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Adapalene 0·1% gel for the treatment of acne vulgaris: its superiority compared to tretinoin 0·025% cream in skin tolerance and patient preference

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Summary One hundred patients with acne vulgaris applied adapalene (Differin®) 0·1% gel to one side of their face and tretinoin 0·025% cream to the other once a day for 4 weeks; the side of application was determined by randomization code. Patient tolerance (assessed as the side of the face least irritated by drug application) was recorded weekly and patient preference (assessed as the preparation more easily spread, absorbed more quickly, smelled better, felt best on the skin and least greasy to the feel) at completion of the study. The investigator measured skin irritation weekly, scoring erythema, skin dryness, desquamation and burning/stinging on a 10-point scale.

After each week of treatment, 64–68% of patients found adapalene 0·1% gel more tolerable than tretinoin 0·025% cream ($P < 0·05$). At study completion, 65% of patients preferred adapalene 0·1% gel over tretinoin 0·025% cream ($P = 0·003$). An overall assessment showed adapalene 0·1% gel was significantly less irritating to the skin in terms of producing erythema, dryness, desquamation and burning/stinging, at Visits 2, 3 and 4 ($P < 0·02$).

Thirty-two patients experienced mild to moderately severe adverse events; three had adverse events considered to be drug related (two with skin discomfort; one with skin dryness). One patient stopped using the study drugs because of dry skin.

This study showed that a majority of patients preferred adapalene 0·1% gel over tretinoin 0·025% cream and that it caused significantly less skin irritation.

Adapalene (Differin®) 0·1% gel, a naphthoic acid derivative with retinoid activity, is approved for the treatment of patients with acne vulgaris; it has shown activity similar to or better than tretinoin 0·025% gel.[1–5] Adapalene is formulated in a water-based gel which results in reduced irritation and epidermal side-effects when compared to tretinoin gel (this issue, pp 34–40)[6] and tretinoin 0·025% cream (this issue, pp 34–40). Other studies have demonstrated the excellent skin tolerance to adapalene 0·1% gel as well as its lack of sensitizing, phototoxic or photoallergic potential. The most common side-effects, which usually decline and disappear within the first two weeks of use, are mild erythema and dryness with occasional stinging. Good tolerance to adapalene 0·1% gel has been experienced over a 6-month period of continuous treatment and it was not associated with systemic intolerance nor quantifiable levels in the plasma.

A preliminary study showed that adapalene 0·1% gel has less cumulative irritation than does tretinoin 0·025% cream (this issue, pp 34–40). However, it was not directly compared to tretinoin 0·025% cream in a study large enough to define their relative patient preference and tolerance and skin irritation during treatment of patients with acne vulgaris. The study described in this report compares (i) the patient preference for and tolerance of adapalene 0·1% gel to that of tretinoin 0·025% cream, applied once daily for 4 weeks in subjects with acne vulgaris and (ii) the skin irritation (in terms of erythema, dryness, desquamation, and stinging/burning) associated with adapalene 0·1% gel and tretinoin 0·025% cream.

Subjects and methods

This was a randomized, investigator-blinded, comparative, bilateral (half-face within patient) study of

adapalene 0·1% gel and tretinoin 0·025% cream in patients with acne vulgaris; the study was carried out at two centres. Men (without beards) and women (neither pregnant nor lactating), between 13 and 30 years of age, with mild to moderately severe facial acne vulgaris, were enrolled in the study, provided they met the following criteria: previous topical acne medication and/or anti-inflammatory therapy had been stopped for two weeks, systemic antibiotics (with the exception of penicillin) for four weeks and systemic retinoid preparations for six months; no underlying diseases or other dermatological conditions were present that required treatment with interfering topical or systemic therapy. Patients diagnosed with acne conglobata, acne fulminans or secondary acne (chlorine, drug-induced acne, etc.) were not enrolled. All patients were considered capable of co-operating with the protocol procedures and gave informed consent.

Patients applied adapalene (Differin®) 0·1% gel and tretinoin (Retin-A®) 0·025% cream, once a day for 4 weeks, to the left or the right side of the face and nose; the side to which each study drug was applied was determined by randomization code. Treatment assignment was by a third party; the investigator did not see the study drug tubes, nor did he discuss the study drug packaging with patients at any time during the study.

