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Therapeutics

Topical adapalene gel 0·1% vs. isotretinoin gel 0·05% in the treatment of acne vulgaris: a randomized open-label clinical trial

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Summary

Background Topical application of isotretinoin and adapalene has proved effective in treating acne vulgaris. Both drugs demonstrate therapeutic advantages and less irritancy over tretinoin, the most widely used treatment for acne. They both act as retinoid agonists, but differ in their affinity profile for nuclear and cytosolic retinoic acid receptors.

Objectives To compare the efficacy and tolerability of adapalene gel 0·1% and isotretinoin gel 0·05% in the treatment of acne vulgaris of the face, in a randomized open-label clinical trial.

Methods Eighty patients were enrolled and were instructed to apply adapalene gel 0·1% or isotretinoin gel 0·05% once daily over a 12-week treatment period. Efficacy determination included noninflammatory and inflammatory lesion counts by the investigator and global evaluation of improvement. Cutaneous tolerance was assessed by determining erythema, scaling and burning with pruritus.

Results Adapalene and isotretinoin gels were highly effective in treating facial acne. Adapalene gel produced greater reductions in noninflammatory and inflammatory lesion counts than did isotretinoin gel, but differences between treatments were not statistically significant. Adapalene gel was significantly better tolerated than isotretinoin gel during the whole treatment period.

Conclusions The two gels studied demonstrated comparable efficacy. When adapalene and isotretinoin were compared, significantly lower skin irritation was noted with adapalene, indicating that adapalene may begin a new era of treatment with low-irritant retinoids.

Key words: acne, adapalene, isotretinoin, treatment

Topical isotretinoin and adapalene have proved effective in treating acne vulgaris. Isotretinoin, the *cis*-isomer of retinoic acid, has been used for many years in the treatment of acne.[1] Adapalene, a newer naphthoic acid retinoid, has also shown good efficacy and is well tolerated.[2] Both drugs demonstrate therapeutic advantages and less irritancy over tretinoin, the most widely used treatment for acne.[3,4] They both act as retinoid agonists, but differ in their affinity profile for nuclear and cytosolic retinoic acid receptors (RARs). Whereas isotretinoin acts primarily through its isomerization to retinoic acid and binds to all RARs (α, β and γ), adapalene has selective affinity to RAR-β and RAR-γ. Additionally, adapalene is very stable and has a considerable anti-inflammatory activity.[5,6]

This randomized, open-label clinical trial was conducted to compare the efficacy and tolerability of adapalene 0·1% gel and isotretinoin 0·05% gel in patients with facial acne vulgaris.

Patients and methods

Eighty patients were enrolled in this study: 44 women and 36 men, age range 15–35 years. To be included, patients had to present with 15–80 facial noninflammatory lesions (open and closed comedones), 10–50 inflammatory lesions (papules and pustules) and no more than three nodulocystic lesions. No other

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cutaneous disease could be present on the face. Patients were not to have used any other topical treatment for 14 days, systemic antibiotics for 30 days, or systemic retinoids for at least 6 months prior to initiation of treatment. Women had not to be pregnant or lactating, and to have discontinued oral contraception at least 3 months before entering the study. A pregnancy test was performed prior to admission, at each follow-up visit and 1 month after the last dose of study medication in those women who were sexually active during the above period.

Patients were randomly assigned to treatment with adapalene gel 0·1% or isotretinoin gel 0·05% using a program that allocated every consecutive group of four patients to two patients in each group. The random numbers were generated by a computer and assigned to the patients by the investigator's assistant. The same assistant enrolled the patients and assigned treatments, while the assessment of efficacy was performed by the investigators, who attempted to make the assessments investigator-independent.

Patients were instructed to apply a thin layer of the study products to the entire face once daily at bedtime during the 12-week treatment period. Efficacy and cutaneous tolerance were assessed five times over the trial period, at baseline and weeks 2, 4, 8 and 12. Efficacy was evaluated by counting the changes in the numbers of facial noninflammatory lesions and inflammatory lesions by the investigator at each follow-up visit. Efficacy determination also included global evaluation of improvement. At each patient's final visit the investigator had to decide whether or not the patient's acne condition had improved. Response was graded as excellent (76–100% reduction of lesions), good (51–75% reduction), fair (26–50% reduction) or poor (< 25% reduction). Cutaneous tolerance was assessed by determining erythema, scaling and burning with pruritus. All cutaneous tolerance evaluations were graded on a 0–3 scale: 0, none; 1, mild; 2, moderate; 3, severe.

