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Evaluation of clinical efficacy and safety of adapalene 0·1% gel versus tretinoin 0·025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life

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Summary A randomized, multicentre, investigator-masked study was conducted in 105 patients with mild to moderate acne vulgaris to compare the efficacy and safety of adapalene 0·1% gel with tretinoin 0·025% gel after three months of treatment, with particular emphasis on reduction in inflammatory lesion counts after one week of treatment and impact on quality of life.

In terms of efficacy, adapalene gel was found to be superior to tretinoin gel after one week of treatment, with respect to reduction in inflammatory lesion counts (32% vs. 17%, respectively; $P = 0{\cdot}001$), total lesion counts (28% vs. 22%, respectively; $P = 0{\cdot}042$) and global severity grade (28% vs. 16%, respectively; $P = 0{\cdot}001$). No significant difference between the two treatments was found after 12 weeks of treatment for any of these variables. Evaluation of facial skin tolerance parameters showed significant differences between the two treatments in favour of adapalene for dryness, erythema, immediate and persistent burning and pruritus for at least one time point. One patient in the adapalene group and three patients in the tretinoin group experienced medical events which lead to discontinuation of treatment (skin irritation; NS). Quality of life scores improved more rapidly in the adapalene group than in the tretinoin group, with significant differences ($P < 0{\cdot}05$) appearing at week 1 for questions related to problems with partners, close friends or relatives and to skin symptoms. There was also a significantly greater improvement in social and leisure activity in the adapalene group at week 12.

Adapalene 0·1% gel reduced inflammatory and total lesion counts more rapidly than tretinoin 0·025% gel, and was also better tolerated. These differences appear to result in an earlier and greater quality of life improvement for the patients receiving adapalene.

Adapalene gel is a naphthoic acid derivative with retinoid receptor agonist properties which has been developed by the Centre International de Recherches Dermatologiques (CIRD) of Galderma Laboratories as a topical treatment for acne.[1] When tested in biochemical and pharmacological assays, adapalene has been clearly shown to modulate keratinization and to possess a broad anti-inflammatory activity.[1]

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Results from clinical trials have confirmed these properties of adapalene in over 1000 patients. These studies have shown that adapalene, in a gel or solution formulation, is effective in reducing both inflammatory and non-inflammatory acne lesions, and that it has an acceptable level of safety.[1–3]

Several clinical studies have proven that adapalene 0·1% gel is at least as effective as tretinoin 0·025% gel after 3 months of treatment, and is better tolerated by the patients.[4–6] In two of these studies, it appeared that

adapalene reduced the inflammatory lesion count more rapidly than tretinoin.[5,6]

This study was therefore designed to compare the onset of action of adapalene 0·1% gel to that of tretinoin 0·025% gel by assessing the reduction in inflammatory acne lesion count after one week of treatment. The secondary objectives were to compare the clinical efficacy and safety of the two products after 3 months of treatment, and to determine their effects on quality of life measurements.

Patients and methods

The study was designed as a multicentre, randomized, investigator-masked study, with a parallel group comparison of adapalene 0·1% gel and tretinoin 0·025% gel. Treatments were to be applied once daily, in the evening, for a period of 12 weeks. Patients were scheduled for four visits: a baseline visit followed by three visits 1, 4 and 12 weeks after the start of the treatment. At each follow-up visit, the patient's response to the treatment was assessed.

Patient selection

Each patient had to meet the following requirements in order to be included in the study: male or female, aged 12–30, with mild to moderate acne vulgaris (grade 1–5 on the Burke and Cunliffe scale[7]); at least 20 facial non-inflammatory lesions (open and closed comedones) *and* at least 10 facial inflammatory lesions (papules, pustules and nodulocystic lesions), with a maximum of three nodulocystic lesions.

