Randomized Comparison of Tazarotene 0.1% Cream and Adapalene 0.3% Gel in Patients With at Least Moderate Facial Acne Vulgaris and Postinflammatory Hyperpigmentation (PIH)

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INTRODUCTION

- One of the goals of acne treatment is to reduce the scarring and postinflammatory pigment changes that can persist for months and years beyond the initial acne lesion.[1-3]
- Topical retinoids are frequently used for the treatment of acne because they effectively reduce the number of noninflammatory and inflammatory acne lesions[4-7] and help reduce PIH that can occur with acne.[1-3]
- Darker-skinned individuals are at greater risk for acne sequelae such as keloidal scarring and PIH.[1]
- Tazarotene and adapalene are 2 commonly used topical retinoids that are considered to be effective and well tolerated[4] and also may be beneficial in the treatment and prevention of PIH.[1-3]
- The purpose of the clinical trial was to evaluate the efficacy and safety of tazarotene 0.1% cream compared with adapalene 0.3% gel in the treatment of at least moderate facial acne vulgaris. We report here the results of an important secondary endpoint, which compared the severity and distribution of PIH in patients with detectable PIH at baseline.

STUDY DESIGN AND METHODS

- This was an analysis of patients who presented with detectable PIH at baseline in a prospective, multicenter, randomized, investigator-blinded, parallel-group comparison of tazarotene 0.1% cream and adapalene 0.3% gel.
- Inclusion criteria:
  - Males and females, ≥ 12 years of age
  - 25 to 100 facial inflammatory lesions (papules and pustules)
  - ≥ 50 facial noninflammatory lesions (open/closed comedones)
  - ≤ 3 facial nodules and/or cysts with a diameter ≥ 1 cm
- Exclusion criteria:
  - Pregnant or planning pregnancy
  - Any condition that might interfere with acne evaluation
  - Cosmetic or surgical procedure complementary to the treatment of facial acne within 14 days of baseline visit
  - Starting estrogens or birth control pills within 90 days of baseline visit
  - Previous isotretinoin usage
- Treatment:
  - Patients were randomized (1:1) to tazarotene 0.1% cream or adapalene 0.3% gel.
  - The treatment kit included study medications, cleanser (Cetaphil® Gentle Skin Cleanser; Galderma Laboratories, L.P., Fort Worth, TX), hydrating moisturizer (MD Forte® Replenish Hydrating Cream; Allergan, Inc., Irvine, CA), and sunscreen (Neutrogena® Healthy Defense SPF 30 Daily Moisturizer; Neutrogena Corp., Los Angeles, CA).
  - Patients were instructed to wash face with provided cleanser and apply moisturizer morning and evening.
  - At night, patients were instructed to wait 20 minutes after applying moisturizer and then to apply a pea-sized amount of study medication to the entire face.
  - Sun exposure was to be avoided, but if it was unavoidable, patients were instructed to use provided sunscreen.
- PIH and tolerability outcome measures:
  - Investigator assessment of PIH severity (6-point scale; 0 = absent to 5 = severe)
  - Investigator assessment of PIH distribution (7-point scale; 0 = none, 1 = 1% to 10% of facial area, 2 = 11% to 20%, 3 = 21% to 30%, 4 = 31% to 40%, 5 = 41% to 50%, 6 = greater than 50%)
  - Overall PIH index reported as the product of distribution and severity scores (maximum score is 5 x 6 = 30)
  - Investigator assessment of erythema, dryness, peeling, and oiliness (5-point scale)
  - Patient assessment of pruritus and burning severity since previous visit (6-point scale)
- Evaluations were conducted at baseline and weeks 2, 4, 8, 12, and 16. Facial photography was performed at baseline and weeks 12 and 16.

RESULTS

There was a statistically significant between-group difference in the number of noninflammatory lesions at baseline. Further analysis determined that the difference in noninflammatory lesions was due to a greater number of patients with > 100 lesions in the tazarotene group (13/90 patients) than in the adapalene group (2/90 patients). Consequently, it was deemed statistically appropriate to exclude the data from patients with > 100 comedones at baseline from the analysis.