Statistical analysis was performed using the Friedman two-way analysis of variance by ranks to test whether the values for one treatment at the five time-points (baseline and weeks 2, 4, 8 and 12) were different. In the case of multiple comparisons, as in our study, the α-level was adjusted according to the Bonferroni adjustment. To compare the treatments at each of the five time-points the Wilcoxon–Mann–Whitney test was used. For the evaluation of tolerance the χ^2 test for homogeneity in a contingency table was performed for each type of irritation and for each time-point.

Results

Sixty-seven patients completed the study, 36 in the adapalene group and 31 in the isotretinoin group. Of the 13 patients who discontinued, five left for acne flare, three in the adapalene and two in the isotretinoin group, one for varicella and one for influenza, and six were lost to follow-up (Fig. 1). The demographic characteristics were similar for the two groups.

The mean baseline lesion count did not differ significantly between the two treatment groups. The mean number of noninflammatory lesions was 88·1 in the adapalene and 86·9 in the isotretinoin treatment groups (Fig. 2), whereas the mean numbers of inflammatory lesions were 19·6 and 20·8 in the two groups, respectively (Fig. 3). For the statistical analysis, with a sample of 36 patients for the adapalene group and 31 patients for the isotretinoin group and a probability level of $\alpha = 0{\cdot}05$, there would be an 80% power to detect a difference of 1·76 in the case of inflammatory lesions and a difference of 3·32 in the case of noninflammatory lesions.

There was a gradual reduction in the counts of noninflamed and inflamed lesions in both treatment groups. At all time-points the reduction in counts within each group was statistically significant from

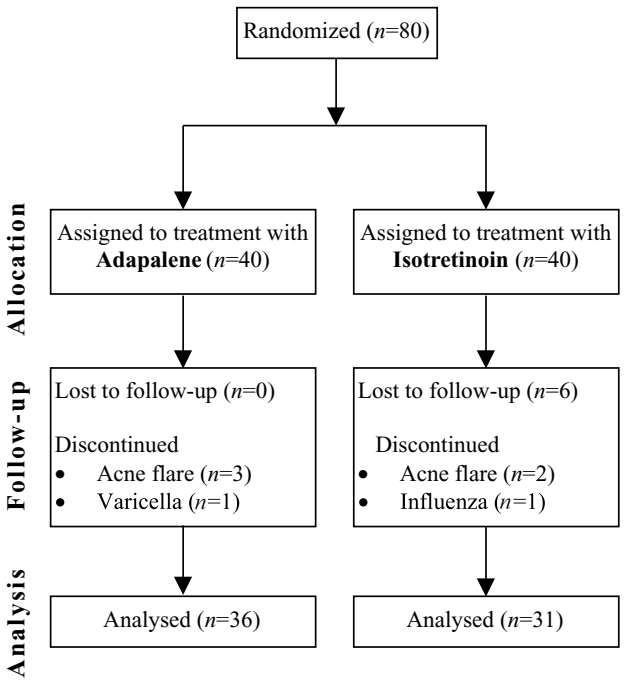

Figure 1. Flow diagram of the number of patients included in the statistical analysis.

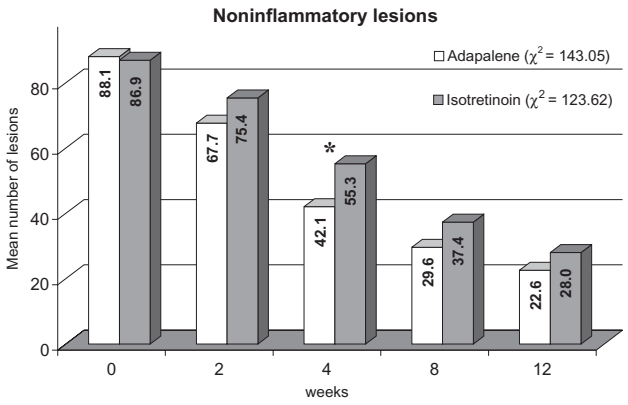

Figure 2. Mean noninflammatory lesion count. There was a statistically significant reduction in the lesion count as compared with the baseline values for both drugs at the $\alpha = 0{\cdot}05$ level ($\chi_4^2 > 13{\cdot}28$, Friedman test with Bonferonni adjustment). Between the two drugs, the difference in reduction was statistically significant only at week 4 of treatment (marked with an asterisk, Mann–Whitney test).

