Phototoxic and Photoallergic Potential of Tazarotene Foam 0.1% in 2 Phase 1 Patch Studies

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Two phase 1 patch studies were conducted to evaluate tazarotene foam 0.1% for phototoxic (study A) and photoallergic (study B) potential. In study A, 38 participants were exposed to patches containing tazarotene foam 0.1%, vehicle foam, or no foam (blank patch) over 24 hours. One set each was exposed to UV irradiation, UV and visible (VIS) light, and no irradiation. In study B, 59 participants received patches containing tazarotene foam 0.1% and vehicle foam; sites were exposed to UVB irradiation and VIS light after each application during the induction phase. After 10 to 17 days, participants received both UVA and UVA/UVB irradiation, UVA/UVB plus VIS irradiation, or no irradiation during the challenge phase. Erythema grades and local skin reactions did not differ systematically by study product or across patch sites, and no pattern of increased reactivity at tazarotene foam 0.1% sites was observed. None of the participants demonstrated conclusive photoallergic reactions. Findings suggest that tazarotene foam 0.1% is not a major photoirritant and has a low potential for phototoxic or photoallergic reactions.

Cutis. 2012;90:266-271.

Topical retinoids are recommended as first-line therapy for the treatment of acne vulgaris.[1] Retinoids are photoreactive molecules with the potential to produce photosensitivity responses.[2-4] Phototoxicity is a light-induced nonimmunologic response that occurs when a photoactive chemical enters the skin by dermal penetration or through systemic circulation and is excited by UV or visible (VIS) photons.[5] Photoallergy is an acquired, immunologically mediated reaction to a photoreactive chemical; reactions only are elicited after repeated exposures (eg, after induction phase). Pharmaceutical vehicles can modify adverse photoproperties of a drug by altering inherent protective mechanisms of skin and decreasing the amount of light reflected, scattered, or absorbed, or by increasing percutaneous absorption of drugs.[5]

An aqueous-based, ethanol-free 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. The US Food and Drug Administration recommends photosafety testing for topical drug products that absorb light in the range of 290 to 700 nm and will be applied to sun-exposed skin.[5] Other topical retinoids have demonstrated a low potential for phototoxic and photoallergic reactions in dermal clinical safety studies.[2] We report the results of 2 phase 1 patch studies that assessed the phototoxic and photoallergic potential of tazarotene foam 0.1%.

Methods

Study Design—Two single-center, evaluator-blinded, randomized, vehicle-controlled, phase 1 patch studies were conducted to evaluate tazarotene foam 0.1% for phototoxic (study A) and photoallergic (study B) potential. 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.

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These clinical studies were sponsored by Stiefel, a GSK company.
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Participant Eligibility—Participants included healthy volunteers 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 taking certain topical and systemic treatments. Participant demographics, medical history, medication history, and minimal erythema doses were determined at screening.

Study Products—Study products were tazarotene foam 0.1% and vehicle foam. The study product was applied to participants as semiocclusive (exaggerating dosing) cotton patches (2×2 cm each) in 200 μL of liquid (ie, collapsed foam) per patch.

Phototoxic Potential (Study A)—All participants were exposed to 3 sets (set A, set B, and set C) of 3 patches during a single 24-hour application period (Figure 1). Inflammatory skin responses and superficial effects were scored using the skin irritation grading scale shown in Table 1. Individuals with an erythema response of grade 2 (moderate) or grade 3 (strong) to tazarotene foam 0.1% or vehicle foam with any UV light exposure were identified and categorized according to the following criteria: potential phototoxicity, potential phototoxicity to VIS light, contact dermatitis, and inconclusive.