The tubes of study drugs were dispensed at Day 1 (baseline); patients were instructed on the application of study drugs and given written instructions which included: to wash hands between the application of each study drug; to gently wash the face with warm water just before applying the study drugs; to apply an amount the size of a pea and gently smooth it into the skin until invisible; to avoid prolonged exposure to the sun and to bring study drug tubes to each visit.

Following the baseline visit, patients returned at weekly intervals for four weeks (visits 1–4) for evaluation of tolerance, skin irritation and overall safety. Patient preference was assessed at the final visit. Patients were free to leave the study at any time and could be terminated because of safety reasons or protocol violations.

Evaluations

Patient tolerance

At visits 1 through 4, patients were asked to respond with 'left' or 'right' to the question: 'On which side of your face did the product you applied irritate the most?'

Patient preference

At the final visit patients were asked to respond with 'left' or 'right' to the following questions:
'On which side of your face did the product you applied: (i) spread easiest; (ii) absorb into your skin the quickest; (iii) have the best smell (lack of odor); (iv) feel the best on your skin and (v) leave your skin feeling greasy?
'Which product do you prefer?'

Skin irritation

At each visit the investigator evaluated patients for stinging/burning (prickling pain sensation), erythema (abnormal skin redness), dryness (brittle and/or tight sensation) and desquamation (abnormal shedding of the stratum corneum). Each of these signs/symptoms was measured on a 10-point scale: 0 = none; 1–3 = mild; 4–6 = moderate; 7–9 = severe. As a measure of overall skin irritation, the scores for each parameter were added together to give a score out of a possible 36 and the total scores for each study drug compared.

Overall safety

Safety was assessed at each visit by recording adverse events reported by patients, either voluntarily or in response to questioning.

Statistical analyses

The intent-to-treat population was analysed. Patient tolerance and preference parameters were analysed by the sign test. Skin irritation parameters (erythema, dryness, desquamation, stinging/burning and overall total score) were analysed by analysis of variance, which included both patient and treatment effects.

Results

One hundred patients (52 men and 48 women) enrolled in the study; 76% were caucasian. The mean age was 18·5 years, 39% being < 17 years of age and 26% being > 21 years of age. The majority (51%) were phototype III, 47% had normal skin, 42% oily skin and 11% dry skin. Three patients did not complete the study. One was lost to follow-up, one requested to withdraw from the study and one stopped applying the study drugs because of dry skin on the adapalene application side.

There were no differences between the study drugs scores for the baseline skin tolerance parameters ($P > 0{\cdot}16$).

Patient tolerance

Figure 1 shows that, at all visits, between 64% and 68% of patients found tretinoin cream 0·025% caused more skin irritation and was a less tolerable medication. The differences between study drugs at each visit were statistically significant ($P < 0{\cdot}05$).

Patient preference

The distribution of responses to the six preference questions asked at visit 4 is shown in Fig. 2. All answers favoured adapalene. The most favoured aspects of adapalene 0·1% gel, as compared to tretinoin 0·025% cream, were that it spread more easily (81% vs. 19% for adapalene 0·1% gel and tretinoin 0·025% cream, respectively); that it smelled better (77% vs. 24%) and that it felt better (74% vs. 26%). Overall, 65% of patients preferred adapalene 0·1% gel ($P = 0{\cdot}003$). The differences between study drugs were statistically significant ($P < 0{\cdot}05$) for all but speed of absorption.

Skin irritation

Table 1 summarizes the mean baseline and visit 4 scores for the four skin tolerance parameters, erythema, dryness, desquamation, stinging/burning and for the total signs/symptoms score. At the completion of the study the scores for all parameters were numerically in favour of adapalene gel, and the differences between study drugs were statistically significant for all but stinging/burning. The mean scores for each parameter over the course of the study are shown in Fig. 3. After the first week of treatment adapalene 0·1% gel consistently caused less erythema, skin dryness, desquamation, and burning/stinging. The differences between adapalene 0·1% gel and tretinoin 0·025% cream were statistically significant ($P < 0{\cdot}05$) for erythema and dryness at visits 2 through 4, for desquamation at visits 3 and 4 and for burning/stinging at visit 2.

An overall assessment (comparison of the total signs/symptoms scores for adapalene 0·1% gel and tretinoin 0·025% cream) showed adapalene 0·1% gel was significantly less irritating to the skin ($P < 0{\cdot}02$) in terms of producing erythema, dryness, desquamation and burning/stinging, at visits 2, 3 and 4.

