in epidermal polarity and an increase in keratinocytic atypia. The topical retinoid tretinoin (all-trans-retinoic acid) has been shown to improve fine wrinkles, mottled hyperpigmentation, and tactile roughness associated with photaged skin. Histologically, the improvement in appearance of photaged skin following topical tretinoin use is associated with compaction of the stratum corneum, thickening of the epidermis, reduced melanin content, and increased glycosaminoglycans. The effacement of wrinkles correlates with a partial restoration of type I procollagen, which is typically reduced in photodamaged skin. Retinoids like tretinoin and tazarotene mediate their responses primarily through activation of nuclear retinoid receptors. There are 2 families of nuclear retinoic acid receptors: the retinoic acid receptor (RAR) family and the retinoid X receptor family. Each receptor family contains 3 receptor subtypes: α, β, and γ.
Tretinoin and tazarotene display different receptor selectivities. Whereas tretinoin activates the RARs α, β, and γ directly, and the retinoid X receptors α, β, and γ indirectly (through conversion of tretinoin to 9-cis-retinoic acid), tazarotenic acid, the metabolite of tazarotene, selectively binds to RARs β and γ. Tazarotene is unable to activate retinoid X receptors, either directly or indirectly. The predominant RAR in human skin epidermis is RAR γ. It is unknown whether the receptor selectivity of tazarotene has any particular clinical significance in the treatment of skin conditions such as photodamage.

As an RAR agonist, tazarotene could be effective in the treatment of photodamage. Preliminary data from a small pilot study in 10 subjects suggest that 0.1% tazarotene gel applied to photodamaged forearm skin for 12 small pilot study in 10 subjects suggest that 0.1% tazarotene gel applied to photodamaged forearm skin for 12

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subjects who achieved treatment success between the active treatment group and the vehicle group at week 24 was at least 15%. Treatment success was defined as at least a 50% improvement in response to treatment, ie, a moderate response or better (grades 0-3 on the 7-point scale for global response to treatment).

SKIN HISTOLOGIC FEATURES

At one investigational site (Department of Dermatology, Boston University, School of Medicine, Boston, Mass), punch biopsy specimens (2-3 mm) were taken from the lateral canthus (crow’s feet) area of the face from 31 subjects at baseline (week 0) and at the end of the treatment period (week 24). Subjects were instructed to avoid applying the study medication to the area that underwent biopsy until it had healed. The biopsy specimens were fixed in formaldehyde solution and routinely processed. Thin sections (3 μm) were cut from paraffin-embedded tissue and stained with hematoxylin-eosin (general cellular architecture), Fontana-Masson (melanin content), colloidal iron (mucin), or the Verhoeff–van Geison (elastic tissue) stain or with an immunostaining procedure designed to assess type I collagen. Slides containing biopsy specimens were coded to enable evaluation in a blinded fashion. Evaluations were performed in a blinded manner by one of us (J.B.). Computer-assisted image analysis was used to evaluate changes in epidermal thickness, melanin content, capillary dermal thickness, and the percentage of total dermis occupied by elastic tissue. The equipment included a light microscope (model BH2; Olympus America Inc, Melville, NY) and a videotape camera (Dage CCTV; Dage MPI, Inc, Michigan City, Ind). The videotaped images were displayed on a monitor (Trinitron; Sony Co, Tokyo, Japan), and the converted analog images were processed by a computer using specialized software (Sub & Micro Instruments, Atlanta, Ga).

OPTICAL PROFILOMETRY

Skin surface replicas of the periorbital region (crow’s feet) of 53 subjects (8 or 9 subjects per treatment group) were obtained at the beginning and at the end of the treatment period at the Skin Study Center, Broomall, Pa. Skin surface replicas were obtained with silicone surface replica dental impression material (Silflo- Flexico-Developments Ltd, Potters Bar, England). Computer-assisted image analysis of surface topographic variables in these replicas was conducted at an independent laboratory (Skin Study Center) following methods described elsewhere. 11,12

