Cumulative Irritation Comparison of Adapalene Gel and Solution With 2 Tazarotene Gels and 3 Tretinoin Formulations

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Forty-two subjects with normal skin were enrolled in a single-center study to assess the cumulative irritancy potential of adapalene (Differin® gel 0.1% and Differin solution 0.1%) compared with tazarotene (Tazorac® gels 0.05% and 0.1%), tretinoin (Retin-A Micro® gel 0.1%, Avita® cream 0.025%, and Avita gel 0.025%), and white petrolatum (negative control). All test materials were applied randomly, under occlusion, to sites located on either side of the midline—the mid thoracic area of the subjects' backs. All patches were applied daily, Monday through Friday, to the same sites, unless the degree of reaction to a test product or adhesive necessitated removal (grade 3).

Thirty-eight of the 42 subjects (90.5%) completed the study. Thirty-four of those 38 subjects (89.5%) had to discontinue using both tazarotene concentrations due to intolerance. Patch discontinuations for the remaining test materials were as follows: 7 subjects discontinued use of tretinoin microsphere gel 0.1%, 3 discontinued tretinoin cream 0.025%, 1 discontinued tretinoin gel 0.025%, and 1 discontinued adapalene gel 0.1%. None of the subjects discontinued use of the white petrolatum or the adapalene solution 0.1%. Adapalene gel and solution 0.1% were statistically (P<.01) less irritating than both tazarotene gels 0.1% and 0.05%, tretinoin microsphere gel 0.1%, and tretinoin gel 0.025%, and they were not statistically different from tretinoin gel 0.025%.

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Adapalene (Differin®) is a naphthoic-acid derivative with retinoid activity that is effective in the treatment of mild to moderate acne vulgaris.[1-4] Adapalene, in both gel and cream formulations, at the marketed and approved concentration of 0.1%, is better tolerated than most tretinoin formulations, including tretinoin microsphere gel 0.1% (Retin-A Micro®) and tretinoin cream 0.025% (Avita®).[5-10] The cumulative irritancy assay (patch test) is designed to assess the irritation potential of topically applied materials. Irritation results obtained from this type of assay are due to direct damage to the epidermal cells, and no immunologic (allergic) mechanism is involved. Results of this standard assay are widely accepted to be indicators of irritation. This study compared the irritation potential of adapalene gel and solution with several retinoid and retinoidlike products containing either tazarotene or tretinoin.

Methods

This cumulative irritancy study was conducted as a single-center, randomized, controlled, investigator/evaluator, double-blind, intraindividual compari-

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Table 1.

Erythema Grading Scale

Grade	Abnormal Redness of the Skin (Erythema)
0	No reaction
0.5	Barely visible
1	Mild
2	Moderate
3	Severe

Table 2.

Irritation Classification*

MCII	Product Classification
<0.25	Nonirritating
0.25–1 (noninclusive)	Slightly irritating
1–2 (noninclusive)	Moderately irritating
2–3 (noninclusive)	Very irritating

*MCII indicates mean cumulative irritancy index.

son involving healthy subjects meeting specific inclusion-exclusion criteria. The cumulative irritancy assay, a 21-day patch test, was designed to assess the irritation potential of topically applied dermatologic materials under stressful conditions (ie, occlusion).[11]

A total of 42 subjects (6 males and 36 females) ranging in age from 22.9 to 74.8 years were enrolled and evaluated. All subjects received adapalene gel 0.1%, adapalene solution 0.1%, tazarotene gel 0.1%, tazarotene gel 0.05%, tretinoin microsphere gel 0.1%, tretinoin cream 0.025%, tretinoin gel 0.025%, and white petrolatum (negative control).

