Tazarotene Cream for Postinflammatory Hyperpigmentation and Acne Vulgaris in Darker Skin: A Double-Blind, Randomized, Vehicle-Controlled Study

Pearl Grimes, MD; Valerie Callender, MD

Previous investigations have reported the efficacy of tazarotene 0.1% cream for the treatment of dyschromia associated with photoaging and for acne vulgaris. The present investigation assessed tazarotene 0.1% cream for the treatment of postinflammatory hyperpigmentation (PIH) in a double-blind, randomized, vehicle-controlled study of 74 patients from darker racial ethnic groups who had acne. Once-daily application of tazarotene cream was shown to be effective against PIH, achieving significantly greater reductions compared with vehicle in overall disease severity and in the intensity and area of hyperpigmentation within 18 weeks (P≤.05). Mean levels of erythema, burning, and peeling were no more than trace in both groups throughout the study, and mean levels of dryness were no more than mild in both groups. In our study, tazarotene cream was effective and well tolerated in the treatment of PIH in patients with darker skin.

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Postinflammatory hyperpigmentation (PIH) is common in people from darker racial ethnic groups (Fitzpatrick skin types IV–VI) and can arise as a result of either disease-induced inflammation (eg, acne) or injury-induced inflammation (eg, burn). PIH can persist for months or years, causing considerable disfigurement and distress in the meantime. The psychologic impact of PIH can be devastating, and many patients resort to extreme measures to try to eradicate it.

Many medications and therapies have been evaluated for the treatment of PIH, including azelaic acid,[1] hydroquinone,[2-3] dexamethasone,[2] salicylic acid,[4] glycolic acid peels,[5] and lasers.[6] However, these treatments often are either unsatisfactory or insufficient as monotherapy. A variety of treatments also are available for acne vulgaris, including topical retinoids, oral isotretinoin, antibiotics, benzoyl peroxide, and blue light. The ideal treatment for PIH in patients with acne would be a single agent that is effective against both PIH and acne. Although most of the aforementioned treatments are effective against only one of these conditions, topical retinoids are an important exception because they offer efficacy against both. In 1975, tretinoin was first reported to offer efficacy in reducing PIH, though only in combination with hydroquinone and dexamethasone.[2] Subsequent reports have used tretinoin as monotherapy[7] and in combination with hydroquinone and either lactic acid[8] or glycolic acid.[5] More recently, efficacy also has been suggested with adapalene monotherapy, though only in a trial without a placebo comparison group.[9]

Tazarotene previously has shown efficacy in reducing PIH associated with pseudofolliculitis barbae,[10] as well as in reducing hyperpigmentation associated with photodamage,[11,12] epidermal nevi,[13] and acanthosis nigricans.[14] Because tazarotene also is a well-established treatment for acne vulgaris[15,16] and has shown antiacne efficacy without the induction of PIH in patients from darker racial ethnic groups,[17] tazarotene is a logical choice to investigate for the treatment of PIH in darker-skinned patients

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Dr. Grimes is from the Vitiligo and Pigmentation Institute of Southern California, Los Angeles. Dr. Callender is from the Callender Skin and Laser Center, Mitchellville, Maryland.
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Reprints: Pearl Grimes, MD, Vitiligo and Pigmentation Institute of Southern California, 321 N Larchmont Blvd, Suite 609, Los Angeles, CA 90004 (e-mail: pegrimesmd@earthlink.net).

with acne. Thus, a double-blind, randomized, vehicle-controlled trial has been performed to evaluate the clinical potential of tazarotene in treating PIH in patients with acne and darker skin.

Methods

Patients—Patients were eligible for inclusion in the study if they had acne-induced PIH that was determined by the investigator to consist of noticeable pigmentary lesions of moderate intensity that covered 26% to 40% of the face and that were circumscribed or diffuse. Patients also were required to be at least 12 years of age, have a Fitzpatrick skin type of III to VI, and have mild to moderate facial acne vulgaris (10–60 facial inflammatory acne lesions; 10–100 facial comedones; and ≤2 facial nodulocystic lesions, neither of which were allowed to exceed a diameter of 5 mm).

Exclusion criteria included seborrheic dermatitis, PIH of solely dermal origin, acne vulgaris known to be resistant to oral antibiotics, and the use of estrogens or oral contraceptives for less than 12 weeks immediately prior to entering the study.

A 2-week washout period was required for topical antiacne medications, medicated cosmetics, and bleaching products. A 30-day washout period was required for oral corticosteroids, oral antibiotics, and oral contraceptives.

The study was approved by the relevant Institutional Review Boards. Written informed consent was obtained from all patients or from a parent or guardian of patients under the legal age of consent.

Treatment Regimen—Patients were randomized to receive either tazarotene 0.1% cream or vehicle cream once daily in the evening for up to 18 weeks.