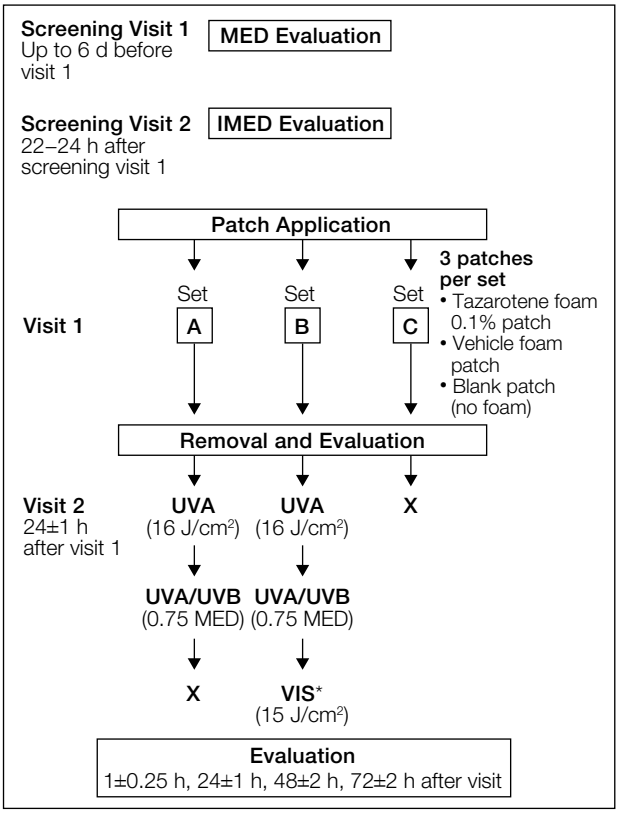

Figure 1. Schedule of assessments in study A. MED indicates minimal erythema dose; IMED, inherent minimal erythema dose; X, no irradiation; VIS, visible light. *VIS light (wavelengths of 400–700 nm).

Photoallergic Potential (Study B)—All participants were exposed to semiocclusive patches containing tazarotene foam 0.1%, vehicle foam, and no foam (eg, negative control; blank patch). Patch sites were scored according to the skin irritation grading scale in Table 1. During the induction phase, all patches in that phase were applied to one side of a participant's back. After each 24-hour application period, all patches were removed and test sites (set A and set B) were irradiated. During the challenge phase, a single, concurrent, 24-hour application of 3 sets of 3 patches (set C, set D, and set E) were placed on naive sites on the participant's back (Figure 2). Modification of occlusive patches from semiocclusive to semiopen was permitted if erythema grade 3 (strong) was observed.

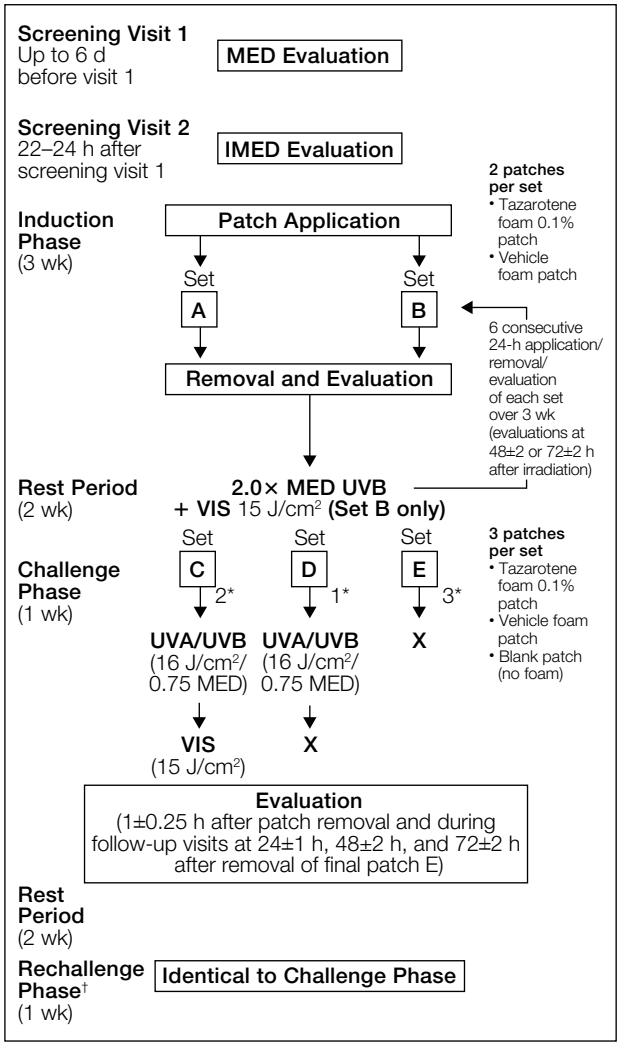

Figure 2. Schedule of assessments in study B. MED indicates minimal erythema dose; IMED, inherent minimal erythema dose; X, no irradiation; VIS, visible light. *Order in which patch sets were removed. †If deemed necessary by the evaluator, rechallenge was scheduled to further assess whether an inflammatory response resulted from a photoallergic reaction.

Table 1.