Approximately 0.2 g of each of the 7 test products and negative control was applied to 8 sites on the upper area of the back according to a predefined randomization list. Application was made under occlusive conditions for 24 hours (4 times per week) and 72 hours (once weekly) for 3 weeks. At each study visit, skin reactions (erythema scores ± other local reactions) were assessed by the same trained board-certified physician evaluator during the study, 15 to 30 minutes after removal of the product, using the grading scale for erythema (Table 1).

In addition, other concomitant cutaneous reactions (eg, dryness, cracking, peeling) on test sites were noted, including adhesive reactions. The principal safety criterion was the mean cumulative irritancy index (MCII) assessed by clinical evaluation of the erythema at each test site. Evaluation of the test product application sites was conducted by the same investigator/evaluator throughout the study. The sites were scored at baseline (day 1) and at each study visit, week 1 (days 2 through 5, inclusively), week 2 (days 8 through 12, inclusively), week 3 (days 15 through 19, inclusively), and week 4 (day 22).

The backs of the subjects were photographed before each reading. When an irritation reaction related to the product was graded 3 for any site, product application was discontinued for the incriminated sites. When an irritation reaction related to the adhesive prohibited the wearing of a patch at a particular site, all patch applications were discontinued for the subject. However, the subject was not discontinued from treatment unless, in the investigator's/evaluator's opinion, there was a safety concern. At that time, an adverse event form would have been completed.

All subjects were informed in accordance with the International Conference on Harmonization guidelines and Good Clinical Practices. A written consent form, approved by the Institutional Review Board, was supplied by the investigator and was understood and signed by each subject before inclusion in the study.

Statistical Methodology

Sample Size, Design, and Randomization—A standard sample size for this type of cumulative irritancy clinical study is 25 subjects. To account for the multiplicity of comparisons, planned enrollment was estimated at 48 subjects. Enrollment was completed at 42 subjects, with the consent of the sponsor. On initiation, each of the 8 products was applied to one of the zones (Z1–Z8) according to the predefined randomization schedule. This ran-

domization schedule was generated by the RANUNI routine of SAS using 8×8 Latin squares.

Statistically Analyzed Variables—For evaluating the cutaneous tolerance, a cumulative irritancy index (CII) was calculated for each treatment and for each subject, as follows: CII=sum of irritation score/number of readings. The following conventions were applied for the CII calculation: baseline (day 1) score was excluded from the calculation. When the irritation reaction was rated 3 for any site, the product application was discontinued for the incriminated sites, and a score of 3 was assigned to the remaining readings (last observation carried forward). When a subject missed a scheduled visit, the scores of the sites from the next visit were assigned to the previously missed visit.

Individual CII scores were averaged across subjects to obtain an MCII score for each treatment. MCII scores were submitted to an analysis of variance with effects for subject, zone, and formulation. To adjust for multiple comparisons, MCII score was compared, and formulations were classified using the Tukey multiple comparisons test performed at the 1% and 5% significance levels. According to MCII values, each test product could be classified into the irritation classes (Table 2).

Table 3.

Demographic Data

	All Products N=42
Age, y	
Mean (range)	47.3 (22.9–74.8)
Gender, n (%)	
Male	6 (14.3)
Female	36 (85.7)
Race, n (%)	
White	39 (92.9)
Black	1 (2.4)
Asian	1 (2.4)
Hispanic	1 (2.4)

Table 4.

Summary of Mean Cumulative Irritancy Index (MCII) Statistical Comparisons

Product	MCII (mean±SD)	Statistical Grouping*
Adapalene gel 0.1%	0.06±0.18	A
Adapalene solution 0.1%	0.05±0.16	A
Tazarotene gel 0.05%	1.69±0.53	D
Tazarotene gel 0.1%	1.81±0.52	E
Tretinoin microsphere gel 0.1%	0.63±0.56	C
Tretinoin cream 0.025%	0.48±0.38	B
Tretinoin gel 0.025%	0.18±0.32	A
White petrolatum	0.02±0.04	A

*MCIIs with the same letter are not statistically significantly different ($P>.05$) from each other but are different from MCIIs of other letters.

