Cumulative Irritation Potential and Contact Sensitization Potential of Tazarotene Foam 0.1% in 2 Phase 1 Patch Studies

Jeffrey E. Berg, BSc, CCRA; James P. Bowman, MS; Alessandra B. Alió Saenz, MD

We performed 2 phase 1 patch studies to evaluate tazarotene foam 0.1% for cumulative irritation potential (study A) and contact sensitization potential (study B). Study A participants wore patches containing active study product, vehicle foam, and positive and negative controls for 24±1 hours for 21 consecutive days. Irritation scores were statistically higher with tazarotene foam 0.1% than vehicle foam and both controls. Fourteen participants (36%) experienced product-related, application-site adverse events (AEs); all of the AEs were mild and transient. Study B participants were exposed to active product and vehicle foam for an induction and challenge phase. At the investigator's discretion, participants were administered a rechallenge to evaluate for contact sensitization. Three participants demonstrated questionable sensitization reactions and underwent a rechallenge; none of the participants displayed conclusive contact sensitization. Three application-site AEs were considered to be product related; none of the AEs led to study discontinuation. Tazarotene foam 0.1% showed potential to induce irritation but a low potential for contact sensitization and an acceptable tolerability and safety profile.

Cutis. 2012;90:206-211.

Topical retinoids are recommended as first-line therapy for acne vulgaris.[1] Tazarotene is a third-generation retinoid prodrug approved by the US Food and Drug Administration in gel and cream formulations for the treatment of acne vulgaris.[1-3] Tazarotene gel and cream formulations reduce the lesions associated with acne vulgaris, which results in sustained clinical benefits with limited local adverse events (AEs).[1,4-6] In clinical dermal safety studies, tazarotene gel and cream formulations did not induce allergic contact sensitization, phototoxicity, or photoallergy.[2,3]

An aqueous-based foam vehicle formulation of tazarotene 0.1% recently was approved by the US Food and Drug Administration for the topical treatment of acne vulgaris in patients 12 years and older.[7] Tazarotene foam 0.1% was developed to provide an ethanol-free formulation that conveniently delivers a topical retinoid in a way that may be more desirable to patients. We report the results of 2 phase 1 patch studies and assess the cumulative irritation potential and contact sensitization potential of tazarotene foam 0.1%.

Methods

Study Design—Two single-center, evaluator-blinded, randomized, vehicle-controlled, phase 1 patch studies evaluated tazarotene foam 0.1% for cumulative irritation (study A) and contact sensitization potential

Mr. Berg is from Hill Top Research, St. Petersburg, Florida.
Mr. Bowman is from Hill Top Research, Miamiville, Ohio.
Dr. Alió Saenz is from Stiefel, a GSK company, Research Triangle Park, North Carolina.
These clinical studies were sponsored by Stiefel, a GSK company.
Mr. Berg and Mr. Bowman are employees of Hill Top Research.
Dr. Alió Saenz is an employee of and stockholder for Stiefel, a GSK company.
Correspondence: Jeffrey E. Berg, BSc, CCRA, Hill Top Research, 6699 13th Ave N, St. Petersburg, FL 33710 (jberg@hill-top.com).

(study B). Both institutional review board–approved studies were conducted at a single study center in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki. Participants provided signed informed consent before entering the study.

Participant Eligibility—Participants included healthy adults aged 18 to 65 years. Women were excluded if they were pregnant, breastfeeding, or planning a pregnancy during the study. Specified washout periods were required for certain topical and systemic treatments. Participant demographics and medical history were determined at screening.

Study Products and Patch Preparation—Study products were tazarotene foam 0.1%, sodium lauryl sulfate 0.5% (positive control), distilled water (negative control), and vehicle foam in study A, and tazarotene foam 0.1% and vehicle foam in study B. In both studies, 200 μL of each study product was applied to semiocclusive or semiopen cotton patches to ensure consistent dosing.