Grading Scales for Inflammatory Skin Responses and Superficial Effects (Study A and Study B)

Grade	Definition
Erythema	
0	No visible reaction
+	Slight, confluent, or patchy erythema
1	Mild erythema (pink)
2[a]	Moderate erythema (definite redness)
3[a]	Strong erythema (very intense redness)
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]Participants with an erythema response of grade 2 or grade 3 with any light exposure (ie, UV only or UV plus visible light) were categorized as follows: (a) potential phototoxicity: moderate or greater reaction to UV only and UV plus visible light; (b) potential phototoxicity to visible light: moderate or greater erythema reaction to UV plus visible light with no significant consistent reactions observed on nonirradiated sites or sites irradiated with UV only; (c) contact dermatitis: moderate or greater erythema reaction to any of the nonirradiated as well as irradiated sites, with significant consistent reactions observed to all of the other light exposures; or (d) inconclusive response: moderate or greater erythema reaction to UV only, with no significant consistent reaction observed with UV plus visible light and/or nonirradiated sites.

Study End Points—The primary end points were evaluated in the per-protocol analysis set. The safety set included all randomized participants who were exposed to study product.

Statistical Analyses—Descriptive statistics were used for safety results and the extent of exposure to study products. Frequency counts of skin irritation scores were tabulated by visit, study patch, and irradiation exposure for the safety and per-protocol analysis sets.

Results

Study Population—In study A, 38 volunteers were enrolled and exposed to study product; 36 (94.7%) participants completed the study and 2 (5.3%) participants discontinued. None of the participants discontinued the study because of adverse events (AEs). In study B, 59 participants were enrolled and exposed to study product; 51 (86.4%) participants completed the study and 8 (13.6%) participants discontinued. The mean age of participants was

Table 2.

Study A: Participants With a Possible Phototoxic Reaction

Participant No.	Study Product	Irradiation	Patch Site Assessment[a] 24 h	48 h	72 h	Investigator Interpretation
1	Tazarotene foam 0.1%	UV+VIS	+	0	0d	Unclear
		UV only	0	+	+	Slight irritation
		None[b]	0	0	0	
	Vehicle	UV+VIS	3	3E	3	Possible photoirritation/ phototoxicity
		UV only	+	+	+	Slight irritation
		None[b]	0	0	0	
2	Tazarotene foam 0.1%	UV+VIS	0	0	0	
		UV only	1	+	+	Slight to mild irritation
		None[b]	0	0	0	
	Vehicle	UV+VIS	3	3	3	Possible photoirritation/ phototoxicity
		UV only	1	1	1	Slight to mild irritation
		None[b]	0	+	0	
3	Tazarotene foam 0.1%	UV+VIS	3	3	3	Possible photoirritation/ phototoxicity
		UV only	2	2P	1	Possible photoirritation/ phototoxicity
		None[b]	1	2P	1P	Irritation
	Vehicle	UV+VIS	2	1P	1	Irritation
		UV only	1	1P	1	Unclear
		None[b]	1	1P	+P	

Abbreviation: VIS, visible light.

[a]Erythema was graded as: 0=no visible reaction; +=slight, confluent, or patchy erythema; 1=mild erythema; 2=moderate erythema; 3=strong erythema. Local skin reaction was graded as: E=edema; P=papule; V=vesicle; B=bullous reaction; S=spreading; W=weeping; I=induration. Superficial effects were graded as: g=glazing; y=peeling; c=scab; d=hyperpigmentation; h=hypopigmentation; f=fissuring.

[b]None indicates that no irradiation was received; only the effect of tazarotene foam 0.1% or vehicle foam was being measured.

43.2 years in study A and 42.7 years in study B, and most participants were women (23 [63.9%] and 38 [74.5%] in study A and study B, respectively). The majority of participants in both studies were white with Fitzpatrick skin types II or III.

Evaluation of Skin Reactions—The majority of participants in study A had no visible reaction (erythema grade 0), or slight, confluent, or patchy erythema (erythema grade +). Erythema scores of grade 0 were less frequent with tazarotene foam 0.1% than vehicle or blank patch in nonirradiated patch sites. Few participants had grade 2 or grade 3 erythema at irradiated or nonirradiated patch sites with tazarotene foam 0.1% or vehicle foam. Inflammatory skin response and superficial effect scores did not demonstrate systematic differences by study product or across patch sites.

Table 3.