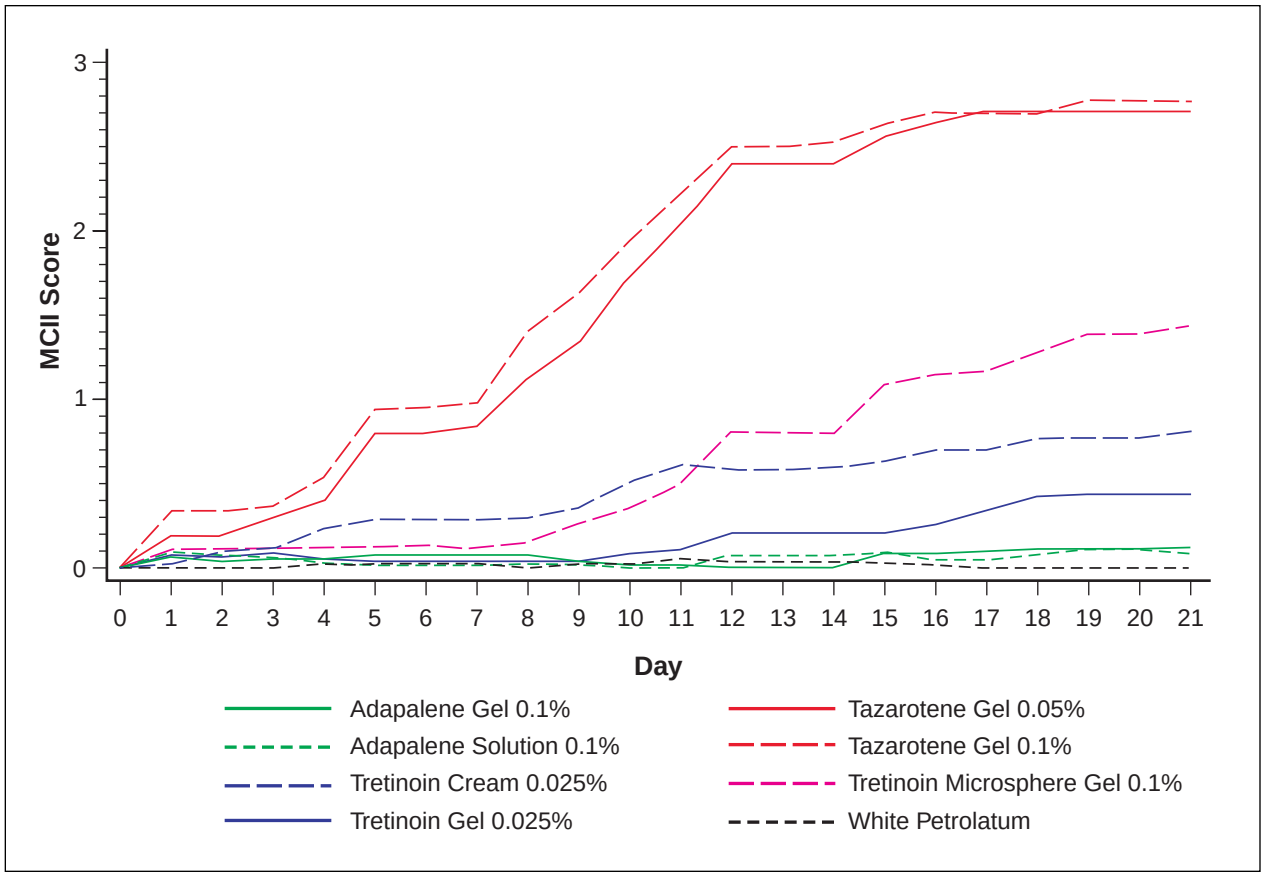

Figure 1. Mean cumulative irritancy index (MCII) scoring over a 21-day patch test.