PHARMACOKINETIC ANALYSES

Therapeutic drug monitoring of tazarotenic acid (the primary metabolite of tazarotene) was conducted at 2 centers (Clinical Research Specialists, Santa Monica, Calif, and University of Michigan Medical Center, Ann Arbor) at weeks 4 and 24. Participating subjects (n=93, 14-18 patients per treatment group) were instructed not to apply the study medication on those evenings before the collection of blood for therapeutic drug monitoring. After the first blood collection (for determination of trough concentrations), subjects applied study medication to their faces from a weighed tube. The tube was reweighed after application of the study medication. Participants were instructed not to wash or shower until after the second blood collection had been performed, 3 to 10 hours later. Application of the study medication was resumed the following evening. All plasma samples obtained from tazarotene-treated subjects were analyzed at an independent laboratory (Oneida Research Services, Inc, Whitesboro, NY) using validated liquid chromatographic–tandem mass spectrometric methods with a lower limit of quantitation of 0.005 ng/mL for tazarotenic acid. The parent compound, tazarotene, was not analyzed because a previous study 13 has shown that plasma concentrations of tazarotene following topical application of tazarotene gel or cream are typically below the limit of quantitation (<0.005 ng/mL).

SAFETY MEASURES

Throughout the study, subjects were monitored for signs and symptoms of adverse events. Each adverse event was rated according to severity and relationship to study medication. Pregnancy tests for women of childbearing potential were performed during the screening visit and at weeks 0, 2, 4, 8, 12, 16, 20, and 24.

STATISTICAL ANALYSES

An intent-to-treat population was used for all analyses. This intent-to-treat population comprised all randomized subjects, including those who discontinued treatment at any time during the treatment period. The proportion of patients who achieved at least a 1-grade improvement from baseline for each of the signs of photodamage was compared by using the Cochran-Mantel-Haenszel method with modified ridit scores and stratified by center. 14 When testing for differences among and between multiple treatment groups, the Fisher protected least significant difference was used (α=.05) level. For analysis of the OIA, scores were dichotomized into clinical improvement (at least a 1-grade improvement from baseline) and nonimprovement. Incidences of patients with clinical improvement were analyzed using the Cochran-Mantel-Haenszel test. Global responses to treatment were dichotomized into treatment success (moderate, marked, almost complete, and complete responses) or failure (slight or no response or condition worsened). Because no primary variable was selected, no adjustments for multiplicity were made.

weeks results in a statistically significant increase in epidermal thickness and a significant decrease in tactile skin roughness.

In the present study, the efficacy and safety of 4 concentrations of tazarotene cream (0.01%, 0.025%, 0.05%, and 0.1%) were evaluated and compared with the efficacy and safety of 0.05% tretinoin cream and with vehicle in the treatment of photodamage.

RESULTS

SUBJECTS

Of the 349 subjects enrolled in the study, 59 were randomly assigned to treatment with 0.01% tazarotene, 58 to 0.025% tazarotene, 58 to 0.05% tazarotene, 58 to 0.1% tazarotene, 58 to 0.05% tretinoin, and 58 to vehicle cream.
A total of 312 subjects (89.4%) completed the 24-week treatment period, and 310 (88.8%) completed the 2-week posttreatment period.

Of the 37 subjects who discontinued participation in the study, 18 discontinued for personal reasons, 11 discontinued because of adverse events, 3 discontinued because of concomitant therapy, 2 discontinued because of relocation, and 2 were lost to follow-up. Of the 2 subjects who did not complete the posttreatment period, one did so for personal reasons and one was lost to follow-up.

CLINICAL EVALUATIONS

Significant improvement was found for fine wrinkling, mottled hyperpigmentation, the OIA of photodamage, and global response to treatment. For fine wrinkling, the proportion of subjects who achieved improvement from baseline of at least 1 grade was significantly higher with 0.01%, 0.05%, and 0.1% tazarotene creams and with 0.05% tretinoin cream than with vehicle at the end of treatment (week 24) (P<.002) (Figure 1). This significant difference over vehicle treatment was observed in all active retinoid groups (except 0.025% tazarotene cream) from week 12 (except for 0.05% tazarotene cream at week 16). At the posttreatment evaluations (week 26), all tazarotene formulations and tretinoin were associated with significantly higher rates of subjects having at least a 1-grade improvement from baseline vs vehicle cream (P≤.02). The differences among the various active study medications (those containing retinoids) were only sporadically significant (data not shown).