Patients were excluded from the study for one or more of the following reasons: acne conglobata, acne fulminans or secondary acne (chloracne, drug induced acne, etc.); underlying diseases or other dermatological conditions that required the use of interfering topical or systemic therapy; topical acne or anti-inflammatory treatment within the previous 2 weeks; systemic anti-inflammatory or antibiotic treatment within the past 4 weeks (excluding penicillins); systemic retinoid treatment within the past 6 months or other systemic anti-acne treatment within the past 4 weeks.

All patients signed an informed consent form (parents in the case of minors).

Treatment

Adapalene 0·1% gel was manufactured by Galderma Laboratories. Tretinoin 0·025% (Retin A® gel, Ortho Laboratories) was purchased commercially and relabelled for use in this study. The two test materials were labelled in an identical fashion, although the gels differ in appearance.

The selected patients were randomly assigned to receive either adapalene gel or tretinoin gel according to their order of entry to the study in each centre, in accordance with a computer-generated code. In order to maintain the investigator-masked procedure, the medications were dispensed and collected by a third party (usually the hospital pharmacist).

Patients were instructed to apply a thin layer of the gel to the face (as well as back and chest when appropriate), once daily in the evening, 15 min after washing and 1 h before retiring. The patients were additionally instructed to avoid exposure to the sun, to avoid the use of cosmetics other than eye and lip make-up (women) and after-shave products or colognes (men). Patient compliance was determined by weighing the returned tubes and by recording the number of missed applications as reported by the patients.

Study evaluations

Efficacy evaluations were carried out at baseline and at each scheduled visit by counting each type of facial lesion and evaluating global severity according to the Leeds technique (Burke and Cunliffe[7]). Global assessment of improvement was evaluated for face, chest and back (when affected) at week 12 in comparison with the baseline, using a 4 point scale:–1 = worsened (exacerbation in the quantitative assessment of lesions; 0 = unchanged (acne shows no changes); 1 = improved (improvement in the quantitative assessment of lesions); 2 = clear (no lesions).

A safety evaluation was carried-out at each scheduled visit, with scoring of the following parameters on a 0–3 scale (absent, mild, moderate, severe): erythema, scaling, dryness, burning and pruritus. Burning and pruritus were each scored separately for symptoms occurring immediately after application of the products, and for those persisting beyond 5 min after application. In addition, all reported adverse events were noted on an ongoing basis.

For the Dermatology Life Quality Index (DLQI), patients completed a quality of life questionnaire at weeks 0, 1 and 12. The questionnaire used was that developed by Finlay *et al.*[8] which can be used for all dermatological conditions. It comprises 10 simple questions including items related to the interference of skin with social interactions, daily activities and self

perception. For the French and Spanish centres, the local language versions of the questionnaire were verified after back-translation into English by parties not involved in the original forward translations.

Study design and statistical methodology

The test was designed to compare two parallel groups (105 patients in total). Within each of the four centres, patients were assigned to one of the two treatment groups using a randomization procedure by blocks of 10, thereby ensuring that treatments were balanced every 10 consecutive patients. Random numbers were generated by the RANUNI routine (SAS; Statistical Analysis System, Inc., N.C. USA). This sample is sufficient to detect a 20% difference in the reduction of inflammatory lesions with 87% power.

The square roots of primary lesion counts were submitted to a parametric analysis of covariance (ANOVA). The square root transformation is often employed to normalize count data having a Poisson distribution. The GLM procedure from SAS was used to test overall treatment differences. A confirmatory non-parametric analysis of primary lesion counts was performed on percentage reductions from baseline, using a generalization of the Mann–Whitney rank test. The Cochran Mantel Haenszel (CMH) test was performed to compare treatments, with centres as strata and the ridit transformation (FREQ procedure from SAS). This last transformation has the advantage of assigning an appropriate weight to each centre, while the rank score would assign too much weight to large centres.

Global severity grade was analysed for percentage reduction from baseline only.