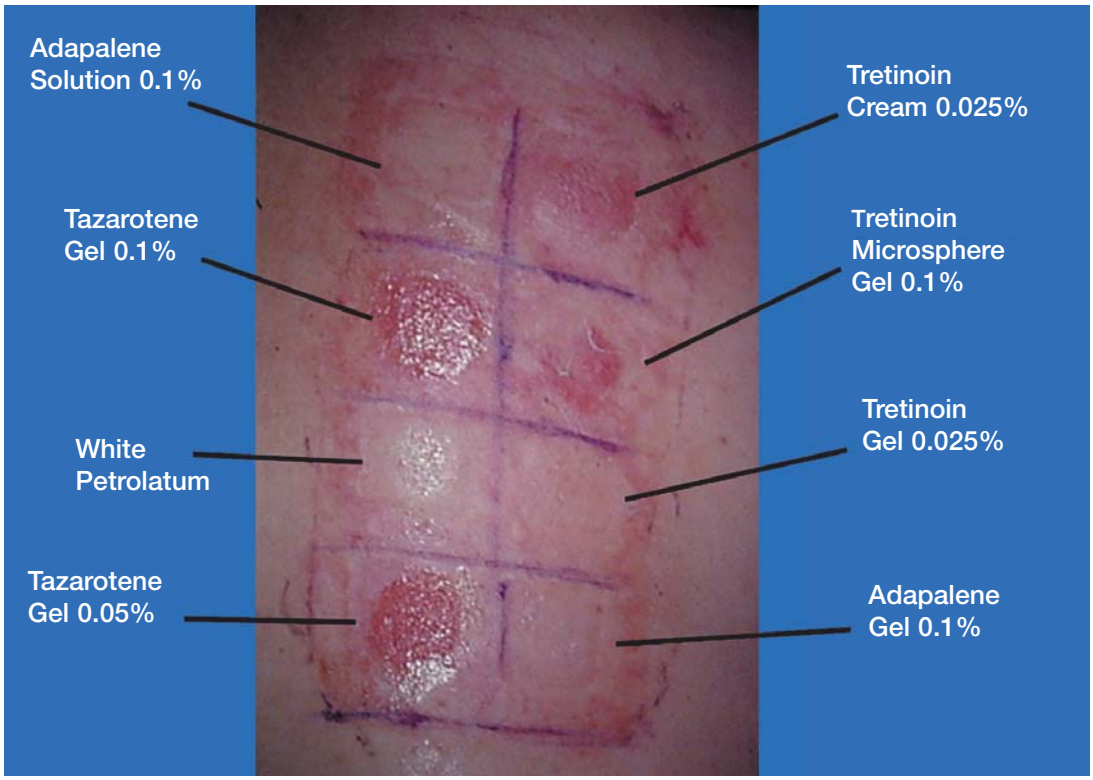

Figure 2. Example of reactions observed during the study.