Study B: Participants With an Unclear/Possible Photoallergic Reaction on Rechallenge

Participant No.	Study Product	Study Phase	Irradiation	Patch Site Assessment[a] 24 h	48 h	72 h	Investigator Interpretation
1	Tazarotene	Challenge	UV+VIS	2	2P	2	Unclear: rechallenge
			UV only	1	2Pg	1	Unclear: rechallenge
			None[b]	2	2P	2	
		Rechallenge	UV+VIS	2g	3E	2y	Unclear
			UV only	2g	3E	2	Unclear
			None[b]	2g	3y	1y	
	Vehicle	Challenge	UV+VIS	2	2P	2	Unclear: rechallenge
			UV only	2	2P	2	Unclear: rechallenge
			None[b]	+	1	+	
		Rechallenge	UV+VIS	2P	2	0d	Not photoallergic reaction
			UV only	2P	2	0d	Not photoallergic reaction
			None[b]	2P	2	1	
2[c]	Tazarotene	Challenge	UV+VIS	1	0d	0d	Not photoallergic reaction
			UV only	1	+	0d	Not photoallergic reaction
			None[b]	1	0	0	
	Vehicle	Challenge	UV+VIS	1	2P	2P	Unclear
			UV only	1	+	0d	Not photoallergic reaction
			None[b]	0	0	0	
3	Tazarotene	Challenge	UV+VIS	2	2	0d	Unclear: rechallenge
			UV only	2	1	0d	Unclear: rechallenge
			None[b]	+	1	0d	
		Rechallenge	UV+VIS	2	2	0d	Not photoallergic reaction
			UV only	2	1	0d	Not photoallergic reaction
			None[b]	2	2	0	
	Vehicle	Challenge	UV+VIS	2	2	0d	Unclear: rechallenge
			UV only	2	1	1	Unclear: rechallenge
			None[b]	0	0	0d	
		Rechallenge	UV+VIS	2	1	0d	Not photoallergic reaction
			UV only	2	2	2	Unclear
			None[b]	1	1	0d	

Abbreviation: VIS, visible light.

[a]Erythema was graded as: 0=no visible reaction; +=slight, confluent, or patchy erythema; 1=mild erythema; 2=moderate erythema; 3=strong erythema. Local skin reaction was graded as: E=edema; P=papule; V=vesicle; B=bullous reaction; S=spreading; W=weeping; I=induration. Superficial effects were graded as: g=glazing; y=peeling; c=scab; d=hyperpigmentation; h=hypopigmentation; f=fissuring.

[b]None indicates that no irradiation was received; only the effect of tazarotene foam 0.1% or vehicle foam was being measured.

[c]Participant was lost to follow-up for rechallenge test.

In study B (challenge phase), under UV irradiation, UV plus VIS irradiation, and no irradiation, numerically more participants experienced mild to moderate erythema, which decreased over 24 to 72 hours, with tazarotene foam 0.1% than with vehicle foam or blank patch. Approximately 50% (after UV irradiation [n=27] or UV plus VIS irradiation [n=25]) and 60% (after no irradiation [n=31]) of tazarotene foam 0.1%–treated patch sites showed no visible reaction at 72 hours. Strong erythema (grade 3)was seen in approximately 4% (n=2) of tazarotene foam 0.1%–treated patch sites immediately after UV irradiation or UV plus VIS irradiation and decreased at subsequent assessments.

Evaluation of Phototoxic Potential (Study A)—Overall, 32 (89%) participants in study A were scored as having no phototoxic reaction and 7 (19.4%) participants had an unclear reaction at 1 or 2 sites. Three (8.3%) participants were considered to have a possible photoirritation or phototoxic reaction (Table 2). However, the results did not show a consistent pattern of increased reactivity at tazarotene foam 0.1%–irradiated sites compared with vehicle foam–irradiated sites or UV-only–irradiated (blank patch) sites.

Evaluation of Photoallergic Potential (Study B)—Following the review of all induction, challenge, and rechallenge data, no conclusive positive photoallergic reactions were observed in study B (Table 3). The investigator considered responses to be irritant responses, as there was no consistent pattern of increased reactivity.

Overall Safety Evaluation—In study A, no AEs were reported. In study B, 6 (10.2%) participants reported 7 AEs; no AEs were considered to be related to the study product. One participant withdrew from the study due to mild viral infection, which was unrelated to the study products.

Comment

Irritant reactions can sometimes be misinterpreted as an allergy. A single 48-hour postpatch reading may not detect all reactions.[6] Longer periods (eg, 72 hours), as in our study, are of value in identifying delayed reactions and can demonstrate the crescendo pattern that is typical of allergic reactions or the decrescendo pattern that is typical of irritant reactions.[7] The pattern of reactivity in our study was consistent with an irritant response rather than an allergy.

Conclusion

Findings from these 2 phase 1 patch studies suggest that tazarotene foam 0.1% and vehicle foam are not major photoirritants and have a low potential for phototoxic or photoallergic reactions.

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

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