Results

One hundred and five patients were enrolled in the study (52 in the adapalene gel group and 53 in the tretinoin gel group). A summary of patient information is presented in Table 1. All patients enrolled in the study were retained for the intention to treat (ITT) analysis and 94 patients (48 in the adapalene gel group and 46 in the tretinoin gel group) were eligible for inclusion in the per-protocol efficacy analysis. There were no significant differences at baseline in disease severity parameters between the two groups.

Efficacy results – lesion counts

Figure 1 shows the efficacy results of both treatments in terms of percentage reduction in inflammatory lesion counts, according to the per-protocol analysis. Both treatment groups showed reductions in inflammatory lesions from baseline to week 1, but the decrease was significantly greater for patients treated with adapalene (33%) than for those treated with tretinoin (16%; $P = 0{\cdot}001$). Using the Kligman scale[9] for the first week results, 70% of adapalene patients showed a fair, good or excellent response ($> 25\%$ reduction from baseline) vs. 35% of tretinoin patients. In patients with papules or pustules, the percentage with fair, good or excellent response at week 1 was significantly greater in the adapalene group than in the tretinoin group (for papules, 62% in the adapalene group vs. 37% in the tretinoin group, and in the case of pustules, 67% in the adapalene group vs. 39% in the tretinoin group): $P < 0{\cdot}01$ and $P < 0{\cdot}05$, respectively.

Both treatment groups showed further reductions in inflammatory lesions from baseline at each subsequent

Table 1 Baseline patient characteristics

	Adapalene 0·1% gel	Tretinoin 0·025% gel
Enrolled	52	53
Sex (Males/Females)	33/19	33/20
Mean age (range)	21 (12–29)	20 (12–30)
Discontinued		
For medical reasons (skin irritation)	1	3
For non-medical reasons (protocol violations, lost to follow-up, etc.)	6	3
Completed study	45	47
Evaluable for efficacy	48	46
Evaluable for safety	52	53
Lesion counts (Mean ± SD):		
Inflammatory	25·8 ± 15·8	23·2 ± 14·4
Non-Inflammatory	42·5 ± 22·9	51·6 ± 32·5
Severity Grade (Mean ± SD):	1·7 ± 0·6	1·7 ± 0·7

evaluation time (4 and 12 weeks); however, there was no significant difference in the lesion counts between the two treatment groups at weeks 4 and 12 (Fig. 1). The ITT analyses at week 1 and endpoint (last available data up to week 12) showed similar results as the per-protocol analysis.

In the case of non-inflammatory lesions, both treatment groups showed reductions in the number of lesions from baseline at each subsequent evaluation time. No significant difference between treatments was found for percentage reductions from baseline either by ITT analysis or by per-protocol analysis (Fig. 2).

Total lesion counts reflected the trend seen for inflammatory lesions. Both groups showed reductions in lesions from baseline at each subsequent evaluation time up to and including week 12. At week 1, a significant difference ($P < 0{\cdot}01$) was found for total lesions in favour of adapalene (31% reduction vs. 22% reduction for tretinoin). There was no significant difference between the two treatments at other evaluation times. The intention-to-treat (ITT) analysis at week 1 and at endpoint showed similar results to the per-protocol analysis.

Efficacy results – severity grade

When the efficacy was determined from the Global Severity Grade (Table 2), the same trend was observed