Patient Baseline Characteristics

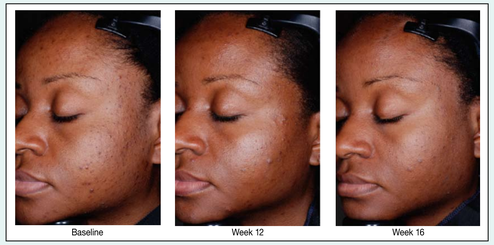
		Tazarotene 0.1% Cream n = 77	Adapalene 0.3% Gel n = 88	*P* value
Age (years)	Mean ± SD Minimum, maximum	20.9 ± 7.7 12.6, 45.7	20.8 ± 7.6 12.6, 51.4	.980
Sex [number of patients (%)]	Male Female	29 (37.7%) 48 (62.3%)	32 (36.4%) 56 (63.6%)	.863
Race [number of patients (%)]	White Black Hispanic Asian Other	28 (36.4%) 25 (32.5%) 14 (18.2%) 7 (9.1%) 3 (3.9%)	34 (38.6%) 24 (27.3%) 10 (11.4%) 15 (17.0%) 5 (5.7%)	.422
Baseline lesion counts (mean ± SD)	Noninflammatory[a] Median Mean ± SD Minimum, maximum Inflammatory[b] Median Mean ± SD Minimum, maximum	 58 62 ± 14 42, 100 28 31 ± 8 25, 66	 55 60 ± 13 41, 95 28 33 ± 11 25, 93	.164 .552
Patients with postinflammatory hyperpigmentation	Patients with detectable PIH PIH index[c] Mean ± SD Median (P25, P75)	50 (64.9%) 3.54 ± 3.41 2.00 (1.00, 4.00)	53 (60.2%) 3.83 ± 4.34 2.00 (1.00, 4.00)	.919

[a] Open and closed comedones.
[b] Papules, pustules, nodules/cysts.
[c] For patients with detectible PIH at baseline.

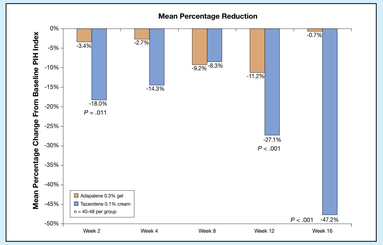
- The mean age was approximately 20 years, and approximately 62% of patients were female. The patient population was racially diverse, with 62% of patients being nonwhite. Approximately 61% of patients had clinically detectible PIH at baseline.
- The mean baseline PIH index (product of PIH distribution and severity scores) was 3.54 ± 3.41 in the tazarotene group and 3.83 ± 4.34 in the adapalene group (*P* = .919); the median PIH index was 2.00 (P25: 1.00; P75: 4.00) in both treatment groups.

Example of Patient With PIH Who Was Treated With Tazarotene 0.1% Cream

Patient 1: Age 29

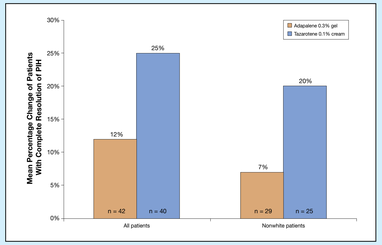


Reduction From Baseline in PIH Index Among Patients With Detectable PIH at Baseline



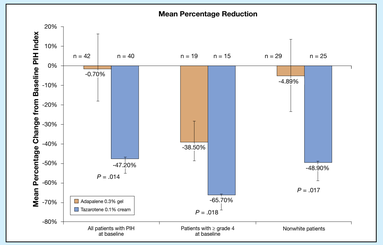
- The mean percentage decrease from baseline in the PIH index was statistically significant in the tazarotene group at weeks 2 (*P* = .011), 12 (*P* < .001), and 16 (*P* < .001); there was no statistically significant percentage decrease from baseline at any time in the adapalene group.

