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Original Research

Tazarotene 0.1% cream versus tretinoin 0.05% emollient cream in the treatment of photodamaged facial skin: a multicenter, double-blind, randomized, parallel-group study

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OBJECTIVES: To compare the efficacy and tolerability of tazarotene 0.1% cream and tretinoin 0.05% emollient cream in the treatment of photodamaged facial skin.

METHODS: Subjects were eligible to enroll in this multicenter, double-blind, randomized, parallel-group study if they had at least mild levels of facial fine wrinkling and mottled hyperpigmentation, and at least moderate levels of one of these. Subjects were randomly assigned to apply either tazarotene cream or tretinoin emollient cream to their faces once each evening for 24 weeks.

RESULTS: A total of 173 subjects were enrolled, of whom 157 completed. All significant between-group differences in efficacy measures were in favor of tazarotene – for fine wrinkling at the study endpoint and, at earlier timepoints, for treatment success (≥50% global improvement), and the overall integrated assessment of photodamage, mottled hyperpigmentation, and coarse wrinkling. Both products were comparable in terms of cosmetic acceptability and tolerability except that tazarotene was associated with a transiently higher incidence of a burning sensation on the skin (in the first week of treatment but not thereafter).

CONCLUSIONS: Tazarotene 0.1% cream can offer superior efficacy over tretinoin 0.05% emollient cream in the treatment of facial photodamage, particularly with respect to the speed of improvement. *J Cosmet Laser Ther* 2004; **6**: 79–85

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Introduction

Exposure to ultraviolet light can prematurely age the skin by promoting the development of wrinkling, dyspigmentation, tactile roughness, elastosis, telangiectasia, and actinic keratoses. Furthermore, excessive exposure to ultraviolet

light increases the risk of skin cancer. Thus, for health as well as cosmetic reasons, it is important not only to minimize exposure to ultraviolet light (to minimize further damage to the skin) but also to attempt to reverse the damage already inflicted.

A wide variety of topical agents claim to mitigate certain signs of photodamage but only two –tazarotene cream (0.1%) and tretinoin emollient cream (0.05% and 0.02%) – have been approved for such use by the US Food and Drug Administration (FDA). Tazarotene 0.1% cream is approved as an adjunctive agent for the reduction of certain signs of facial photodamage (fine wrinkling, mottled hyper- and hypopigmentation, and benign lentigines). The efficacy of tazarotene in this regard is supported by the results of two multicenter, double-blind, randomized, vehicle-controlled trials.[1,2] Tretinoin 0.05% emollient cream is approved as an adjunctive agent for the mitigation of fine wrinkles, mottled hyperpigmentation, and the tactile roughness of facial skin in subjects who do not achieve such palliation using comprehensive skin care and sun-avoidance programs alone. Tretinoin 0.02% emollient cream is only approved as an adjunctive agent for the mitigation of fine wrinkles (and not for mottled hyperpigmentation or tactile roughness). The efficacy of these tretinoin emollient cream formulations is supported by the results of multicenter, double-blind, randomized, vehicle-controlled trials.[3,4]

Tazarotene 0.1% cream was approved for the mitigation of certain signs of facial photodamage relatively recently (late 2002), although it was previously approved for plaque psoriasis (in 2000) and acne vulgaris (in 2001). Before all of these, a gel formulation of tazarotene was approved for plaque psoriasis and acne vulgaris in 1997. Because of its recent arrival into the marketplace, there are few data comparing the efficacy and tolerability of tazarotene cream with those of tretinoin emollient creams. The single published report to date is of a dose–response study with tazarotene 0.1% cream in which tretinoin 0.05% emollient cream was also included as a comparator.[1] In order to confirm the findings of that study, a multicenter, double-blind, randomized, parallel-group study has now been performed with larger treatment groups.

Subjects and methods

Subjects

Adult subjects with skin types I–IV were eligible for the study if they had at least mild levels of facial fine wrinkling and mottled hyperpigmentation – and at least moderate levels of one of these. Both parameters were assessed using a five-point scale of: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, or 4 = severe.

Subjects were excluded if they: had undergone a cosmetic or therapeutic procedure on the face in the previous 4 months; were planning such a procedure during the study; required or desired prolonged exposure to ultraviolet light during the study; had a history of basal or squamous cell carcinoma on the face in the previous 3 months; were pregnant, nursing, or planning a pregnancy during the study; or were unable or unwilling to use reliable forms of contraception during the study.

The following washout periods were required: 7 days for oral vitamin A supplements (>5000 IU/day) or vitamin E supplements (>400 IU/day); 14 days for topical products containing salicylic acid, alpha- or beta-hydroxy acids, or vitamins A, C, or E; 30 days for topical retinoids, antibiotics, and investigational drugs; and 180 days for oral retinoids.

The study was approved by the relevant Institutional Review Boards serving the various study sites, and written informed consent was obtained from all subjects.

Treatment regimen

Subjects were randomly assigned to receive either tazarotene 0.1% cream or tretinoin 0.05% emollient cream once daily in the evening for 24 weeks. Subjects were instructed to ensure their face was dry and free of make-up before applying a pea-sized amount of the study medication to lightly cover their face. They were requested to allow sufficient time for drying of the medication before going to bed.

Subjects were also instructed to apply a sunscreen with a sun protective factor $\geqslant 15$ at least every morning, to avoid excessive exposure to the sun, and to wear protective clothing (e.g. a hat or visor) in the sun. The use of moisturizers was permitted providing the skin was allowed to dry between the application of the moisturizer and the study medication.

Outcome measures

The primary efficacy variable was the incidence of subjects achieving $\geqslant 50\%$ global improvement (referred to as treatment success). The global response to treatment was assessed at every post-baseline visit (weeks 2, 4, 8, 12, 16, 20, and 24) using the following seven-point scale: 0 = complete response, 1 = almost complete response (~90% improvement), 2 = marked response (~75% improvement), 3 = moderate response (~50% improvement), 4 = slight response (~25% improvement), 5 = no response, and 6 = worsening.

Facial skin was also evaluated at each visit in terms of fine wrinkling, mottled hyperpigmentation, coarse wrinkling, irregular depigmentation, lentigines, elastosis, tactile roughness, telangiectasia, and actinic keratoses (all evaluated using a five-point scale of: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe). In addition, the appearance of pore size was evaluated using a different five-point scale (0 = barely visible, 1 = very small, 2 = small, 3 = medium, and 4 = large) and the overall integrated assessment of photodamage was assessed using a six-point scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe). Photonumeric guidelines were provided to assist with the evaluation of the overall integrated assessment of photodamage, fine wrinkling, and mottled hyperpigmentation.

Subjects were asked to complete a cosmetic acceptability

questionnaire at their last visit in which they rated their study medication in terms of its appearance before and after application, its feel before and after application, its ability to spread over the skin, its ability to blend into the skin, and its odor. Each of these parameters was rated as one of the following: highly favorable, favorable, neutral, unfavorable, or highly unfavorable. The subjects also recorded whether or not they would use the study medication if they chose to continue treating their photodamage after the study. Finally, the subjects rated their overall satisfaction with the study medication compared with treatments they had used for photodamage before the study (using a scale of much more satisfied, more satisfied, somewhat more satisfied, neutral satisfaction, somewhat more dissatisfied, or more dissatisfied).

Blinding methods and statistical analyses

The randomization code was computer-generated and both study medications were packaged in identical-looking masked tubes.

The data were analyzed on an intent-to-treat basis (i.e. including all subjects randomized to the study) and a *p*-value of $\leqslant 0.05$ was considered to be statistically significant. The baseline comparability of the treatment groups was evaluated using analysis of variance for continuous variables (e.g. age) and a chi-squared test for categorical variables. Between-group differences in the primary efficacy variable – the incidence of treatment success – were analyzed using Fisher's exact test. The sample size necessary for Fisher's exact test was calculated to be 184 (92 per treatment group), assuming an alpha of 0.05, a power of 0.8, and a 10% dropout rate. Between-group differences in the mean score for the overall integrated assessment of photodamage, and in the incidence of subjects achieving at least a 1-grade improvement in each of the other secondary efficacy variables, were analyzed using a chi-squared test. Between-group differences in the results from the cosmetic acceptability questionnaire and in the incidence of adverse events were compared using a chi-squared test or Fisher's exact test (two-sided probability) when, given the small cell sizes, the normal approximation to the binomial was not applicable.

Results

Subjects

A total of 173 subjects were enrolled (88 tazarotene, 85 tretinoin), of whom 157 (91%) completed the study. The study was performed at five investigational sites (both

	Tazarotene 0.1% cream ($n=88$)	Tretinoin 0.05% emollient cream ($n=85$)
Mean age (years)	55	55
Females	93%	93%
Race		
Caucasian	93%	94%
Hispanic	2%	2%
Black	0%	2%
Asian	2%	0%
Other	2%	1%
Fine wrinkling		
Minimal	0%	0%
Mild	19%	22%
Moderate	58%	55%
Severe	23%	22%
Mean score[a] ± SD	3.03 ± 0.65	3.00 ± 0.67
Mottled hyperpigmentation		
Minimal	2%	1%
Mild	30%	22%
Moderate	49%	62%
Severe	19%	14%
Mean score[a] ± SD	2.85 ± 0.75	2.89 ± 0.64
Coarse wrinkling (mean score[a] ± SD)	2.26 ± 1.12	2.28 ± 1.06
Irregular depigmentation (mean score[a] ± SD)	1.72 ± 0.98	1.67 ± 0.90
Lentigines (mean score[a] ± SD)	2.45 ± 0.91	2.56 ± 0.93
Appearance of pore size (mean score[b] ± SD)	2.58 ± 0.87	2.47 ± 0.87
Elastosis (mean score[a] ± SD)	2.48 ± 0.93	2.56 ± 0.89
Telangiectasia (mean score[a] ± SD)	2.05 ± 0.82	2.00 ± 0.77
Actinic keratoses (mean score[a] ± SD)	0.18 ± 0.58	0.11 ± 0.35
Overall integrated assessment (mean score[c] ± SD)	3.24 ± 0.68	3.24 ± 0.67

[a]0 = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = severe.
[b]0 = none; 1 = very small; 2 = small; 3 = medium; 4 = large.
[c]0 = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe.

Table 1
Subject characteristics at baseline.

private and institutional practice) – four in the USA and one in Canada – with enrollment generally occurring from the investigators' existing patients or from individuals who responded to an advertisement. The study was conducted between January 2002 and March 2003.

The subjects were predominantly female Caucasians, with a mean age of 55 years and moderate levels of fine wrinkling and mottled hyperpigmentation (Table 1). There were no significant between-group differences in the subjects' characteristics at baseline.

Nine subjects in the tazarotene group discontinued prematurely: three (3%) due to adverse events (facial irritation, acne, and eyebrow skin irritation), two (2%) were lost to follow-up, one (1%) due to protocol violation, one (1%) due to withdrawal of consent, and two (2%) for other reasons. Five subjects in the tretinoin emollient group discontinued prematurely: two (2%) due to adverse events (irritation/redness of face), two (2%) were lost to follow-up, and one (1%) due to withdrawal of consent. The exit status was missing for two subjects.

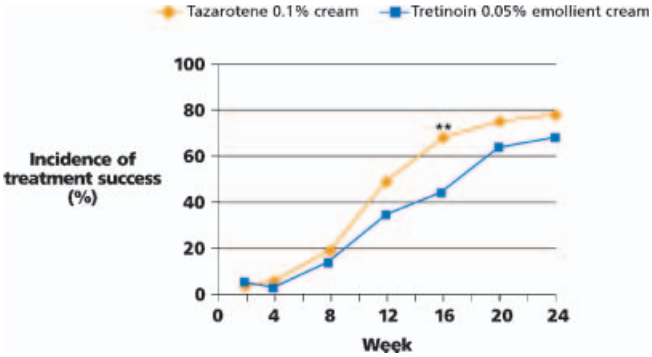


Figure 1
*Incidence of subjects achieving treatment success (⩾50% global improvement). **p⩽0.01 vs tretinoin emollient.*

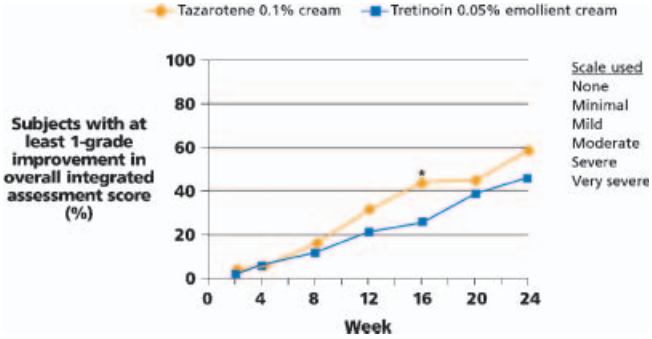


Figure 2
*Incidence of subjects achieving at least a 1-grade improvement in the score for the overall integrated assessment of photodamage. *p⩽0.05 vs tretinoin emollient.*

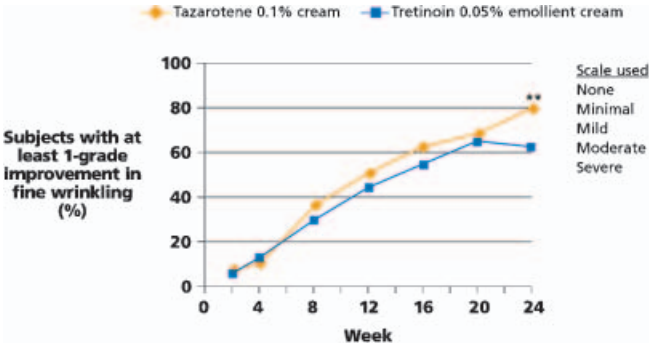


Figure 3
*Incidence of subjects achieving at least a 1-grade improvement in fine wrinkling. **p⩽0.01 vs tretinoin emollient.*

Efficacy

The incidence of treatment success (⩾50% global improvement) at the study endpoint was 78% in the tazarotene group and 67% in the tretinoin emollient group (Figure 1), with statistical significance in favor of tazarotene being achieved at week 16. All other significant between-group differences in efficacy measures were also in favor of tazarotene – for the overall integrated assessment of photodamage at week 16, fine wrinkling at week 24, mottled hyperpigmentation at weeks 12 and 16, and coarse wrinkling at week 4 (Figures 2–5). There were no significant between-group differences in the incidence of subjects achieving at least a 1-grade improvement in irregular

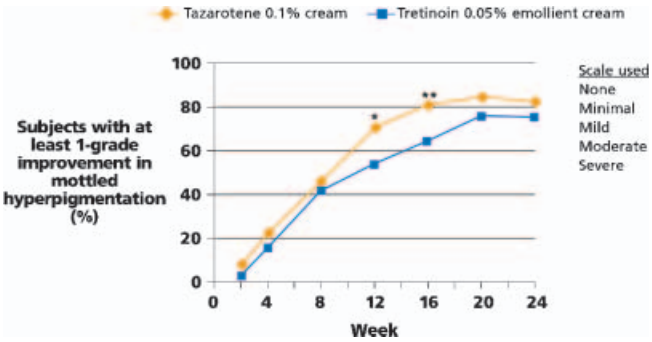


Figure 4
*Incidence of subjects achieving at least a 1-grade improvement in mottled hyperpigmentation. *p⩽0.05, **p⩽0.01 vs tretinoin emollient.*

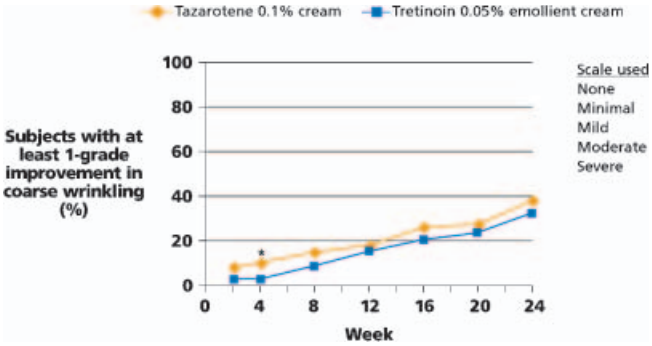


Figure 5
*Incidence of subjects achieving at least a 1-grade improvement in coarse wrinkling. *p⩽0.05 vs tretinoin emollient.*

depigmentation (Figure 6), lentigines (Figure 7), appearance of pore size (Figure 8), elastosis, tactile roughness, telangiectasia and actinic keratoses. Examples of improvements in mottled hyperpigmentation and fine wrinkling are shown in Figure 9.

Subject evaluations

There were no significant between-group differences in any of the evaluations on the cosmetic acceptability questionnaire. The incidence of subjects in the tazarotene and tretinoin emollient groups, respectively, who assigned a favorable or highly favorable rating to their study medication was: 73% versus 78% for appearance before application; 84% versus 74% for appearance after application; 78% versus 80% for feel before application; 80% versus 73% for feel after application; 88% versus 83% for ability to spread; 90% versus 81% for ability to blend into the skin; and 72% versus 80% for odor. A total of 77% versus 67% of subjects in the tazarotene and tretinoin emollient groups, respectively, were at least somewhat more satisfied with their study medication than with treatments they had used previously for photodamage. Finally, 81% versus 84% of subjects reported that they would use their study medication if they chose to continue treating their photodamage after the study.

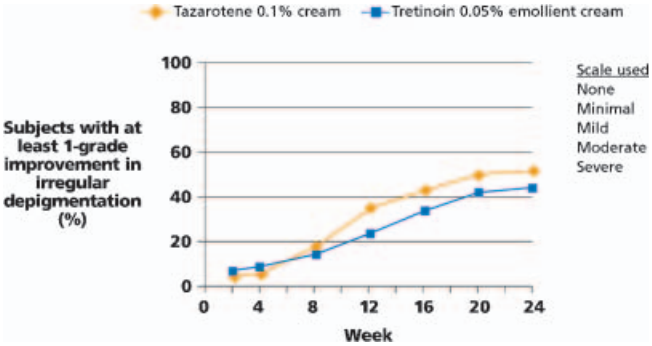


Figure 6
Incidence of subjects achieving at least a 1-grade improvement in irregular depigmentation.

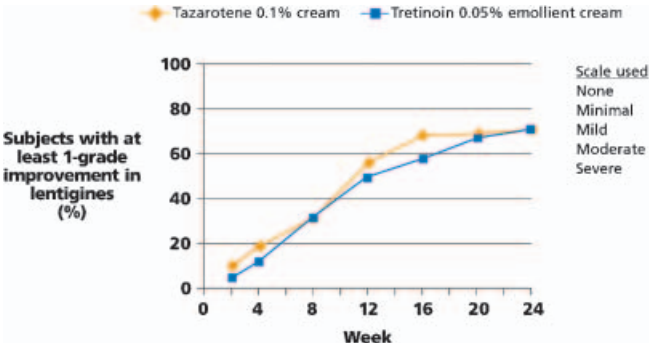


Figure 7
Incidence of subjects achieving at least a 1-grade improvement in lentigines.

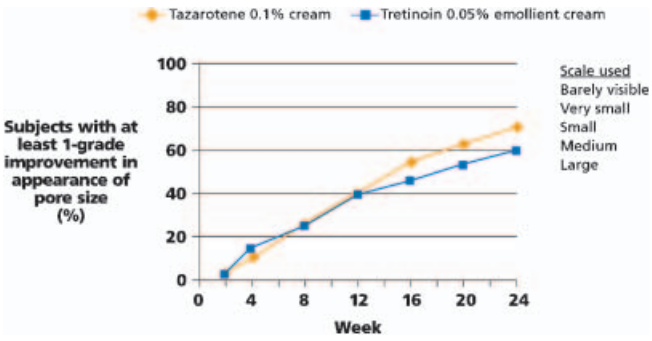


Figure 8
Incidence of subjects achieving at least a 1-grade improvement in appearance of pore size.

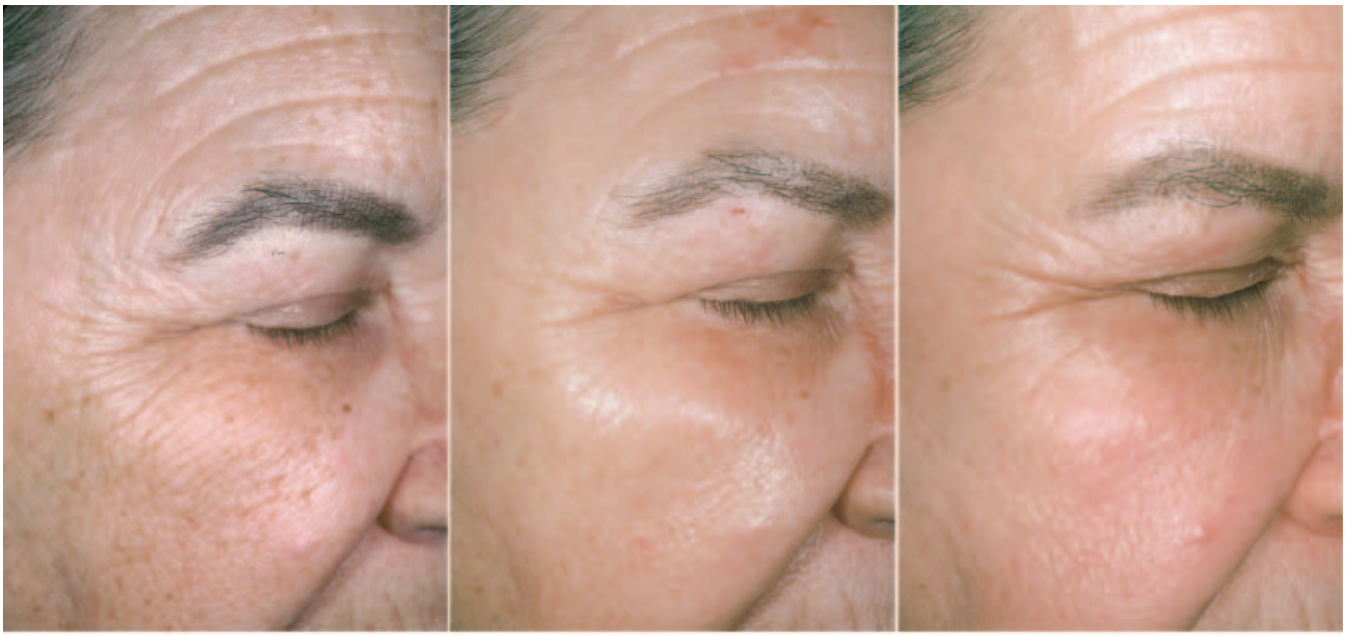
Tolerability

The most commonly reported treatment-related adverse events were irritation, retinoid dermatitis, dryness, peeling, redness, and a sensation of burning on the skin (Table 2), and all were of mild or moderate severity. The only treatment-related adverse event showing a significant between-group difference was for the sensation of burning on the skin, the incidence of this being significantly higher with tazarotene than with tretinoin emollient cream. However, the sensation of burning was significantly different between groups only in the first week of treatment and there was no between-group difference thereafter. The sensation of burning occurred predominantly in the first week of treatment (it was reported in eight tazarotene-treated subjects in the first week compared with one in each of the succeeding 3 weeks and one at the last visit) and was of 1 or 2 days' duration in the majority (8/12) of subjects.