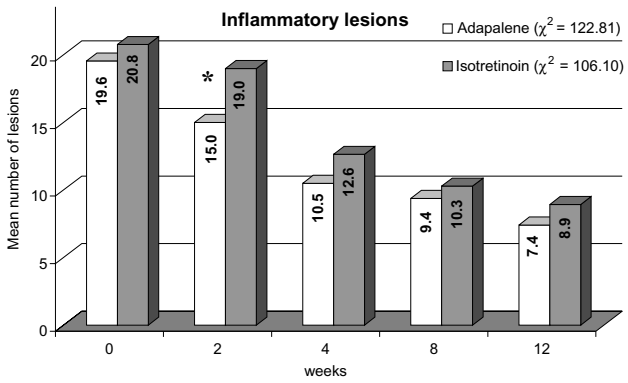

Figure 3. Mean inflammatory lesion count. There was a statistically significant reduction in the lesion count as compared with the baseline values for both drugs at the $\alpha = 0{\cdot}05$ level ($\chi_4^2 > 13{\cdot}28$, Friedman test with Bonferonni adjustment). Between the two drugs, the difference in reduction was statistically significant only at week 2 of treatment (marked with an asterisk, Mann–Whitney test).

baseline using the Friedman two-way analysis of variance by ranks. Adapalene gel produced greater reductions in noninflammatory and inflammatory lesion counts than isotretinoin gel at all follow-up visits. The difference in reduction was statistically significant between the two treatments using the Wilcoxon–Mann–Whitney test at week 4 for the noninflammatory lesions, and at week 2 for the inflammatory lesion counts. In both cases, there was no statistical difference at the end of the study treatment period.

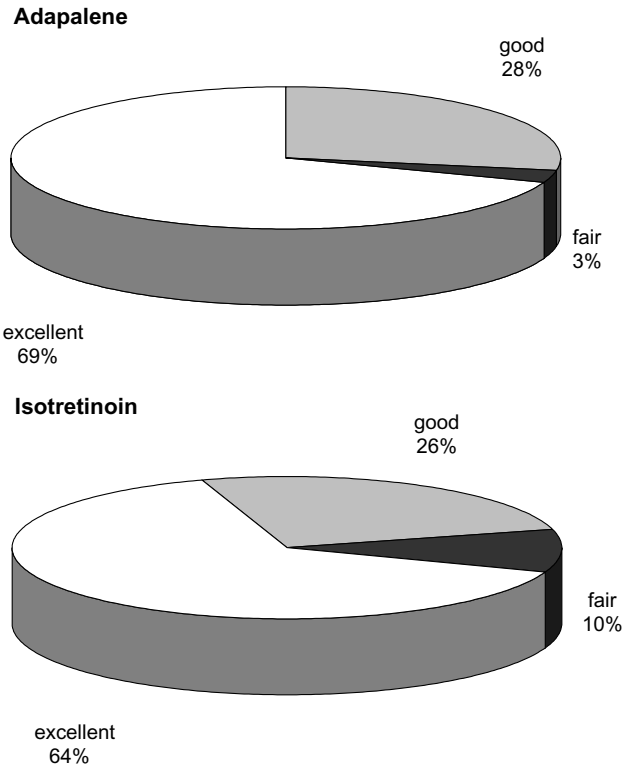

Figure 4. End results with both types of treatment.

The global evaluation of improvement resulted in similar figures for the two groups. The improvement was excellent in 25 patients (69%) using adapalene gel and 20 (64%) using isotretinoin gel, good in 10 (28%) and eight (26%), and fair in one (3%) and three (10%) patients, respectively (Fig. 4).