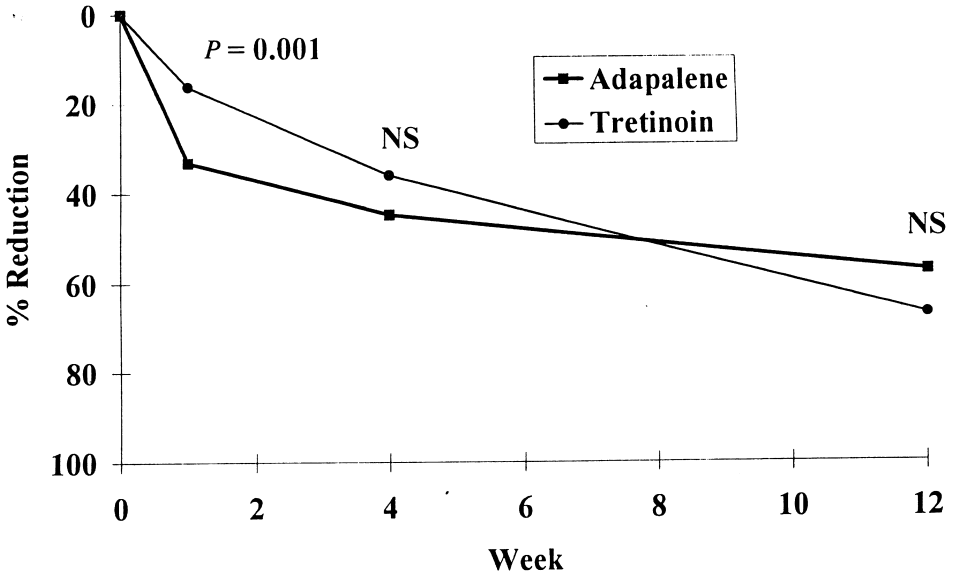

Figure 1. Percentage reduction from baseline in inflammatory lesion counts for adapalene 0·1% gel and tretinoin 0·025% gel at each visit (per-protocol population).

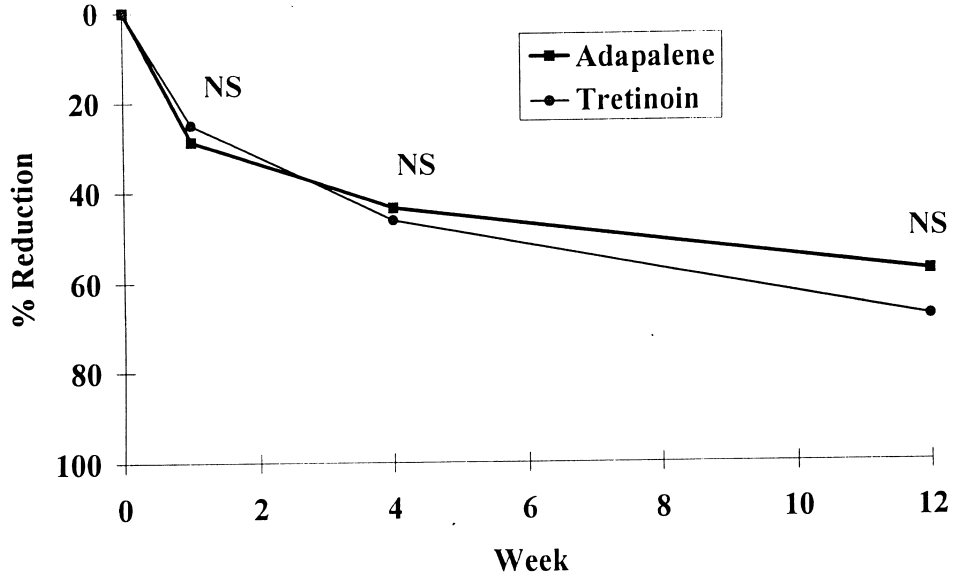

Figure 2. Percentage reduction from baseline in non-inflammatory lesion counts for adapalene 0·1% gel and tretinoin 0·025% gel at each visit (per-protocol population).