Patients were instructed to wash their face twice daily with a nonmedicated, nonsoap cleanser and then to rinse their face thoroughly and dry it with a soft towel. They were requested to apply their study medication approximately 15 to 20 minutes after washing their face in the evening by placing a pea-sized amount in the palm of their hand and, using the tip of a finger, placing a dab on their chin, cheeks, and both sides of their forehead and gently spreading the medication to cover the entire face in

Table 1.

Grading Scale of Outcome Measures

Grade	Overall Disease Severity	Pigmentary Intensity of Hyperpigmented Lesions	Area of Hyperpigmented Lesions	Degree of Hypopigmentation	Erythema, Burning, Peeling, Dryness
0	Normal	None (normal)	None	None	None
1	Present, but < mild	Trace (mild and localized)	Trace (1%–10% of face)	Trace (slight and localized)	Trace
2	Mild (slightly noticeable)	Mild (mild and diffuse)	Mild (11%–25% of face)	Mild (slight and diffuse)	Mild
3	Between mild and moderate	Moderate (moderate and diffuse)	Moderate (26%–40% of face)	Moderate (noticeable and diffuse)	Moderate
4	Moderate (noticeable)	Marked (moderate and dense)	Marked (41%–50% of face)	Marked (noticeable and dense)	Marked
5	Between moderate and marked	Severe (prominent and dense)	Severe (>50% of face)	Severe (complete lack of melanin pigmentation)	Severe
6	Marked (distinctive)	—	—	—	—
7	Between marked and severe	—	—	—	—
8	Severe (very distinctive)	—	—	—	—

a thin film. A specified broad-spectrum UVA/UVB sunscreen with a sun protection factor of 30 was required to be applied to the face each morning.

Patients who experienced facial dryness were allowed to use a moisturizing cream (Cetaphil®) during the day, but the use of any other lotions, creams, medicated powders, or solutions on the face was prohibited. The use of nonmedicated cosmetics could be continued if their use did not alter during the course of the study and if they were not used on study visit days. The use of nonmedicated shampoos was allowed as often as needed.

Outcome Measures—The primary efficacy variable was the overall disease severity of PIH. Patients also were evaluated for the pigmentary intensity of hyperpigmented lesions, area of hyperpigmented lesions, and degree of hypopigmentation. In addition, the tolerability of the medication was evaluated for erythema, burning, peeling, and dryness. The grading scales for these parameters are detailed in Table 1.

Table 2.

Patient Demographics

	Tazarotene 0.1% Cream (n=36)	Vehicle Cream (n=38)
Mean age, y (range)	34 (14–61)	36 (12–84)
Females, n (%)	31 (86)	34 (92)*
Race, n (%)		
African American	33 (94)*	36 (95)
Hispanic	1 (3)*	0
Asian	0*	1 (3)
Other	1 (3)*	1 (3)
Skin type, n (%)		
Oily	6 (17)	7 (18)
Normal to oily	12 (33)	13 (34)
Normal	1 (3)	1 (3)
Normal to dry	0	2 (5)
Dry	9 (25)	10 (26)
Mixed oily/dry	8 (22)	5 (13)
Fitzpatrick skin type, n (%)		
Type I	0	0*
Type II	0	0*
Type III	1 (3)	0*
Type IV	6 (17)	8 (22)*
Type V	21 (58)	20 (54)*
Type VI	8 (22)	9 (24)*
Overall disease severity, mean score ± SD	4.3±1.53	4.2±1.27
Pigmentary intensity of hyperpigmented lesions, mean score ± SD	3.5±0.70	3.4±0.63
Area of hyperpigmented lesions, mean score ± SD	3.5±0.77	3.4±0.59
Degree of hypopigmentation, mean score ± SD	0.4±0.87	0.6±1.22

*Data not available for one patient.

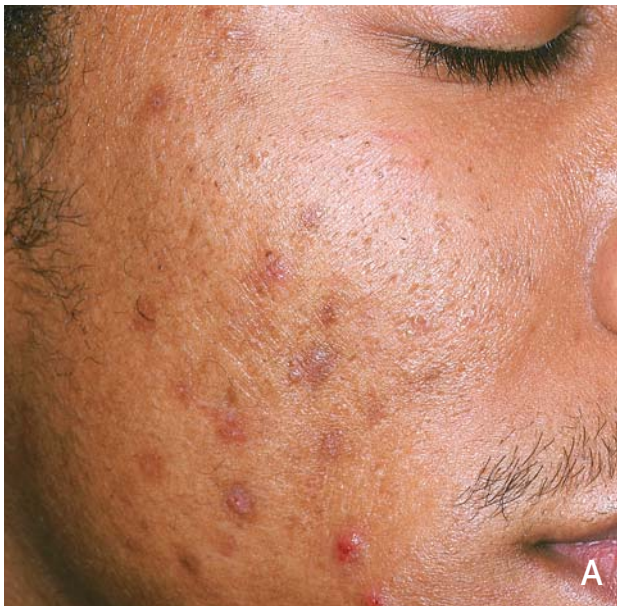
Statistical Analyses—The sample size necessary to detect a clinically significant between-group difference (ie, at least a 1-grade difference) in the overall disease severity of PIH was calculated to be 74 patients, with 58 evaluable for efficacy. These calculations assumed: 2-sided α=.05; a standard deviation of 1; 80% power; and 20% drop-out rate.