Mean Percentage of Patients With Complete Resolution of PIH at Week 16



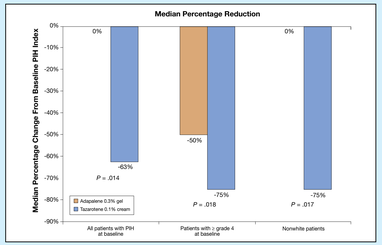
- At week 16, the percentage of patients with complete resolution of their PIH was 25% (10/40) in the tazarotene group and 12% (5/42) in the adapalene group.
- The percentage of nonwhite patients with complete resolution of their PIH at week 16 was 20% (5/25) in the tazarotene group and 7% (2/29) in the adapalene group.

Reduction From Baseline at Week 16 in PIH Index Among Patients With Detectable PIH at Baseline



Error bars represent the standard errors of the means.

- **Mean** percentage reduction from the baseline PIH index was significantly greater in the tazarotene group than in the adapalene group for all patients with detectible PIH at baseline (*P* = .014), for patients with at least a grade 4 PIH index (at least mild, stratification above median) at baseline (*P* = .018), and for nonwhite patients (*P* = .017).



- Qualitatively similar results were obtained when the results were expressed as **median** percentage decrease from baseline in the PIH index. For all patients, the median percentage reduction in the PIH index was over 60% in patients treated with tazarotene 0.1% cream but was near zero in patients treated with adapalene 0.3% gel (*P* = .014).

Safety Results

Signs and Symptoms

- Median scores for all signs/symptoms of irritation (erythema, dryness, peeling, oiliness, pruritus, and burning) were generally less than 1 (trace) in both treatment groups at baseline and at all follow-up visits throughout the study.
- There was no statistically significant between-group difference in oiliness or pruritus at any time during the study.
- At week 2 there was a statistically significant between-group difference for the percentage of patients with an increase in dryness of ≥ 3 grades (tazarotene: 7.0%; adapalene: 0%; *P* = .021), peeling of ≥ 1 grade (tazarotene: 46.5%; adapalene: 30.0%; *P* = .037), and burning of ≥ 1 grade (tazarotene: 50.7%; adapalene: 30.0%; *P* = .010).
- After week 2, the only between-group differences were for the percentage of patients with an increase in erythema of ≥ 2 grades at week 8 (tazarotene: 6%; adapalene: 0%; *P* = .042) and a ≥ 2 grade increase in peeling at week 16 (tazarotene: 11.5%; adapalene: 1.4%; *P* = .024).

Adverse Events

- Treatment-related adverse events (possibly, probably, or definitely related to study medication) occurred in 9 patients in the tazarotene group and in 8 patients in the adapalene group.
- The most common adverse events were burning and dryness.

DISCUSSION

- This study represents the first direct comparison between tazarotene 0.1% cream and adapalene 0.3% gel.
- Tazarotene 0.1% cream effectively reduced PIH in patients with at least moderate acne.
- There was a significant reduction of PIH with tazarotene usage in nonwhite patients and in patients with a PIH index of ≥ grade 4 at baseline.
- The results of the present study are consistent with an earlier study that reported benefits of tazarotene 0.1% cream on PIH in darker-skinned patients.[3]
- The percentage reduction in the PIH index was significantly greater following treatment with tazarotene 0.1% cream compared with adapalene 0.3% gel (*P* ≤ .018).
- The potential benefits of adapalene in the treatment of PIH still need clarification. After 16 weeks of treatment with adapalene gel in the current study, there was some improvement in PIH in patients with severe PIH at baseline, but very little improvement in nonwhite patients or in patients with less severe PIH.
- Both tazarotene 0.1% cream and adapalene 0.3% gel were well tolerated.

CONCLUSIONS

In this study, tazarotene 0.1% cream was significantly more effective than adapalene 0.3% gel in the treatment of PIH in patients with at least moderate acne.

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