For mottled hyperpigmentation only, 0.1% tazarotene cream and 0.05% tretinoin cream vs vehicle yielded significantly higher rates of subjects who achieved improvement of 1 or more grades from baseline to the end of the study period (week 24) (P=.007) (Figure 3). The 0.1% tazarotene cream continued to yield higher improvement rates than vehicle through week 26 (P≤.002). The 0.05% tretinoin cream yielded higher improvement rates than vehicle from week 12 through week 26 (P=.007). At the end of the study period (week 24), all tazarotene formulations and tretinoin yielded significantly higher improvement rates than vehicle (P≤.03). This effect lasted through the posttreatment period (week 26) (P≤.03). After 24 weeks of treatment, the proportion of subjects who achieved at least a 1-grade improvement from baseline was 29 (50%) in the 0.1% tazarotene–treated group, 24 (41%) in the 0.05% tazarotene–treated group, 21 (36%)
in the 0.025% tazarotene–treated group, 24 (41%) in the 0.01% tazarotene–treated group, 29 (50%) in the tretinoin–treated group, and 11 (19%) in the vehicle–treated group.

Global response to treatment, a variable that compared the severity of the condition after treatment with the severity of the condition before treatment, was deemed successful if treatment resulted in at least 50% improvement (ie, treatment success). Starting as early as week 8 and lasting through the posttreatment period, treatment success rates in the 0.1% and 0.05% tazarotene–treated groups were significantly higher than in the vehicle–treated group (P = .02) (Figure 4). The 0.1% tazarotene cream–treated group demonstrated significantly higher success rates than the 0.05% tretinoin cream–treated group at weeks 12 and 20 (P = .02). The 0.05% tazarotene cream– and the 0.05% tretinoin cream–treated groups showed a similar global response to treatment, except at week 8, where the 0.05% tazarotene–treated group, but not the 0.05% tretinoin–treated group, had significantly higher treatment success rates than the vehicle–treated group (P = .02). Treatment success rates in the 0.01% tazarotene–treated group were significantly higher than in the vehicle–treated group at week 12 and from week 20 through week 26 (P < .03). The 0.05% tretinoin cream yielded significantly higher success rates than vehicle from week 12 through week 26 (P = .02). At the end of the study (week 24), 39 (67%) of the patients in the 0.1% tazarotene–treated group achieved treatment success, as did 30 (52%) in the 0.05% tazarotene–treated group, 21 (36%) in the 0.025% tazarotene–treated group, 24 (41%) in the 0.01% tazarotene–treated group, and 32 (55%) in the 0.05% tretinoin–treated group. Only 13 (23%) of the subjects in the vehicle–treated group achieved treatment success by week 24. Thus, the criterion of effectiveness, which stated that a 15–percentage point or greater difference between an active treatment group and a vehicle–treated group in the incidence of treatment success at week 24 would be considered clinically significant, was met by all treatment groups, except the 0.025% tazarotene cream–treated group.

Significant differences among the 6 treatment groups could also be shown at various time points for the following efficacy variables: lentigines, elastosis, and, to a lesser degree, irregular depigmentation (data not shown). No statistically significant differences among the 6 treatment groups could be shown for the following efficacy variables: coarse wrinkling, tactile roughness, pore size, and telangiectasia. The severity of actinic keratoses was decreased in all treatment groups. Of the subjects who had actinic keratoses at the beginning of the study, 73% to 82% (6 of 8 subjects in the 0.1% tazarotene–treated group, 8 of 10 subjects in the 0.05% tazarotene–treated group, 9 of 12 subjects in the 0.025% tazarotene–treated group, 9 of 12 subjects in the 0.01% tazarotene–treated group, and 9 of 11 subjects in the tretinoin–treated group) improved by more than 1 grade, vs 60% (3 of 5 subjects) in the vehicle–treated group (difference not statistically significant [P = .41 at week 24]).

**BIOPSY SPECIMEN EVALUATIONS**

Baseline and posttreatment facial biopsy specimens were obtained in 31 subjects: 4 treated with 0.1% tazarotene, 16 with lower concentrations of tazarotene, 7 with tretinoin, and 4 with vehicle cream. Examination of the baseline specimens by light microscopy revealed minimal cellular atypia in most of the subjects, which was consistent with the moderate degree of photodamage exhibited by the subjects. Keratinocytic atypia was absent, and minimal melanocytic atypia was present in only 3 (10%) of the 31 specimens. The usual basket-weave pattern of the stratum corneum was seen in 18 (58%) of the baseline samples, and a mixed pattern of compaction and basket weave was seen in 5 (16%) of the specimens. Dermal solar elastosis was present in all specimens, and a lymphocytic perivascular infiltrate in the dermis was observed in 4 (13%) of all specimens.