Study A (Cumulative Irritation Potential)—Each set of patches was applied to the same randomized site on the participant's back once daily for 21 days. Patches were removed after 24±1 hours, and patch sites were evaluated for signs of irritation using numeric and letter grading scales (Table 1). The same trained skin evaluator performed all of the skin evaluations and was blinded to the randomized test site assignments. Any skin reactions not captured by the grading scales, which were considered to be related to the patch-site applications, were documented as AEs.

Study B (Contact Sensitization Potential)—The study duration was 6 or 9 weeks and consisted of an induction phase (3 weeks), rest period (2 weeks), challenge phase (1 week), second rest period (2 weeks), and an additional challenge phase if deemed necessary by the study investigator (Figure). Patches were removed at the end of each application period, and inflammatory skin responses at patch sites were visually assessed and scored according to grading scales in Table 1. Subsequent patches were applied to the same initial test sites on each participant's back immediately after patch-site evaluation. At the investigator's discretion, study product could be applied using semiopen patches if a strong erythema reaction (score of 3) was observed during the induction phase; participants with a strong erythema reaction after the second evaluation received subsequent study product applications under open-application conditions.

Study End Points—The primary end points were cumulative irritation potential of tazarotene foam 0.1% in study A and contact sensitization potential of tazarotene foam 0.1% in study B.

Table 1.

Skin Response Grading Scales

Grade	Definition
Study A: Irritation[a]	
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Moderate erythema, readily visible or minimal papular response
3	Strong erythema or erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site
A	Slight and glazed appearance
B	Marked glazing
C	Glazing with peeling and cracking
F	Glazing with fissures
G	Film of dried serous exudates covering all or portion of patch site
H	Small petechial erosions and/or scabs
Study B: Contact Sensitization	
Erythema	
0	No visible reaction
+	Slight, confluent, or patchy erythema
1	Mild erythema (pink)
2	Moderate erythema (definite redness)
3	Strong erythema (very intense redness)

TABLE CONTINUED ON PAGE 208

Table 1. (continued)

Grade	Definition
Study B: Contact Sensitization (continued)	
Local skin reaction	
E	Edema, swelling spongy feeling when palpated
P	Papule, red solid elevation
V	Vesicle, small elevation containing fluid
B	Bullous reaction, fluid-filled lesion (blister)
S	Spreading, evidence of reaction beyond exposed area
W	Weeping, result of a vesicular or bullous reaction (serous exudate)
I	Induration with solid, elevated, hardened, thickened skin
~	Response occurs in ≤25% of test site
Superficial effects	
g	Glazing
y	Peeling
c	Scab, dried film of serous exudate of vesicular or bullous reaction
d	Hyperpigmentation, reddish brown discoloration of test site
h	Hypopigmentation, loss of visible pigmentation at test site
f	Fissuring, grooves in superficial layers of skin

[a]One numeric grade and 1 letter grade were assigned for study A.