Safety

Thirty-two patients (32%) experienced adverse events. The most commonly reported were headache (9%) and flu-like syndrome (8%); none of these events were considered to be related to either adapalene 0·1% gel or tretinoin 0·025% cream. Three patients had drug-related episodes of mild to moderate skin discomfort (two patients, one on the tretinoin application side and

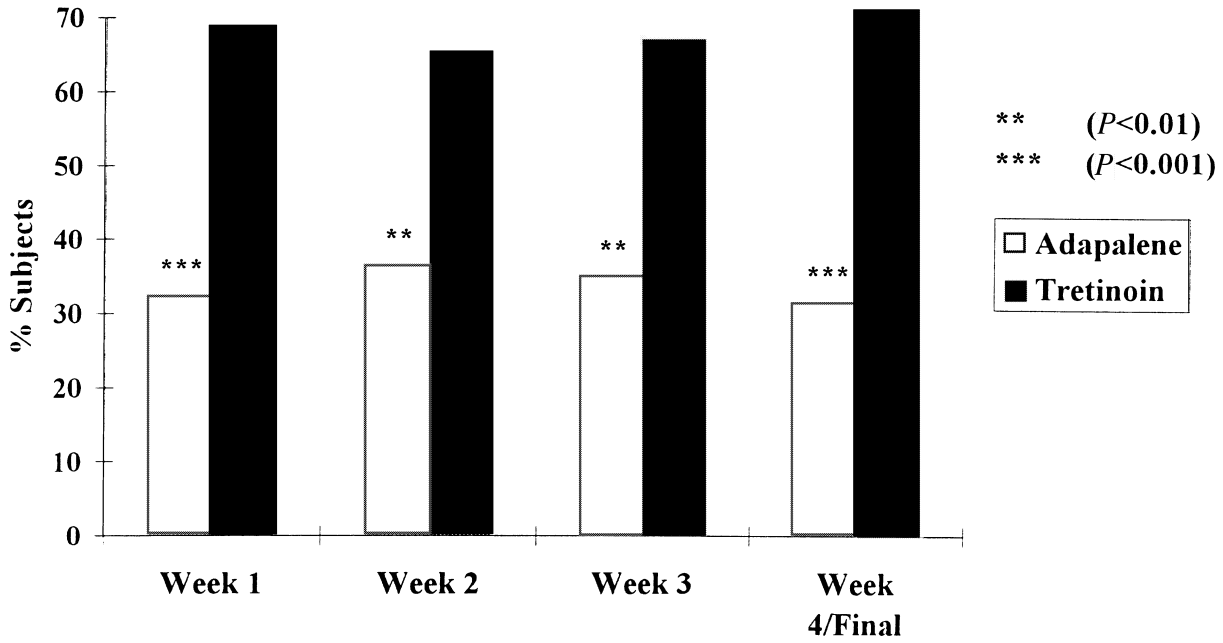

Figure 1. Patient tolerance scores at visits 1, 2, 3, and 4 (most irritating product).