After 24 weeks, all active treatments with topical retinoids increased the epidermal thickness. These increases in epidermal thickness were statistically significant compared with baseline (P < .001) but not with vehicle (Table). All topical retinoids significantly reduced the melanin content during the study (P ≤ .04). Topical retinoid treatment also appeared to result in more compact morphologic features of the stratum corneum, especially treatment with 0.1% tazarotene cream, but the changes were not statistically significant. Furthermore, all topical retinoid treatment resulted in an increase in the number of granular cell layers. No statistically significant changes were noted in cellular atypia, epidermal mucin level, dermal elastosis, perivascular inflammation, or type I collagen immunostaining.

**OPTICAL PROFILOMETRY**

Optical profilometric analysis of skin surface replicas revealed a modest decrease from baseline in surface roughness in all treatment groups. No statistically significant differences between the treatment groups were detected.
PHARMACOKINETIC ANALYSES

Therapeutic drug monitoring was conducted at 2 centers during weeks 4 and 24. Blood samples were collected from subjects before application of the study medication and 3 to 10 hours after application, to determine plasma concentrations of tazarotenic acid (the active metabolite of tazarotene). Results showed that the mean plasma tazarotenic acid concentrations generally increased with increasing strength of tazarotene cream. At week 24, plasma tazarotenic acid concentrations after application of the creams were 0.02±0.01 ng/mL in the 14 subjects who had used 0.01% tazarotene cream, 0.02±0.02 ng/mL in the 12 subjects who had used 0.025% tazarotene cream, 0.09±0.05 ng/mL in the 13 subjects who had used 0.05% tazarotene cream, and 0.10±0.09 ng/mL in the 13 subjects who had used 0.1% tazarotene cream (data are given as mean±SD). The highest individual plasma concentration detected was 0.34 ng/mL (in a subject who used 0.1% tazarotene cream). Comparison of posidose concentrations during weeks 4 and 24 showed that the tazarotenic acid concentrations were not significantly different, indicating that drug accumulation did not occur.

ADVERSE EVENTS

Adverse events were reported by most patients (249 [71.3%] of the 349 patients). Most of the reported adverse events were determined to be treatment related (206 [59.0%] of 349). Although there was a relatively high incidence of treatment-related adverse events in subjects treated with the higher concentrations of tazarotene, the adverse events were generally mild to moderate. The most frequent adverse events were signs and symptoms of local skin irritation, such as mild to moderate desquamation, burning sensation, erythema, pruritus, and dry skin. Such skin-associated adverse events are typical of topical retinoid therapy.\(^{15}\) Treatment-related adverse events rated by the investigator as “severe” were reported by less than 2 (3%) of the subjects in the 0.1%, 0.05%, and 0.01% tazarotene–treated groups and by 3 (5%) of the subjects in the 0.05% tretinoin–treated group. In each treatment group, 3 (5%) of the subjects or less discontinued participation in the study due to adverse events.

SUBJECT SELF-ASSESSMENT AND EVALUATION OF COSMETIC CHARACTERISTICS

Subjects were asked to evaluate their overall response to treatment compared with their condition at baseline at all follow-up visits, using a 5-point scale. Significant differences among the treatments were noted from week 4 through week 26; 0.1% tazarotene cream and 0.05% tretinoin cream were favored over vehicle (except for 0.05% tretinoin at week 20) (data not shown).

At the end of the study (week 24), subjects were asked to rate the cosmetic characteristics of the study medication they had been using. Significant differences in ratings were found for the “appearance of skin (immediately) before application,” for which 0.1% and 0.05% tazarotene received significantly higher ratings than 0.05% tretinoin (P<.02), and for the “ability to blend into skin,” for which 0.1% tazarotene was favored over 0.05% tretinoin (P=.03). When comparing the study medication with previously used photodamage therapies, subjects gave significantly higher ratings to the 0.1% and 0.05% tazarotene and the 0.05% tretinoin creams than to vehicle (P<.04) (data not shown).