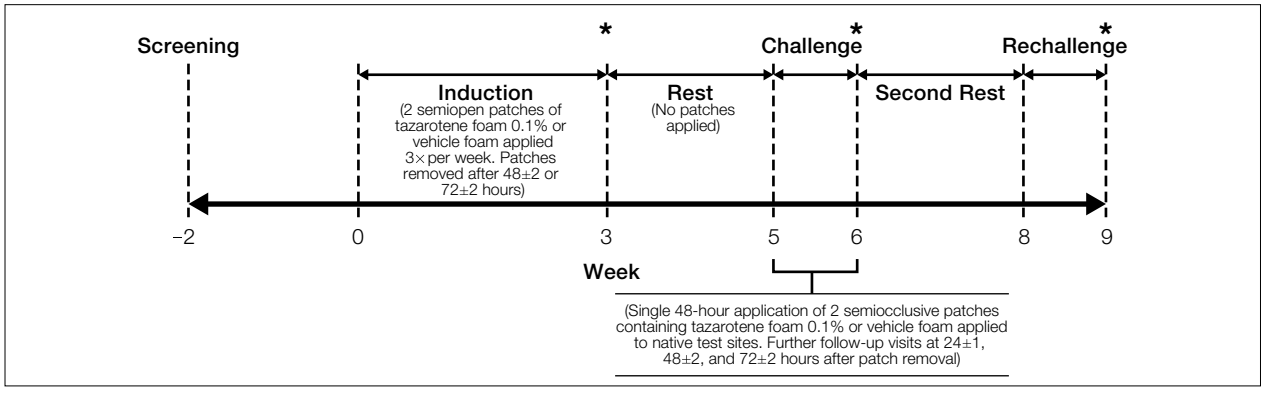
Statistical Analyses—For each skin assessment in study A, letter grades were converted to numeric equivalents as follows: A=0, B=1, C=2, F=3, G=3, H=3. For each participant, a combined score was derived by adding the numeric grade and the numeric equivalent of the letter grade at each evaluation time point (eg, 2C [2+2=4]); a maximum score of 3 was allowed for each analyzed site. A score of 3 was carried forward for any application sites discontinued due to strong skin reactions.

The mean cumulative irritation score was computed for each volunteer as the sum of dermal response irritation scores from day 2 through day 22 (inclusive) divided by the number of irritation scores (from a possible total of 21 scores). The mean cumulative irritation score was analyzed using 2-way analysis of variance with the effects of the participant and study product. If the 2-way analysis of variance was significant ($P<.05$), a 1-tailed, protected Fisher least significant difference test was performed to investigate pair-wise differences between tazarotene foam 0.1%, vehicle foam, positive control, or negative control. Except when noted, all statistical tests were 2-tailed and were performed at $\alpha=.05$. All statistical analyses were performed using SAS (version 9). No formal statistical analysis of the skin sensitization data was performed in study B.

Results

Study Population—Thirty-nine participants were enrolled in study A and received study product. Thirty participants (76.9%) completed the study and 9 participants (23.1%) discontinued early. No participants discontinued the study early because of AEs.

Overall, 254 participants were enrolled in study B and received study product. Two hundred fifteen participants (84.6%) completed the study; 39 participants (15.4%) discontinued the study early,



The study duration of study B for contact sensitization potential was 6 or 9 weeks and consisted of an induction phase (3 weeks), rest period (2 weeks), challenge phase (1 week), second rest period (2 weeks), and an additional challenge phase if deemed necessary by the study investigator. *Indicates evaluation time point.

Table 2.

Study B: Individual Assessment Scores (Erythema, Local Skin Reaction, and Superficial Effects) for 3 Participants Who Underwent Repeat Challenge[a,b]

		Induction									Challenge				Repeat Challenge			
Participant No.	Study Product	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	Day 19	Day 22	30 min	24 h	48 h	72 h	30 min	24 h	48 h	72 h
1	TF 0.1%	0	+	2gy	2gy	2gy	2gy	2gy	2gy	2gy	2	2	1P	1gy	1	0	0	0
	Vehicle	0	0	0	0	0	1gy	1g	1g	+g	+	1	0	0	1	0	0	0
2[c]	TF 0.1%	1	3	2g	1gyc	0c	0	0	+	+c	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Vehicle	0	0	0	0	0	0	0	0g	0	2	2P	2	1	0	0	0	0
3	TF 0.1%, O	1	2	3	3gy	2gc	1c	1	1	1	2	2gy	3gy	2gyf	2	3	2	2 y
	TF 0.1%, M1	N/A	N/A	N/A	0	0	0	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Vehicle	0	1	0	0	0	0	0	+y	0	1	1	1	0P	1	2	1	1

Abbreviations: TF, tazarotene foam; N/A, not applicable; O, original patch site; M1, moved first patch site.

[a]Induction scores are for the original patch site, unless otherwise specified. Challenge and repeat challenge scores are for native sites.