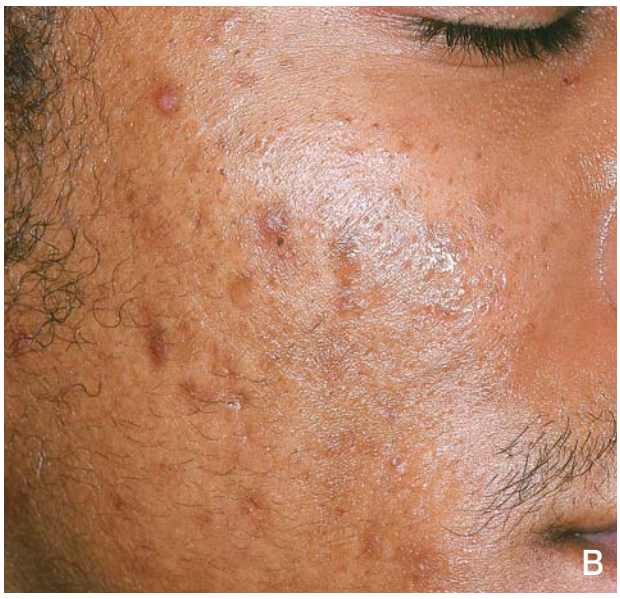
The data were analyzed on an intent-to-treat basis (ie, including all patients randomized to the study), with all statistical tests being 2-sided and $P \leq .05$ considered to be statistically significant. At baseline, between-group differences were evaluated using a χ^2 test for categorical variables and a *t* test for continuous variables. During the treatment period, between-group differences in the overall disease severity, pigmentary intensity of hyperpigmented lesions, area of hyperpigmented lesions, and degree of hypopigmentation were analyzed using change-from-baseline values and an analysis of variance test.

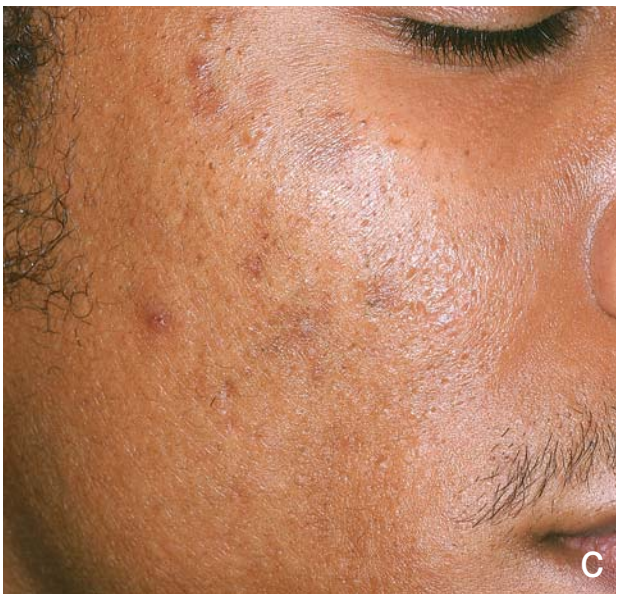
Results

Patients—A total of 74 patients were enrolled (36 tazarotene, 38 vehicle) in the study. Of these, 53 (72%) completed the study, 11 discontinued because of missed visits, 7 discontinued because of personal reasons, and 3 had a missing exit status. The patients were predominantly female (89%; 65/73), African American (95%; 69/73), and of Fitzpatrick skin type V (56%; 41/73)(Table 2). There were no significant between-group differences in demographics or disease severity measures at baseline.

Efficacy—Tazarotene treatment was effective in reducing PIH (Figure) and, at the study endpoint, was associated with significantly greater improvements compared with vehicle in all the efficacy outcome measures for PIH (overall disease severity, pigmentary intensity of hyperpigmented lesions, and area of hyperpigmented lesions)(Table 3). First, the overall disease severity score was reduced by a mean of 1.2 with tazarotene compared with 0.2 with vehicle (*P*=.010). The reduction in the tazarotene group was clinically significant (ie, it was more than a 1-grade reduction). Second, the pigmentary intensity of hyperpigmented lesions was reduced by a mean of 1.1 versus 0.5 grades (*P*=.044). Third, the







Patient with postinflammatory hyperpigmentation and acne shown at baseline (A) and after 6 weeks (B) and 18 weeks (C) of once-daily application of tazarotene 0.1% cream.

area of hyperpigmented lesions was reduced by a mean of 0.9 versus 0.4 grades (*P*=.026). There was no significant between-group difference in degree of hypopigmentation.