Table 2 Global severity grade (Burke and Cunliffe scale[7])

		Adapalene		Tretinoin		
Grade		*N*	Mean ± SD	*N*	Mean ± SD	*P*-value
Per-protocol analysis						
Week 0	Grade	48	1·7 ± 0·6	46	1·7 ± 0·7	—
Week 1	Grade	47	1·2 ± 0·5	46	1·4 ± 0·7	—
	% reduction from baseline	47	29·8 ± 21·9	46	16·7 ± 27·1	< 0·001
Week 4	Grade	47	1·0 ± 0·7	43	1·1 ± 0·7	—
	% reduction from baseline	47	42·3 ± 36·4	43	34·1 ± 36·7	NS
Week 12	Grade	43	0·7 ± 0·6	39	0·5 ± 0·4	—
	% reduction from baseline	43	56·3 ± 36·1	39	72·4 ± 21·2	NS
Intention to treat analysis						
Baseline (ITT)	Grade	52	1·7 ± 0·6	53	1·7 ± 0·8	—
Week 1 (ITT)	Grade	52	1·2 ± 0·5	53	1·4 ± 0·7	—
	% reduction from baseline	52	28·3 ± 21·9	53	15·7 ± 26·3	< 0·001
Endpoint (ITT)	Grade	52	0·8 ± 0·6	53	0· 7 ± 0·6	—
	% reduction from baseline	52	51·1 ± 36·6	53	62·2 ± 31·3	NS

as in the case of inflammatory and total lesions. Both groups had similar mean global assessment scores at baseline. The scores of both groups decreased from baseline to week 12, but significantly more rapidly in the adapalene group compared to the tretinoin group: 30% vs. 17% reduction at week 1 ($P < 0·001$).

Efficacy results – global assessment of improvement

The distribution of patients across levels of improvement for the face was not significantly different between the two groups at endpoint (week 12): over 90% were rated as improved or clear for both treatments. For patients presenting lesions on the back and chest, the majority were also rated as improved or clear for both adapalene and tretinoin, with no significant difference between treatments.

Safety results

Signs and symptoms of skin irritation (erythema, dryness, scaling, burning and pruritus) were most noticeable during the first week of the study, then declined in frequency and intensity. Each parameter was significantly more intense ($P < 0·05$) in the tretinoin group than in the adapalene group for at least one time point over the treatment period, except scaling for which there was a trend in favour of adapalene ($P = 0·07$) at week 4. Dryness, persistent facial burning and immediate facial pruritus were significantly milder in the adapalene group at week 1. Erythema was significantly lower in the adapalene group at week 4. Persistent pruritus was significantly lower in the adapalene group at week 12. Immediate facial burning was significantly lower in the adapalene treated patients at each visit. Figure 3 shows the percentage of patients with scores of moderate to severe intensity at any time during the study (''worst score'' analysis).

In addition to the above scheduled evaluations, one patient in the adapalene group and three patients in the tretinoin group reported skin irritation which was severe enough to lead to their discontinuation from the study.

Dermatology Life Quality Index

For both treatment groups, there was a significant improvement in DLQI indices by week 12 ($P < 0·05$), both for the total score and for a number of individual items which contributed the most to the initial impairment in quality of life in these patients (Table 3). On examining the responses to individual questions, scores were significantly lower in the adapalene group than the tretinoin group at week 1 for items related to problems with close contacts and skin symptoms, and at week 12 for social interactions and skin symptoms. The differences in favour of adapalene in total score at week 1 and week 12 showed only a non-significant