[b]Erythema graded as: 0=no visible reaction; +=slight, confluent, or patchy erythema; 1=mild erythema (pink); 2=moderate erythema (definite redness); 3=strong erythema (very intense redness). Local skin reaction graded as: E=edema; P=papule; V=vesicle; B=bullous reaction; S=spreading; W=weeping; I=induration; ~=response occurs in ≤25% of test site. Superficial effects were graded as: g=glazing; y=peeling; c=scab; d=hyperpigmentation; h=hypopigmentation; f=fissuring.

[c]Participant 2 was not exposed to TF 0.1% at challenge or rechallenge because of strong irritation scores that were observed during induction.

3 because of AEs and 1 because of death (not related to the study).

The mean age of participants was 41.9 and 47.3 years for study A and study B, respectively; most of the participants were women (23 [59%] and 152 [59.8%] for study A and study B, respectively). The majority of participants in both studies were white with Fitzpatrick skin types II or III.

Tolerability—In study A, the mean converted cumulative irritation (MCCI) score (standard deviation [SD]) with tazarotene foam 0.1% was 2.72 (0.2). No participant experienced more than 9 days of exposure to tazarotene foam 0.1% under semiocclusive (exaggerated dosing) patch-testing conditions; scores on subsequent days were assigned using the last-observation-carried-forward method. The negative control was associated with minimal to no irritation (MCCI score, 0.23 [0.27]), and the positive control produced an expected level of irritation (MCCI score, 1.62 [0.95]). Vehicle foam also was associated with irritation (MCCI score, 2.02 [0.83]), which was slightly less than that of tazarotene foam 0.1%. Overall, the MCCI score was statistically higher with tazarotene foam 0.1% than positive control ($P<.0001$), negative control ($P<.0001$), and vehicle foam ($P<.0001$).

In study B, vehicle foam was associated with less irritation than tazarotene foam 0.1% during the induction and challenge phases. The majority of participants showed no visible erythema (score of 0) to either tazarotene foam 0.1% (129 [64.5%]) or vehicle foam (169 [81.3%]) at any assessment during the challenge phase. Of the participants who showed a reaction, almost all of them had slight or mild erythema (score of + or 1). At tazarotene foam 0.1% patch sites, moderate erythema was observed in 11 of 200 participants (6%) at 24 hours but only 2 participants at 72 hours; strong erythema was observed in 1 participant at 48 hours. At vehicle foam patch sites, moderate erythema was observed in 3 participants at 30 minutes and 0 participants at 72 hours; there were no instances of strong erythema.

A rechallenge was conducted on 3 participants. Individual participant assessment scores for the rechallenge phase are shown in Table 2. The investigator concluded that 2 participants did not show any evidence of contact sensitization on rechallenge. One participant was considered to have an irritant skin response at rechallenge, though contact sensitization could not be ruled out.

Safety—Seventeen of 39 participants (43.6%) experienced 1 or more AEs in study A, with no deaths or serious AEs reported. Table 3 shows the most common AEs associated with application sites and study products. All AEs associated with application sites were mild and transient and typically resolved within 2 to 5 days. Five AEs associated with application sites did not resolve within the study period.

Table 3.

Study A: Adverse Events Associated With Application Sites (N=23)[a]

	No. of Adverse Events Associated With a Specific Patch Site			
Study Product	Application-Site Discomfort	Application-Site Paresthesia	Application-Site Pruritus	Total No. of Adverse Events Associated With Study Products
Tazarotene foam 0.1%	1	0	3	4
Positive control (SLS 0.5%)	1	2	5	8
Negative control (distilled water)	0	5	3	8
Vehicle foam	0	1	2	3

Abbreviation: SLS, sodium lauryl sulfate.

[a]Of the total number of reported application-site adverse events, 16 were associated with the positive and negative controls.

In study B, 3 participants reported 3 mild to moderate application-site AEs that were considered to be related to the study product. Mild skin irritation and mild pruritus were considered to be related to tazarotene foam 0.1%.