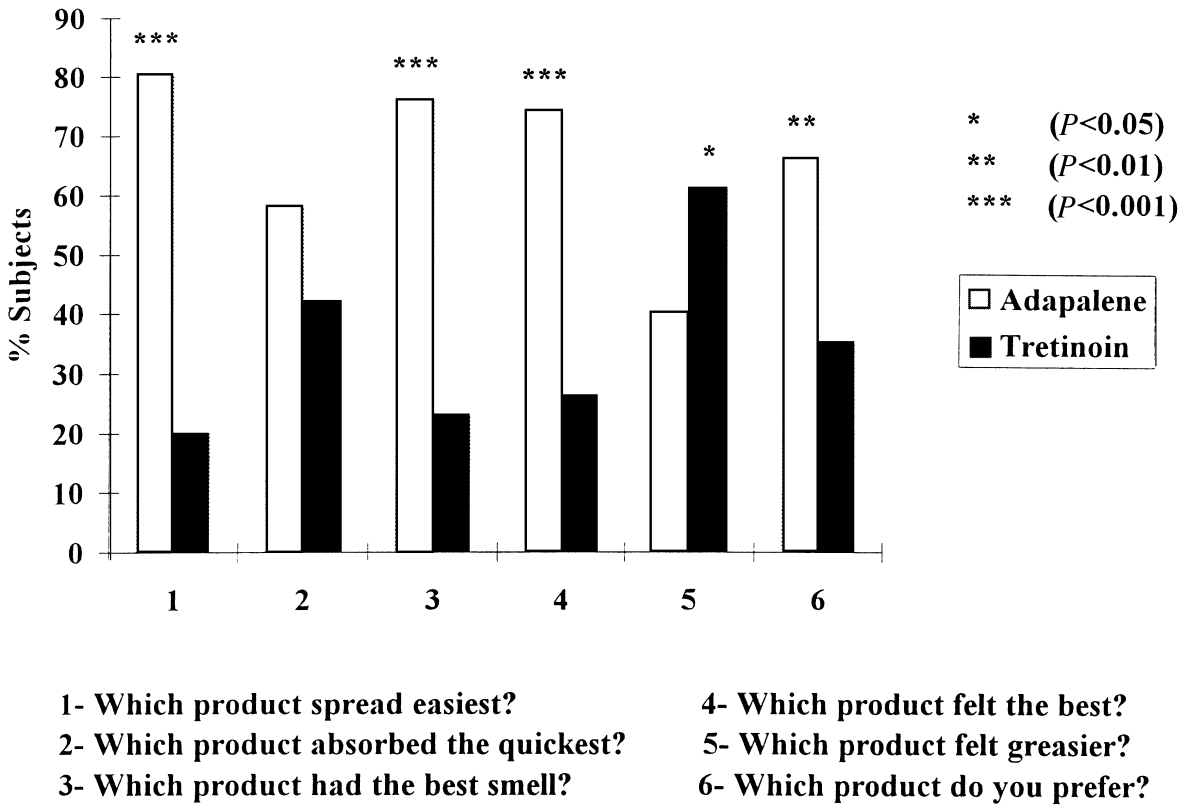

Figure 2. Patient preferences at the final visit

Table 1. Skin irritation parameters: summary of baseline and visit 4 scores

Parameter	Time point*	Mean score		*P*-value
		Adapalene 0·1% gel	Tretinoin 0·025% cream	
Erythema	Baseline	0·51 ± 0·52	0·53 ± 0·52	0·158
	Visit 4	1·70 ± 0·87	1·98 ± 0·97	0·021
Dryness	Baseline	0·11 ± 0·31	0·11 ± 0·31	1·00
	Visit 4	1·23 ± 0·78	1·46 ± 0·89	0·017
Desquamation	Baseline	0·04 ± 0·24	0·04 ± 0·20	1·00
	Visit 4	0·37 ± 0·71	0·55 ± 0·87	0·034
Stinging/burning	Baseline	0·00 ± 0·00	0·00 ± 0·00	1·00
	Visit 4	0·38 ± 0·82	0·55 ± 0·85	0·184
Total signs/symptoms scores	Baseline	0·66 ± 0·70	0·68 ± 0·68	0·417
	Visit 4	3·68 ± 2·33	4·54 ± 2·64	0·011

*For Baseline: $N = 100$; visit 4: $N = 97$

one on both sides) and dryness (one patient, on the tretinoin application side). One patient discontinued the study because of dry skin on the adapalene application side.

Discussion

Previous studies showed that adapalene 0·1% gel is equal to or better than tretinoin 0·025% gel for the treatment of patients with acne vulgaris.[1–5] A preliminary study has indicated that it is significantly less irritating than several gel and cream formulations of tretinoin (this issue, pp 34–40). This study confirms these preliminary preference and tolerance data.

Better patient tolerance for adapalene 0·1% gel became apparent after the first week of treatment. During the subsequent three weeks of therapy, it was consistently less irritating to the face in 64–68% of