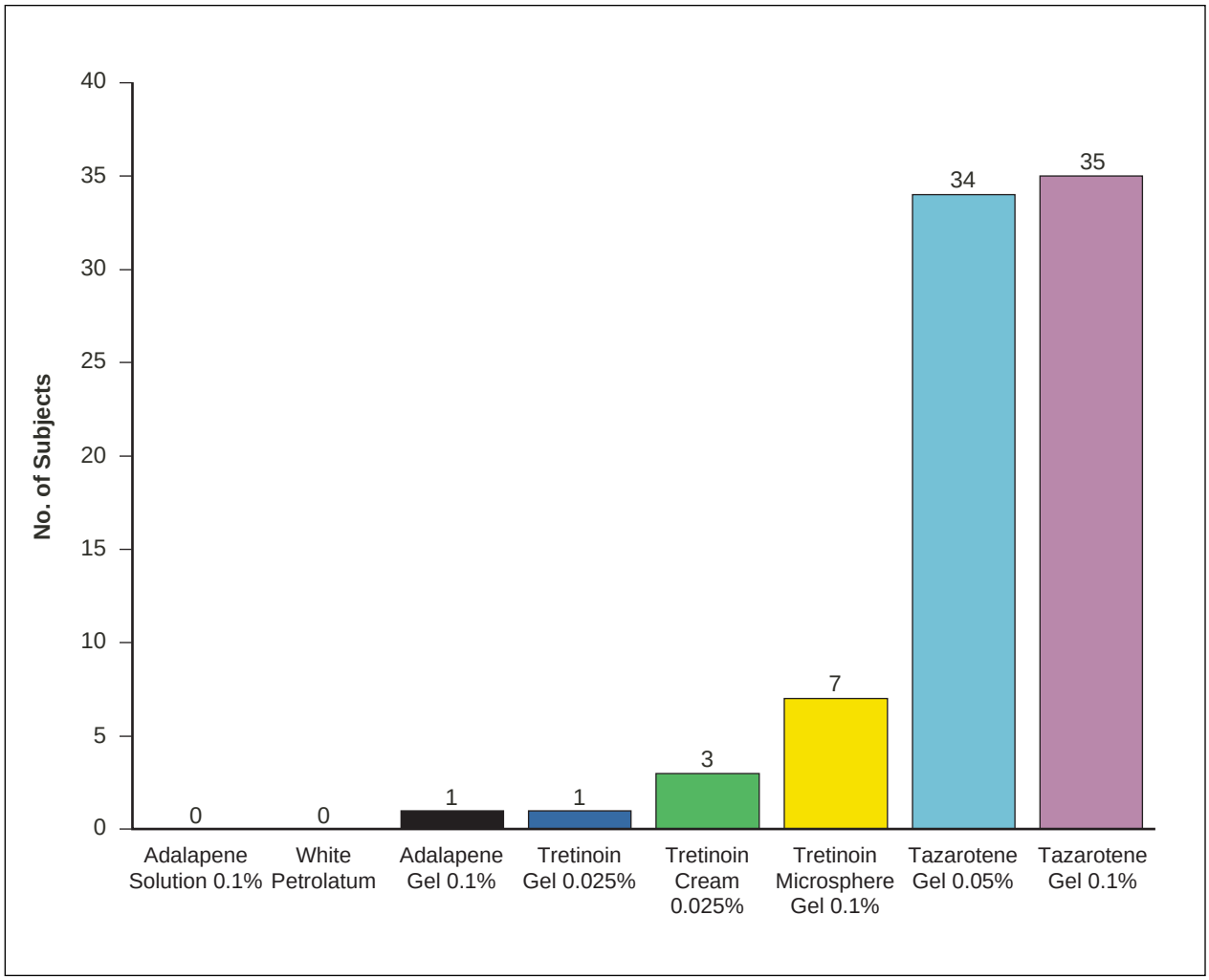

Figure 3. Patches prematurely discontinued.

Results

Of the 42 subjects enrolled, 38 subjects (90.5%) completed the study. Demographic data are presented in Table 3. Results are summarized in Table 4 and Figure 1. Figure 2 shows a clinical photograph of typical irritation observed during the study.

In the study, the reasons for treatment discontinuation were not always due to an erythema score of 3 but also because of other clinical aspects of severe intolerance, such as epidermal peeling with subsequent superficial erosion (without severe erythema). Figure 3 shows the number of subjects who discontinued wearing the patches due to an irritation score of 3.

Adapalene gel and solution 0.1% were each significantly less irritating during sustained use than tazarotene gels 0.05% and 0.1%, tretinoin microsphere gel 0.1%, and tretinoin cream 0.025%. Although tretinoin gel 0.1% MCII was numerically superior to both adapalene gel and solution MCIIs, no statistically significant difference could be depicted between the 3 products. Repeated applications of adapalene gel or solution resulted in levels of irritation that were not significantly different from the white petrolatum control.

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