In this double-blind investigator-masked comparison study, tazarotene was shown to be effective in the amelioration of the signs of photodamage. Significant im-
provement compared with vehicle was seen for mottled hyperpigmentation as early as week 8 and for fine wrinkling as early as week 12 of this 24-week study. Overall, 0.1% tazarotene cream had the best efficacy, but at certain points, efficacy for several of the variables could also be shown for the lower concentrations of tazarotene. As early as week 8, 0.1% tazarotene cream also produced significantly higher rates of clinical improvement in the OIA of photodamage. Similarly, treatment success rates, defined as a global response to treatment of at least 50% improvement compared with baseline, were significantly higher in the group of subjects treated with 0.1% tazarotene cream than in the vehicle-treated group, from week 8 throughout the rest of the study.

Topical tazarotene also induced favorable histologic changes in photodamaged skin, similar to those described in an earlier pilot study and those described for tretinoin. These changes were significant when compared with baseline and included increases in epidermal thickness and decreases in melanin content. No increases in cellular atypia in either keratinocytes or melanocytes were observed with topical retinoid treatment.

Optical profilometry, a method often proposed for the objective quantitative evaluation of facial wrinkles, did not reveal any statistically significant differences among the various treatments used in this study. The sample size (8 or 9 subjects per treatment group) may have been too small. In an earlier 12-week study of the safety and efficacy of 0.1% tazarotene gel on photodamaged forearm skin, statistically significant smoothing of the skin surface, when compared with baseline, was detected using this method. Optical profilometry results also have been found to be consistent with clinical evaluations in reports of the efficacy of 0.05% tretinoin emollient cream in the treatment of photodamaged facial skin.

Systemic exposure to tazarotenic acid, the active metabolite of tazarotene, following once-daily topical application of tazarotene-containing creams for the treatment of facial photodamage, appears to be limited. Results of therapeutic drug monitoring during this study showed that mean plasma concentrations of tazarotenic acid stayed low, although they increased with increasing strength of tazarotene cream, from 0.02 ng/mL in subjects using the 0.01% cream to 0.10 ng/mL in subjects using the 0.1% cream. Such plasma concentrations are considerably lower than the endogenous plasma concentrations of tretinoin and its metabolites isotretinoin and o xoisotretinoin, which have been reported to range from 1 to 4 ng/mL.

Although there was a relatively high incidence of treatment-related adverse events in the subjects treated with the higher concentrations of tazarotene, these adverse events were generally mild to moderate. Most frequent were signs and symptoms of local irritation, and these were readily tolerated. In each tazarotene treatment group, fewer than 3% (5%) of the subjects discontinued their participation in the study because of adverse events.

Topical tazarotene improved photoaged skin like already established topical tretinoin. For fine wrinkling and mottled hyperpigmentation, 0.1% tazarotene cream and 0.05% tretinoin cream achieved a similar degree of improvement throughout the study. Although almost identical OIA improvement rates were seen with 0.1% tazarotene cream and 0.05% tretinoin cream at the end of the treatment period (week 24), a trend toward quicker response was noted with 0.1% tazarotene. The 0.1% tazarotene cream produced significantly higher treatment success rates than the 0.05% tretinoin cream at weeks 12 and 20. Between the 0.05% formulations, tazarotene and tretinoin were comparable in treatment success rates, although in OIA, tretinoin tended to provide higher improvement rates.

The results of this study indicate that the synthetic retinoid tazarotene is safe and is associated with positive changes in the treatment of photodamaged facial skin. Tazarotene cream reduces the severity of fine wrinkles and mottled hyperpigmentation and ameliorates the overall condition of photodamaged skin when compared with treatment with inactive vehicle cream. Overall, 0.1% tazarotene cream had the best efficacy of the 4 tazarotene concentrations evaluated. For local irritation, tazarotene was reasonably well tolerated, although somewhat more irritating at higher concentrations.

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Richard B. Stoughton Memorial Travel Fellowship applications are invited from US dermatology residents. The fellowship will enable a dermatologist in training to present a poster and attend the British Association of Dermatologists Annual Scientific Meeting in Edinburgh from July 9 to July 12, 2002. The winner will receive free registration and admittance to the president’s reception and annual dinner. Accommodation will also be offered free of charge.

The closing date for completed applications is Friday, February 8, 2002. For further details and application forms please contact the BAD Fellowship Co-ordinator, British Association of Dermatologists, 19 Fitzroy Square, London W1T 6EH, England. Phone: 44-20-7383-0266; Fax: 44-20-7388-5263 (e-mail: admin@bad.org.uk).