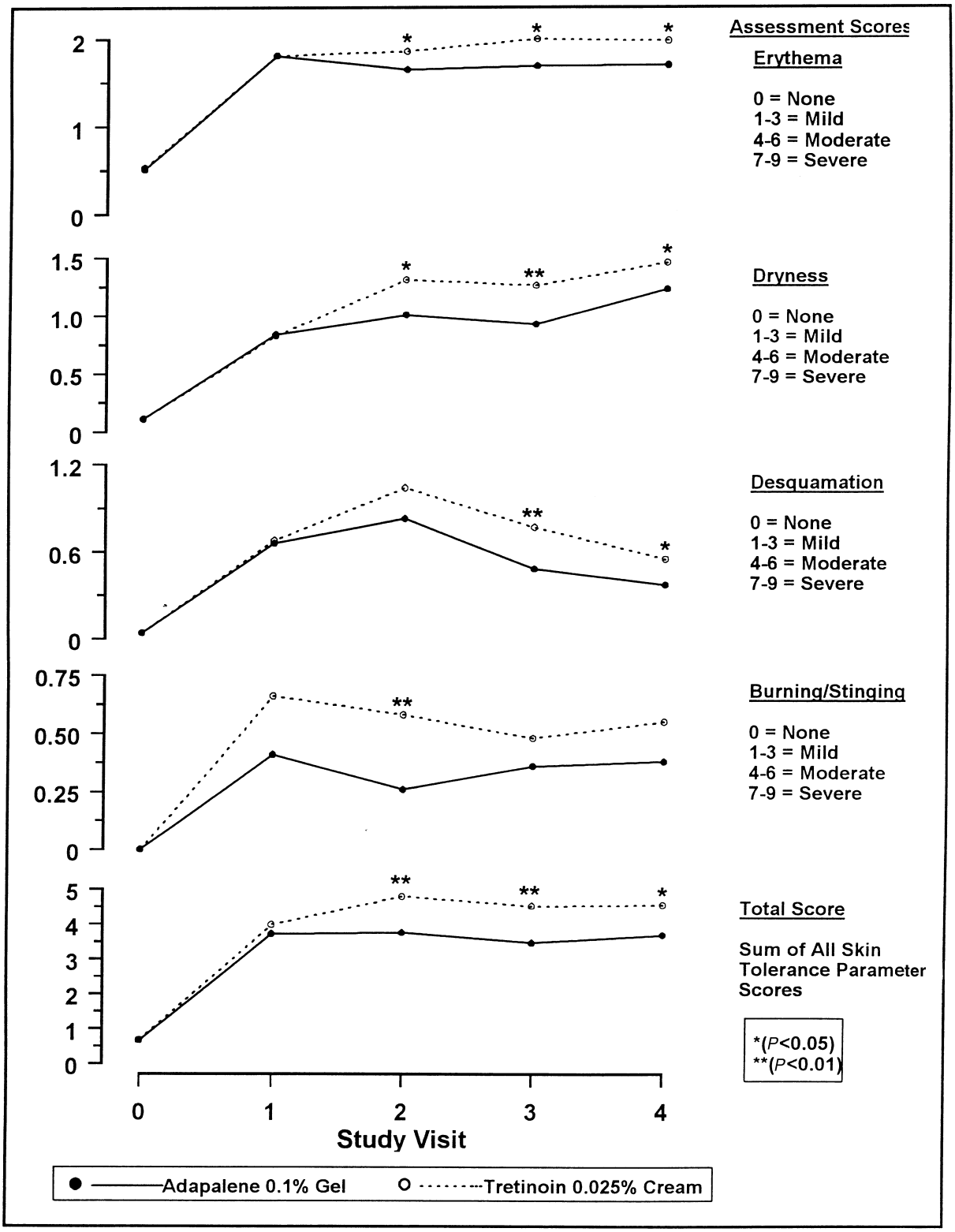

Figure 3. Mean scores of skin irritation parameters over the duration of treatment

patients, making it a more tolerable treatment for patients than tretinoin 0·025% cream. At the end of the study the majority of patients perceived that, compared to tretinoin 0·025% cream, the gel formulation of adapalene spread more easily (81% of patients), was absorbed more quickly (57%), smelled better (77%), felt better (74%) and was less greasy to the feel (61%). Overall, adapalene 0·1% gel was preferred by 65% of patients.

After the first week of treatment, compared to tretinoin 0·025% cream, adapalene 0·1% gel consistently gave less skin irritation, in terms of causing erythema, dryness, desquamation and stinging/burning over the remaining three weeks of treatment. An overall assessment of these skin irritation parameters (the sum of scores for each parameter) showed that adapalene 0·1% gel was statistically superior to tretinoin 0·025% cream at visits 2, 3 and 4. This overall assessment score (which reflected the investigators' assessments) agreed with the subjective choices for tolerance made by the patients.

Adverse events, all mild to moderate in intensity, occurred in 32 patients. Three episodes (two of skin dryness; one of skin discomfort) were considered related to the study drugs. One patient stopped study medications because of skin dryness. No other patients discontinued study drugs because of adverse events.

In conclusion, this study showed that a majority of patients preferred and tolerated adapalene 0·1% gel over tretinoin 0·025% cream and that it caused significantly less skin irritation. These results confirm the very good tolerance of adapalene that has already been shown by other studies. These results make adapalene 0·1% gel the treatment of choice for patients with acne vulgaris.

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