Tolerability—Throughout the study, the mean levels of erythema, burning, and peeling were no more than trace in both groups, and the mean levels of dryness were no more than mild in both groups.

Comment

The results of this study show that once-daily application of tazarotene 0.1% cream can be effective in reducing PIH in patients from darker racial ethnic groups. At week 18, tazarotene was significantly more effective than vehicle in lessening PIH overall (*P*=.010) and, more specifically, in reducing the intensity (*P*=.044) and area of hyperpigmented lesions (*P*=.026). The results of this study confirm and extend those from an earlier pilot study that showed tazarotene 0.05% gel could be used in patients from darker racial ethnic groups to treat acne vulgaris without inducing PIH.[17] The present report is the first to demonstrate that tazarotene also can be effective in treating PIH. The dual action of tazarotene in reducing both PIH and acne allows both conditions to be treated simultaneously using tazarotene monotherapy, which maximizes convenience and, likely, patient satisfaction.

In studies on photodamaged skin, tazarotene has been shown to be effective in the reduction of mottled hyperpigmentation and fine wrinkling, with significant (*P*<.05) improvements relative to vehicle noted more rapidly for mottled hyperpigmentation (week 12) than fine wrinkling (week 24).[11,12] Thus, the speed of improvement in PIH also is of interest. In the study reported here, tazarotene was first shown to achieve a significant advantage over vehicle at week 10 (*P*=.04). In the only report of

Table 3.

Mean Change in Grade of Outcome Measures

Parameter	Week	Mean Change in Grade From Baseline ± SD: Tazarotene 0.1% Cream	Mean Change in Grade From Baseline ± SD: Vehicle Cream	Between-Group *P* value
Overall disease severity	6	−0.2±0.97	+0.1±0.85	.175
	10	−0.8±1.05	−0.2±0.94	.040
	14	−1.3±1.46	−0.3±1.18	.014
	18	−1.2±1.26	−0.2±1.22	.010
Pigmentary intensity of hyperpigmented lesions	6	−0.6±0.86	−0.3±0.64	.164
	10	−1.1±1.09	−0.7±1.01	.172
	14	−1.3±1.16	−0.7±0.94	.063
	18	−1.1±1.14	−0.5±0.94	.044
Area of hyperpigmented lesions	6	−0.4±0.59	−0.2±0.37	.143
	10	−0.6±0.79	−0.3±0.70	.158
	14	−0.9±1.15	−0.6±0.77	.264
	18	−0.9±0.83	−0.4±0.64	.026
Degree of hypopigmentation	6	0.0±0.86	−0.2±0.77	.455
	10	−0.2±0.89	−0.5±1.06	.360
	14	−0.2±0.88	−0.4±0.99	.576
	18	−0.2±0.99	−0.4±0.97	.783

treating PIH with tretinoin monotherapy, a significant advantage of tretinoin over vehicle was first reported at week 12.[7] Thus, it is possible that tazarotene may act slightly more rapidly than tretinoin. Although the 2 trials differed slightly in the cause of the patients' PIH—uniformly attributable to acne in the tazarotene trial but attributable to acne, shaving irritation, eczema, ingrown facial hairs, or folliculitis in the tretinoin trial—this difference would not be expected to affect clinical efficacy or the speed of clinical improvement. Because the only trial discussing the efficacy of adapalene in the treatment of PIH was not vehicle controlled, it is not possible to compare the speed of action of adapalene with that of tazarotene or tretinoin.[9]

Although tazarotene cream has been shown to be an effective treatment for PIH, prevention of PIH is the ultimate goal. Because darker skin is prone to PIH, it is particularly important to ensure that patients with darker skin and inflammatory acne lesions receive adequate treatment for their acne from the outset. Topical retinoids such as tazarotene are the mainstay of acne therapy because they help resolve microcomedones (the precursor of all acne lesions, both inflammatory and noninflammatory); thus, the use of retinoids helps treat acne and prevent the development of new lesions, which helps prevent PIH. Other measures that may be helpful in preventing PIH include protecting the skin from the sun and eliminating exacerbating factors such as oil-containing cosmetic and hair products.

The proven effectiveness of tazarotene in reducing hyperpigmentation in a variety of skin conditions suggests that it also may be useful in the treatment of other pigmentary disorders, including melasma. Indeed, the authors have had good results in the clinic using tazarotene as maintenance therapy for melasma after initial hydroquinone treatment.

In our study, tazarotene 0.1% cream was effective and well tolerated in the treatment of PIH in patients from darker racial ethnic groups.

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