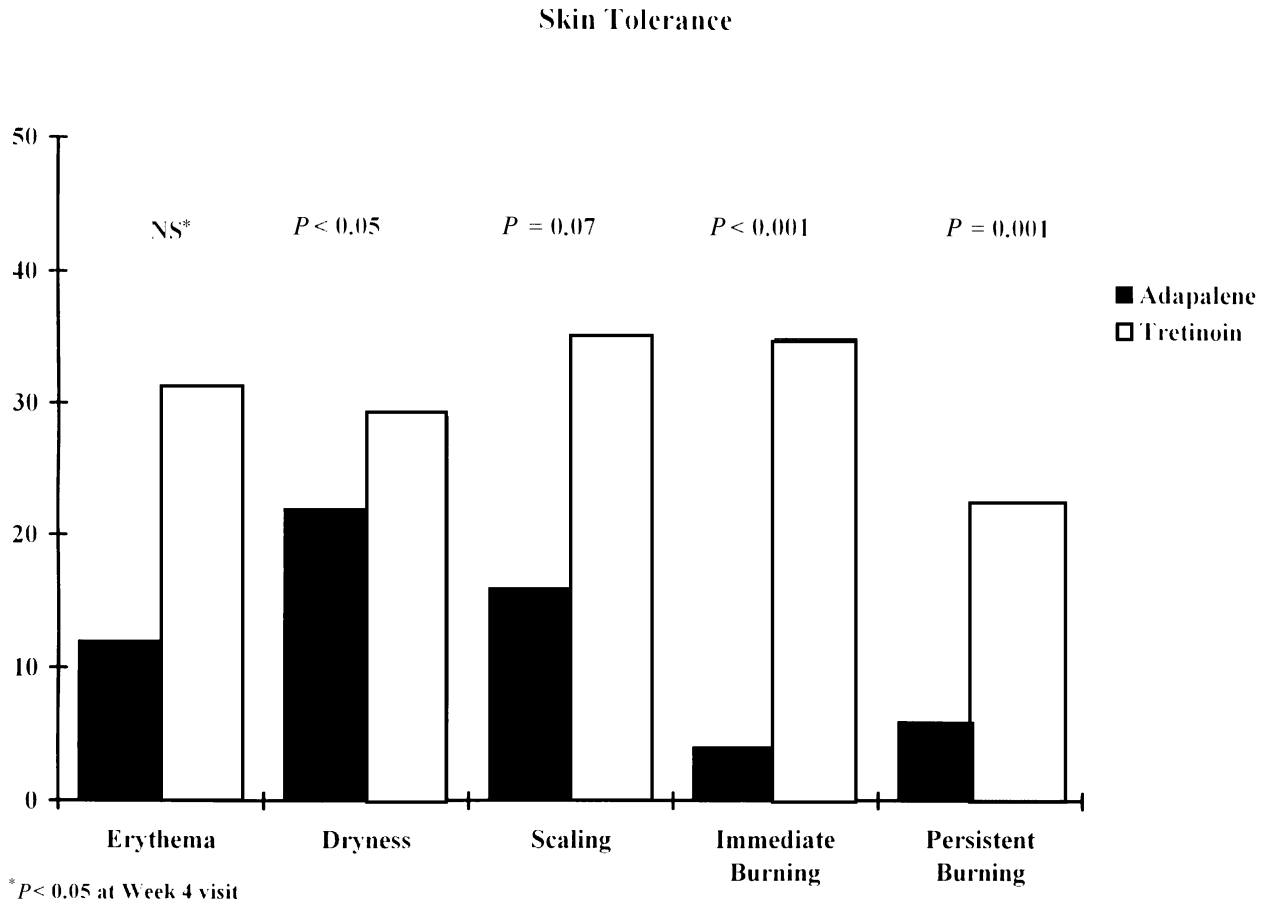

Figure 3. Percentage of patients with scores corresponding to moderate or severe intensity of signs and symptoms of skin irritation for adapalene 0·1% gel and tretinoin 0·025% gel (all patients with available data).

trend in statistical terms, although the analysis is difficult to interpret because of a difference in baseline scores and high intersubject variability.

Discussion

In several previous studies comparing adapalene 0·1% gel to tretinoin gel, there was evidence of a more rapid onset of action of adapalene in acne patients, as manifested by trends towards greater reduction in inflammatory lesion counts after 1, 2 or 4 weeks of treatment.[5,6] The present study was specifically designed to address this issue, and indeed confirmed these earlier observations. In this study, adapalene 0·1% gel showed superior efficacy in terms of a reduction of inflammatory lesion count after one week of treatment, when compared to tretinoin 0·025% gel. This difference is highly significant ($P = 0·001$) and clinically relevant, as illustrated by the number of patients who demonstrated at least a 25% reduction in lesion count: 70% for adapalene compared to 35% for patients in the tretinoin treatment group. This difference was also found for total lesion count and for the global severity grade.