Irritation was generally mild for both treatments, and no discontinuation was reported because of adverse events. The number of patients who had erythema, scaling and burning with pruritus steadily decreased from week 2 to week 12, at which point a significantly lower number of patients was observed with adapalene than with isotretinoin for all tolerance features using the c^2 test. In the case of scaling the significant difference started from week 4 (Fig. 5). No dosage regimen alteration was required during the study period and no systemic effects were observed with either of the products tested.

Discussion

The results of this study indicate that adapalene and isotretinoin gels were highly effective in treating facial acne. Adapalene gel produced greater reductions in

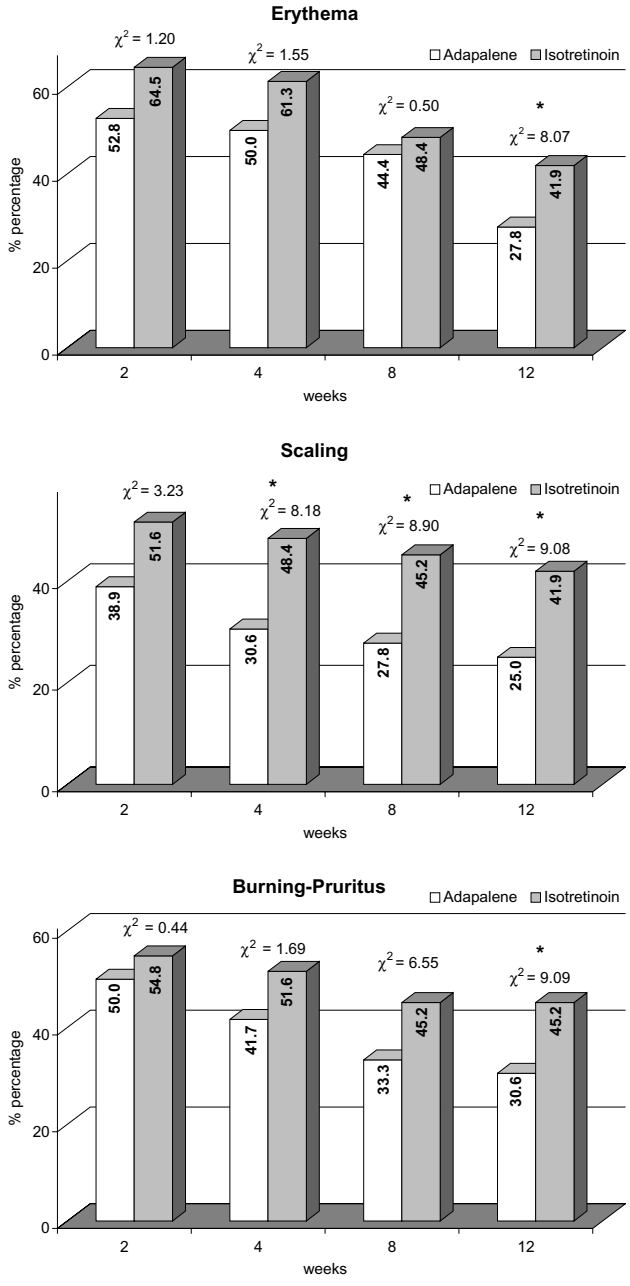

Figure 5. Mean percentage of patients at each visit experiencing erythema, scaling and burning with pruritus, graded at least as mild. Adapalene produced significantly less irritation than isotretinoin at the $\alpha = 0{\cdot}05$ level, when χ^2 (found by performing a χ^2 test for homogeneity in a contingency table) $> \chi_3{}^2 = 7{\cdot}81$ (marked with an asterisk).

noninflammatory and inflammatory lesion counts than isotretinoin gel, during the 12-week period of once-daily application. The differences in reduction between treatments were not significant at the end of the study. Adapalene gel was significantly better tolerated than isotretinoin gel during the whole treatment period.

Topical isotretinoin has proved effective in the treatment of acne. In a study of 268 patients, topical application of 0·05% isotretinoin gel significantly improved inflammatory lesions within 5 weeks and noninflammatory lesions within 8 weeks.[1] