
A multicenter, randomized, double-blind trial of tazarotene 0.1% cream in the treatment of photodamage

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Background: Previous studies indicate that tazarotene is efficacious in reducing signs of photodamage.

Objective: We sought to confirm the efficacy and tolerability of tazarotene 0.1% cream in the treatment of facial photodamage.

Methods: A total of 568 patients with at least moderate fine wrinkling or mottled hyperpigmentation applied tazarotene 0.1% cream or vehicle cream to their face once daily for 24 weeks.

Results: Tazarotene cream was significantly more effective than vehicle in reducing fine wrinkles, mottled hyperpigmentation, lentigines, irregular depigmentation, apparent pore size, elastosis, tactile roughness, and an overall integrated assessment of photodamage. Significance was achieved as early as week 2 for some parameters and had not plateaued by week 24. The majority of patients reported improvements in their photodamage as early as week 4. Adverse events were predominantly mild or moderate signs or symptoms of skin irritation.

Conclusion: Once-daily tazarotene 0.1% cream is effective in ameliorating multiple signs of facial photodamage. (J Am Acad Dermatol 2005;52:268-74.)

Repeated exposure of the skin to UV light can result in both premature aging of the skin (eg, wrinkling, dyspigmentation, lentigines, and telangiectasia) and skin cancer. Therefore, for both medical and cosmetic reasons, it is important to prevent the development of photodamage as much

as possible by protecting the skin from UV light. In terms of treatment, many cosmeceuticals and other products claim to improve the appearance of photodamaged skin but objective evidence to support such claims is generally lacking. Two notable exceptions to this are the topical retinoids, tretinoin and tazarotene. Both tretinoin 0.05% emollient cream and tazarotene 0.1% cream have been demonstrated to ameliorate some of the signs of photodamage and both have been approved for this purpose by the Food and Drug Administration—tretinoin 0.05% emollient cream in 1995 and tazarotene 0.1% cream in 2002. Data from one of the pivotal phase III trials that led to this approval for tazarotene have been published recently¹ and data from the other pivotal trial are presented here.

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METHODS

Patients

Adult patients with facial fine wrinkling and mottled hyperpigmentation were eligible for enrollment in the study if one of these parameters was at

least moderate in severity and the other was at least mild (these parameters were assessed using photonumeric guidelines and graded as none, minimal, mild, moderate, or severe). Patients were also required to have skin type I, II, III, or IV.

Patients were excluded if they had a history of basal or squamous cell carcinoma on the face in the preceding 3 months, or if they had undergone a cosmetic procedure on the face in the preceding 4 months (or were planning to have such a procedure during the study). In addition, female patients who were pregnant, nursing, or planning a pregnancy during the study were excluded.

Patients were required to have adhered to the following medication washout periods before entering the study: 1 week for vitamin A supplements > 5000 IU or vitamin E supplements > 400 IU; 2 weeks for the topical use of products containing glycolic acid, alpha-hydroxy acid, salicylic acid, lactic acid, beta-hydroxy acid, or vitamins A, C, or E; 1 month for topical retinoids; and 6 months for systemic retinoids. Female patients of childbearing potential were also required to use a reliable method of contraception during the study.

The study protocol was approved by the appropriate institutional review boards and all clinical investigations were conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from all patients.

Treatments

In this multicenter, double-blind, randomized, vehicle-controlled, parallel-group study, patients were instructed to lightly cover their face with a pea-sized amount of either tazarotene 0.1% cream or vehicle cream once daily in the evening for up to 24 weeks. Patients were requested to ensure their face was clean (eg, free of makeup) and dry before applying the study medication. Washing of the face was not a prerequisite to the topical application. If washed, however, face had to be dry, but no time restriction was given (ie, waiting 30 minutes) before applying the study medicine. As an additional attempt to ensure treatment compliance, patients were queried at each study visit as to their medication usage.

During the study, patients were requested to: avoid excessive exposure to UV light; avoid exposure to extremes in weather (eg, wind or cold); wear protective clothing (eg, hat, visor) when in the sun; and apply a sunscreen with a sun protection factor of at least 15 at least every morning. Use of a facial moisturizer was permitted as long as it was not applied concurrently with the study medication.

Randomization and blinding procedures

Each patient qualifying for enrollment was assigned a unique identifying number used on all patient documentation. Numbers were assigned to the two treatment groups in ascending order in a 1:1 ratio following a randomization schedule generated by the sponsor using a block size of 4. The assignment of patient numbers was not necessarily continuous, but was always in blocks of 4. The code was kept at a site remote from the study sites and both study medications, with identical texture and color, were provided in identical-looking tubes.

Efficacy evaluations

Evaluations were conducted at the screening visit (day -21 to -1) and at weeks 0, 2, 4, 8, 12, 16, 20, and 24. The primary efficacy outcome measures were fine wrinkling and mottled hyperpigmentation (which were evaluated on a 5-point scale where 0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe). Clinical improvement was defined as at least a 1-grade improvement from baseline. Clinically significant improvement was defined as at least a 10% between-group difference in the incidence of patients with at least a 1-grade improvement from baseline in fine wrinkling or mottled hyperpigmentation. To help optimize the reliability and consistency of their ratings, investigators were provided with a set of photonumeric guidelines for fine wrinkling and another for mottled hyperpigmentation. These contained 3 large representative color photographs for each grade of fine wrinkling or mottled hyperpigmentation (except 0) and have been validated for reliability and consistency.²

Secondary efficacy outcome measures included lentigines, irregular depigmentation, elastosis, apparent pore size, tactile roughness, coarse wrinkling, telangiectasia, and an overall integrated assessment of photodamage. Lentigines, irregular depigmentation, elastosis, tactile roughness, coarse wrinkling, and telangiectasia were evaluated using the same scale as used for fine wrinkling and mottled hyperpigmentation. Apparent pore size was evaluated visually using a different 5-point scale (0 = barely visible, 1 = very small, 2 = small, 3 = medium, and 4 = large). The overall integrated assessment of photodamage was evaluated using a 6-point scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe) with the assistance of a photonumeric guideline that contained representative photographs of all grades except 0.³ For all the above-mentioned primary and secondary efficacy outcome measures, clinical improvement was defined as at least a 1-grade improvement from baseline.

Other secondary efficacy outcome measures were actinic keratosis count, global response to treatment, and patients' overall assessment of photodamage. The global response to treatment from baseline was assessed using a 7-point scale (0 = complete response [complete resolution of photodamage], 1 = almost complete response [approximately 90% improvement], 2 = marked response [approximately 75% improvement], 3 = moderate response [approximately 50% improvement], 4 = slight response [approximately 25% improvement], 5 = no response, and 6 = condition worsened). Treatment success was defined as at least a moderate response to treatment ($\geq 50\%$ improvement). Investigators used standardized photographs taken at the screening visit, and processed by a central photography laboratory, to assist them in evaluating the response to treatment at subsequent visits. Patients' overall assessment of photodamage was evaluated as much improved, somewhat improved, no change, somewhat worse, or much worse.

Tolerability evaluations

Patients were monitored for signs and symptoms of adverse events at every postbaseline visit.

Statistical evaluations

The intent-to-treat population (all patients who were randomized) was used for all demographic and efficacy analyses. The safety population (all patients who were randomized and treated) was used for all safety analyses.

The clinical hypothesis under evaluation was that tazarotene 0.1% cream is more effective than vehicle in reducing the severity of photodamaged facial skin, as measured by the incidence of patients with at least a 1-grade improvement from baseline in fine wrinkling, mottled hyperpigmentation, or both at week 24. Assuming a type I error rate of 0.025 (2-sided), it was calculated a priori that a sample size of 212 patients per group would provide an 80% power to detect a 15% between-group difference in the incidence of clinical improvement for fine wrinkling (expected incidence rate of 45%) and mottled hyperpigmentation (expected incidence rate of 70%).

The null hypothesis of no difference in clinical improvement rates between treatment groups was tested by the Cochran-Mantel-Haenszel test, stratified by investigator.⁴ All statistical analyses used 2-sided tests, with a *P* value of .05 or less considered statistically significant. To adjust for multiple comparisons because of the two primary efficacy analyses, the Hochberg procedure was used.⁵ This procedure rejects both null hypotheses if the two

P values are .05 or less simultaneously. Otherwise, if the smaller of the two *P* values is .025 or less, the procedure rejects the null hypothesis associated with the smaller *P* value. The Cochran-Mantel-Haenszel test was used for between-group comparisons of all investigator assessments of efficacy, and patients' overall self-assessment of photodamage. The Pearson chi-square test or the Fisher's exact test was used for between-group comparisons of adverse events. A Pearson's chi-square test was performed to evaluate the equality of proportions between treatment groups. If 25% or more of the cells had expected counts less than 5, then Fisher's exact test was used instead.

RESULTS

Patients

A total of 568 patients with photodamaged facial skin were enrolled from 15 investigational sites in the United States (see "Acknowledgments" for principal investigators and site locations). The sites included both private and institutional practice, and enrollment was generally performed by investigators from private patients or from patients who responded to advertisements. The study was started on September 29, 1999, and completed on September 21, 2000.

Of the 568 patients randomized to treatment with tazarotene cream or vehicle cream, all received their allocated treatment and 505 (89%) completed the study (Fig 1). Baseline demographics were comparable between the groups (Table I). The majority of patients were Caucasian (98%) and female (86%), with 91% of the patients at least 40 years old and 18% older than 65 years. At baseline, fine wrinkling and mottled hyperpigmentation were of at least moderate severity in the majority of patients—449 (79%) for fine wrinkling and 374 (66%) for mottled hyperpigmentation.

The randomization code was not broken prematurely for any patient. The most common protocol deviations were: enrollment outside the screening visit range (day -21 to -1) as a result of scheduling conflicts or delay in site receiving color transparency from central photography laboratory (40); patient number inadvertently assigned out of sequence (22); week 24 visit at least 3 weeks late (4); and removal of actinic keratosis during study, resulting in suspension of actinic keratosis count (4).

Efficacy evaluations

Compared with vehicle, tazarotene treatment was associated with a significantly higher percentage of patients achieving clinical improvement (ie, at least a 1-grade improvement) at week 24 in fine wrinkling (63% vs 24%, *P* < .001), mottled hyperpigmentation

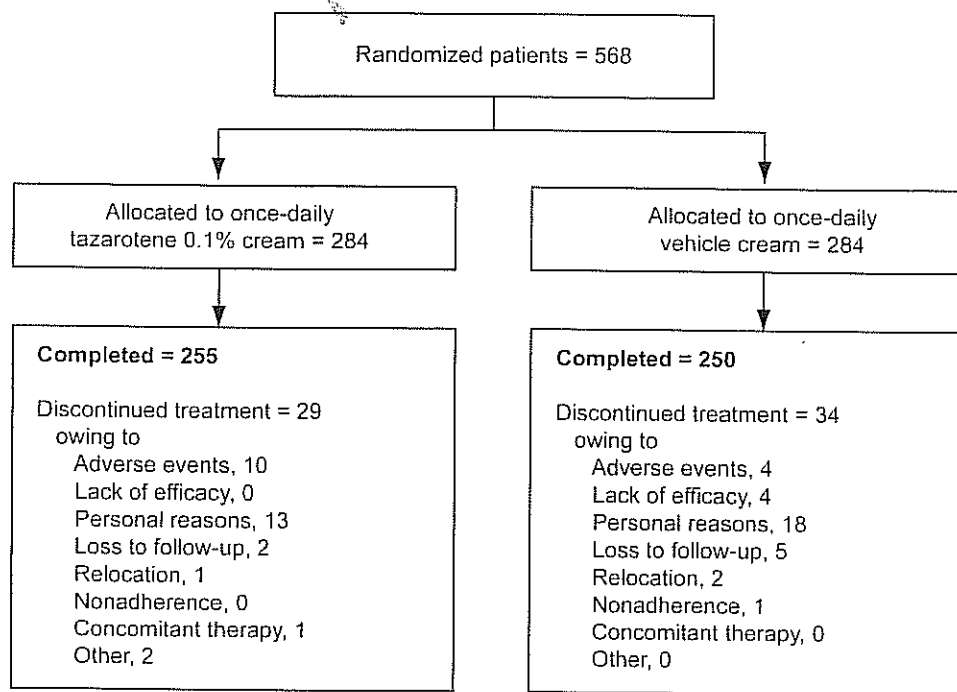


Fig 1. Participant flow through trial.

(87% vs 43%, $P < .001$), lentigines (59% vs 28%, $P < .001$), irregular depigmentation (24% vs 14%, $P = .001$), apparent pore size (42% vs 20%, $P < .001$), elastosis (30% vs 11%, $P < .001$), tactile roughness (47% vs 40%, $P = .032$), and the overall integrated assessment of photodamage (58% vs 18%, $P < .001$) (Fig 2). The superiority of tazarotene over vehicle was significantly different at: every study visit (including as early as week 2) for fine wrinkling, mottled hyperpigmentation, and lentigines; from week 8 onward for apparent pore size, elastosis, and the overall integrated assessment of photodamage; from week 16 onward for irregular depigmentation; and at weeks 16 and 24 for tactile roughness. At week 24, there were no significant between-group differences in coarse wrinkling (Fig 2, *H*) or in telangiectasia or actinic keratoses.

The percentage of patients achieving treatment success ($\geq 50\%$ global improvement) was significantly higher with tazarotene than vehicle from week 4 onward (Fig 3). The patients' overall assessments of their photodamage showed that 68% of patients treated with tazarotene considered their photodamage to be somewhat or much improved at week 4, increasing to 93% at week 24 (Fig 4). In comparison, for patients treated with vehicle, improvement in photodamage was reported by 31% of patients at week 4 and 49% at week 24. The distribution of patients' overall self-assessment of

photodamage scores in the tazarotene-treated group demonstrated significantly greater improvement from baseline compared with the vehicle-treated group from week 2 onward.

Tolerability

Adverse events considered to be possibly, probably, or definitely treatment-related were reported significantly more frequently in the tazarotene group than the vehicle group (206/284 [73%] vs 25/284 [9%]). The most common such events were desquamation (42% vs 2%), erythema (37% vs 3%), burning (21% vs <1%), dry skin (17% vs 2%), irritation (16% vs <1%), pruritus (9% vs 1%), irritant contact dermatitis (5% vs <1%), stinging (3% vs <1%), and rash (3% vs 0%). The vast majority of these were of mild or moderate severity and only 10 of 284 (4%) patients in the tazarotene group and 4 of 284 (1%) patients in the vehicle group discontinued as a result of adverse events.

DISCUSSION

The results from this study demonstrate that tazarotene 0.1% cream is significantly more effective than vehicle in reducing multiple signs of photodamage—fine wrinkling, mottled hyperpigmentation, lentigines, irregular depigmentation, apparent pore size, elastosis, and tactile roughness. Significant improvements in some of these parameters were

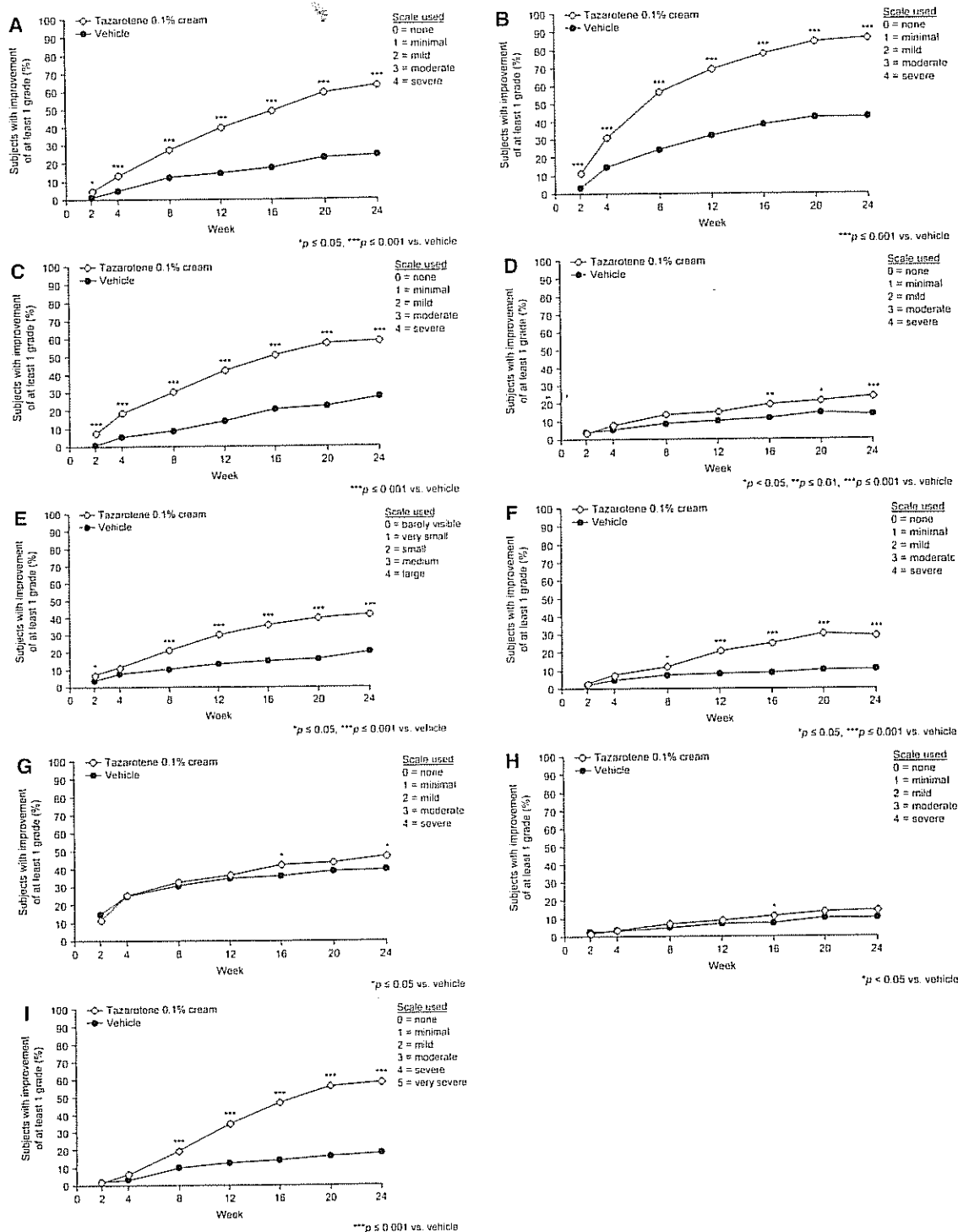


Fig 2. Percentage of patients who achieved clinical improvement in fine wrinkling (A), mottled hyperpigmentation (B), lentigines (C), irregular depigmentation (D), apparent pore size (E), elastosis (F), tactile roughness (G), coarse wrinkling (H), and overall integrated assessment of photodamage (I). Clinical improvement was defined as at least 1-grade improvement. All parameters except overall integrated assessment of photodamage and apparent pore size were assessed on following scale: 0 = none; 1 = minimal; 2 = mild; 3 = moderate; and 4 = severe. Overall integrated assessment of photodamage was assessed on following scale: 0 = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = severe; and 5 = very severe. Apparent pore size was assessed on following scale: 0 = barely visible; 1 = very small; 2 = small; 3 = medium; and 4 = large.)

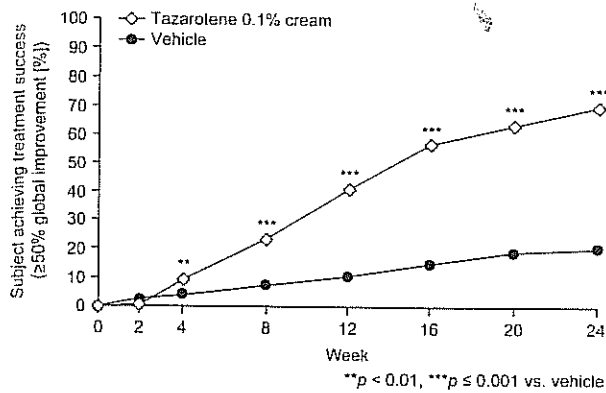


Fig 3. Percentage of patients who achieved treatment success ($\geq 50\%$ global improvement).

evident as early as week 2 and continued treatment resulted in progressively greater improvements that had not plateaued after 6 months of treatment (or 12 months of treatment in a previous trial).¹

These results are in agreement with those from a similar multicenter, double-blind, randomized trial.¹ Although the improvement in coarse wrinkling did not attain statistical significance in this study (but had done so in the other trial) the studies were powered only to detect differences in the primary efficacy outcome measures of fine wrinkling and mottled hyperpigmentation. The level of superiority of tazarotene over vehicle was similar between the two trials—the increased incidence of clinical improvement achieved with tazarotene at week 24 (over and above that achieved with vehicle) was: 39% in this trial vs 27% in the previous trial for fine wrinkling; 44% vs 44% for mottled hyperpigmentation, 31% vs 39% for lentigines, 10% vs 11% for irregular depigmentation, 22% vs 20% for apparent pore size, 19% vs 18% for elastosis, 8% vs 12% for tactile roughness, 4% vs 7% for coarse wrinkling, and 40% vs 26% for overall integrated assessment of photodamage.

Both trials also showed a noticeable placebo effect in the vehicle group. Depending on the parameter, this may be at least partly attributable to the emollient activity of the vehicle cream and/or the requirement for patients to minimize exposure to UV light and to use a sunscreen on a daily basis. Such measures are known to prevent the development of further photodamage and may promote the repair of existing photodamage.⁶

The efficacy of topical retinoids in reducing wrinkling may be attributable to a retinoid-induced increase in collagen synthesis.⁷ The apparent improvement in pore size with tazarotene may be related to this pharmacologic effect.¹ Alternatively, tazarotene may be reducing the appearance of pore size through its comedolytic effect.

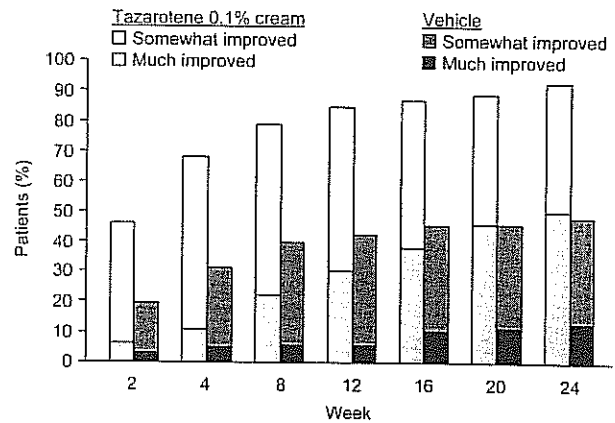


Fig 4. Percentage of patients reporting improvements in photodamage. (Patients reported their overall assessment of photodamage as much improved, somewhat improved, no change, somewhat worse, or much worse).

To our knowledge, tazarotene is the only medication for which investigator evaluations have shown a significant reduction in apparent pore size. Given the level of patient interest in reducing pore size, it is likely that improvements in this parameter make an important contribution to overall patient satisfaction.

The investigator's evaluation of global treatment response from baseline has been criticized in the past because of a misperception that this measure was reliant on the investigator's memory of a patient's pretreatment appearance.⁸ However, investigators were able to compare a patient's appearance at any study visit with photographs taken at the screening visit. The attempt to analyze quantitatively a measure such as global response to treatment has also been questioned. Although it is recognized that this measure of assessment is imperfect, it is included as supportive evidence only to assist clinicians' understanding of the degree of improvement possible and to aid comparisons with previously published data using the same scale.^{1,9}

As can occur with any topical retinoid, tazarotene treatment was associated with signs or symptoms of local skin irritation, which were generally mild or moderate in severity. Clinical experience has demonstrated that tolerability issues associated with topical retinoids are most likely to arise during the first few weeks of treatment during the time the skin is accommodating to the retinoid. In everyday clinical practice (ie, outside the restrictions of a trial protocol) such issues are minimized by initiating treatment with alternate-day applications (or twice weekly applications for patients with sensitive skin) for the first few weeks. Tolerability can also be optimized by applying the medication sparingly, avoiding astringents, washing with a nonsoap

Table I. Patient demographics at baseline

Variable	Treatment group		
	Tazarotene 0.1% cream (N = 284)	Vehicle cream (N = 284)	Total (N = 568)
Mean age \pm SD, y (range)	53.7 \pm 11.71 (29-88)	53.9 \pm 11.60 (27-85)	53.8 \pm 11.65 (27-88)
Sex, n (%)			
Male	35 (12%)	45 (16%)	80 (14%)
Female	249 (88%)	239 (84%)	488 (86%)
Skin type			
I	34 (12%)	26 (9%)	60 (11%)
II	72 (25%)	76 (27%)	148 (26%)
III	118 (42%)	117 (41%)	235 (41%)
IV	60 (21%)	65 (23%)	125 (22%)
Race, n (%)			
White	279 (98%)	276 (97%)	555 (98%)
Hispanic	5 (2%)	5 (2%)	10 (2%)
Asian	0 (0%)	2 (1%)	2 (<1%)
Other	0 (0%)	1 (<1%)	1 (<1%)

cleanser, using a moisturizer if the skin is dry, and waiting 20 to 30 minutes or more after washing before applying tazarotene.

CONCLUSIONS

Treatment with tazarotene 0.1% cream is significantly more effective than vehicle cream in achieving significant and clinically relevant reductions in fine wrinkling, mottled hyperpigmentation, lentigines, irregular depigmentation, apparent pore size, elastosis, tactile roughness, and an overall integrated assessment of photodamage. Investigator assessments demonstrated significant improvements in fine wrinkling, mottled hyperpigmentation, and lentigines after only 2 weeks (with continued treatment resulting in progressively greater improvements). The patients' self-assessments also indicated that improvements were noticeable early in the treatment period, with the majority of patients reporting their photodamage to be improved after only 4 weeks of treatment. Overall, once-daily tazarotene 0.1% cream is effective in ameliorating multiple signs of facial photodamage.

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