None of the AEs reported in study A or study B resulted in study discontinuation.

Comment

Topical retinoids have been shown to have the potential to irritate the skin[8]; therefore, the finding in study A that tazarotene foam 0.1% was associated with skin irritation was anticipated and consistent with findings for other topical retinoids. Furthermore, the application of study products in our study under semiocclusive (exaggerated dosing) patch-testing conditions may have increased the irritancy of tazarotene foam 0.1%. Considerably less irritation would be expected under open-application conditions (eg, intended use) with a lighter layer of foam coverage. One limitation of our study was that it did not compare tazarotene foam 1% with other topical retinoids with known efficacy and irritancy.

Study B was designed to differentiate between a true sensitization reaction, which is a delayed hypersensitivity response with immune-mediated skin inflammation, and the type of skin irritation that commonly is observed with application of a retinoid. Based on strong erythema reactions (score of 3) during the induction phase of study B, the rechallenge exposure could be under semiocclusive or less irritating semiopen conditions at the investigator's discretion. However, all participants in study B displayed an irritation response during the induction phase that was sufficient to predispose susceptible participants to a contact sensitization response. The majority of participants in study B showed no visible erythema to either tazarotene foam 0.1% or vehicle foam at any assessment during the challenge phase. Based on scores observed during the rechallenge phase, the investigator concluded that 2 of 3 participants with questionable sensitization reactions during the rechallenge phase did not show evidence of contact sensitization. Although contact sensitization could not be ruled out in the third participant, the observed skin responses were considered to be irritant in nature and not indicative of allergic contact sensitization. Therefore, both tazarotene foam 0.1% and vehicle foam appear to have a low potential for contact sensitization reactions.

All AEs associated with application sites in both studies were considered to be mild or moderate and followed until resolution. Moreover, the frequency of application-site AEs with tazarotene foam 0.1% was similar to vehicle foam and not higher than those AEs with either positive or negative controls in study A.

Conclusion

The results of these 2 phase 1 dermal safety studies demonstrated that tazarotene foam 0.1% when applied under semiocclusive (exaggerated dosing) conditions showed the potential to induce irritation with a low potential for contact sensitization reactions. Tazarotene foam 0.1% demonstrated an acceptable tolerability and safety profile for use as a topical retinoid.

Acknowledgments—Assistance with editorial preparation of this manuscript was provided by Andy Kerr, PhD, Sydney, Australia, and Joelle Suchy, PhD, Hamilton, New Jersey. Assistance with copyediting and fact-checking was provided by Sue Landry of MediTech Media, Hamilton, New Jersey. Editorial assistance was funded by Stiefel, a GSK company.

REFERENCES

1. Talpur R, Cox K, Duvic M. Efficacy and safety of topical tazarotene: a review. *Expert Opin Drug Metab Toxicol.* 2009;5:195-210.
2. Tazorac (gel)[package insert]. Irvine, CA: Allergan, Inc; 2001.
3. Tazorac (cream)[package insert]. Irvine, CA: Allergan, Inc; 2011.
4. Shalita AR, Berson DS, Thiboutot DM, et al. Effects of tazarotene 0.1 % cream in the treatment of facial acne vulgaris: pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. *Clin Ther.* 2004;26:1865-1873.
5. Shalita AR, Chalker DK, Griffith RF, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. *Cutis.* 1999;63:349-354.
6. Tanghetti E, Dhawan S, Green L, et al. Randomized comparison of the safety and efficacy of tazarotene 0.1% cream and adapalene 0.3% gel in the treatment of patients with at least moderate facial acne vulgaris. *J Drugs Dermatol.* 2010;9:549-558.
7. Fabior [package insert]. Research Triangle Park, NC: Stiefel, a GSK company; 2012.
8. Leyden J, Grove G, Zerweck C. Facial tolerability of topical retinoid therapy. *J Drugs Dermatol.* 2004;3:641-651.