A possible explanation for the more rapid effect of adapalene may be its intrinsic anti-inflammatory activity, possibly mediated by inhibition of the lipo-oxygenase pathway.[10] Alternatively, its lower irritant potential may lead to less of the early inflammatory ''flares'' which are known to occur with tretinoin therapy.

Indeed, in terms of skin irritation, as shown in previous studies,[3–6] adapalene 0·1% gel was significantly better tolerated than tretinoin 0·025% gel as regards most of the parameters studied.

The differences in efficacy and tolerance between the two treatments are reflected in the patients' opinion of the impact of the disease and its treatment on their

Table 3 Dermatology Life Quality Index Results (Mean ± SD)

Treatment	Adapalene			Tretinoin		
Item	Week 0	Week 1	Week 12	Week 0	Week 1	Week 12
Q. 1: Skin itchiness, soreness, painfulness or stinging?	0·69 ± 0·56	0·68[a] ± 0·64	0·41[a] ± 0·65	0·83 ± 0·76	1·11[a,b] ± 0·88	0·65[a] ± 0·61
Q. 2: Embarrassment or self-consciousness because of skin?	1·09 ± 0·76	0·84 ± 0·64	0·57[bb] ± 0·81	1·17 ± 0·70	1·13 ± 0·92	0·63[bb] ± 0·66
Q. 3: Skin affected shopping, or looking after home or garden?	0·44 ± 0·66	0·25 ± 0·53	0·11[bb] ± 0·31	0·47 ± 0·75	0·47 ± 0·94	0·21[b] ± 0·60
Q. 5: Skin affected social and leisure activities?	0·58 ± 0·84	0·45 0·73	0·26[a,b] ± 0·57	0·74 ± 0·77	0·51 ± 0·76	0·53[a] ± 0·74
Q. 8: Skin created problems with partner, close friends or relatives?	0·40 ± 0·54	0·20[a] 0·46	0·22 ± 0·51	0·62 ± 0·80	0·53[a] ± 0·73	0·33 ± 0·61
Subtotal of remaining questions (4, 6, 7, 9, 10).	0·75 —	0·68 —	0·57 —	1·30 —	1·34 —	1·00 —
Total score	3·95[a] ± 3·32	3·10 ± 2·99	2·14[b] ± 3·02	5·13[a] ± 3·42	5·09 ± 5·11	3·35[b] ± 4·39

[a] = $P < 0{\cdot}05$ for comparison adapalene vs. tretinoin; [b] = $P < 0{\cdot}05$, [bb] = $P < 0{\cdot}01$ for change from baseline.
Note: a high score reflects a greater impairment in quality of life.

quality of life, as assessed here by the DLQI questionnaire. Several of the items which contribute most to the impairment in quality of life in this population (mostly related to problems with interpersonal relationships) decreased to a greater extent at week 1 in patients using adapalene than in the patients using tretinoin.

In two previous studies using the DLQI in acne, the mean score in patients with acne of sufficient severity to start isotretinoin[11] was 7·5 and the mean score in patients with mild to moderate acne[12] was 5·6. The subjects in this study had a mean score of 4·6, compatible with this group of patients being appropiate for topical therapy. An important finding from this study is that the differences between the two treatment groups which were detected by classical methods of clinical investigation (i.e. lesion counts and symptom scores), were confirmed to have a significant impact on quality of life parameters which could be measured by this relatively simple and easy-to-use instrument.

Overall, the more rapid onset of action of adapalene on inflammatory lesions (i.e. those which are most visible for the patient), together with the lower intensity of symptoms and signs of skin irritation, should lead to increased patient satisfaction with the treatment over the critical early stages of therapy. This is important not just for the patient's quality of life (as demonstrated by the DLQI results), but should also help in maintaining compliance in this patient population who are particularly prone to discontinue any treatment which does not appear to be leading to a speedy resolution of their condition.

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