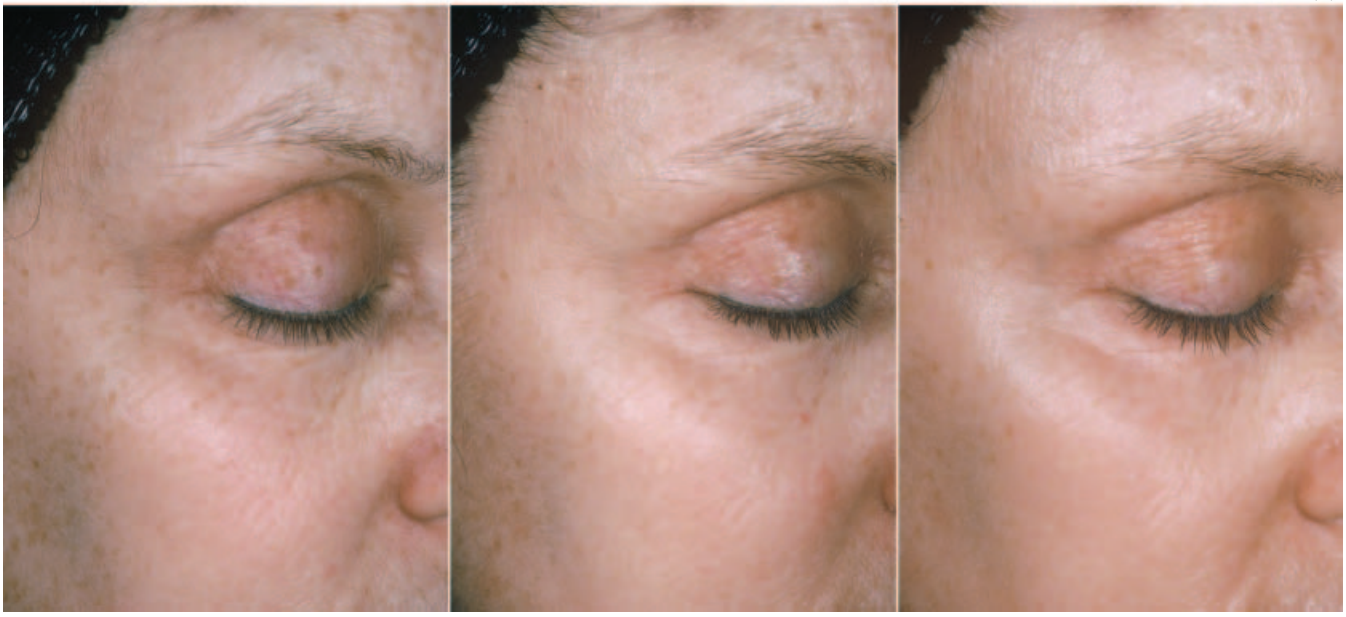
Discussion

The results from this study suggest that tazarotene 0.1% cream offers significant superiority over tretinoin 0.05% emollient cream in the treatment of photodamaged skin, particularly with respect to the speed of improvement. All significant between-group differences in efficacy were in favor of tazarotene – at the study endpoint this was the case for fine wrinkling and, at earlier timepoints, this was the case for the overall integrated assessment of photodamage, treatment success ($\geqslant$50% global improvement), mottled hyperpigmentation, and coarse wrinkling. These significant differences were achieved even though the study was not powered to detect significant between-group differences in any of the secondary efficacy parameters.

A similar comparison of tazarotene 0.1% cream and tretinoin 0.05% emollient cream has previously been reported as part of a dose-ranging study for tazarotene cream.[1] The efficacy and tolerability results of that study are in broad agreement with those reported here. They showed a statistical superiority in the incidence of treatment success for tazarotene cream over tretinoin emollient cream at weeks 12 and 20 (compared with at week 16 in the study reported here). At week 24, the



(A)



(B)

Figure 9

Improvement in signs of photodamage with once-daily topical retinoid cream. Note the improvements in dyspigmentation and fine wrinkling evident in the early weeks of treatment. (A) Courtesy of Emil Tanghetti, MD; (B) courtesy of Sewon Kang, MD.

incidence of treatment success in the dose-ranging study was 67% with tazarotene and 55% with tretinoin emollient cream, compared with 78% and 67%, respectively, in the study reported here. Thus, both studies showed an 11–12% higher incidence of treatment success with tazarotene cream than with tretinoin emollient cream. Although the global response measure used in both studies has been criticized as being dependent on the investigator's memory,[5] the overall integrated assessment compensates for this potential deficiency by providing a global evaluation of photodamage that is not memory-dependent. The inclusion of both measures in the current trial affords maximum opportunity to compare and contrast the results from the two studies.

The results from the studies showed slight differences in the significance of between-group differences for fine wrinkling, mottled hyperpigmentation, the overall integrated assessment of photodamage, and coarse wrinkling (significant differences occurring only in the present study and not in the previous study – perhaps because the group sizes were larger in the present study), as well as elastosis (a significant between-group difference occurring only in the previous study, at week 8, but not in this study).[6] Nevertheless, the results from the two studies were consistent for the other secondary efficacy variables, with neither study demonstrating any significant between-group differences in the incidence of subjects achieving at least a 1-grade improvement in tactile roughness, irregular

Adverse event	Tazarotene 0.1% cream ($n=88$)	Tretinoin 0.05% emollient cream ($n=85$)
Irritation	21%	35%
Retinoid dermatitis	16%	11%
Dryness	9%	15%
Peeling	12%	11%
Redness	10%	7%
Sensation of burning	15%[a]	0%
Erythema	3%	4%
Stinging	3%	6%
Dermatitis	4%	2%
Itching	1%	4%
Acne	5%	0%
Herpes	0%	4%
Scaling	3%	0%
Swelling	0%	2%

[a] $p \leqslant 0.001$ versus tretinoin emollient cream.

Table 2
Incidence of treatment-related adverse events.

depigmentation, lentigines, appearance of pore size, telangiectasia, or actinic keratoses during 24 weeks of treatment with tazarotene 0.1% cream or tretinoin 0.05% emollient cream.[1,6]

The tolerability data from the previously reported dose-ranging study were also in broad agreement with the results from the trial presented here – the most common treatment-related adverse events were signs or symptoms of local skin irritation and the majority of these were of mild or moderate severity (100% of such events were of mild or moderate severity in the trial presented here). In addition, the incidence of discontinuations due to adverse events was <5% in each treatment group (compared with ⩽3% in the study reported here).

In this trial, the only significant between-group difference in adverse events was for the sensation of burning and only in the first week of treatment. In everyday clinical practice, initiating tazarotene therapy with alternate-day treatment (which was not possible within the protocol of this clinical trial) will likely prevent or reduce any potential for this adverse event.

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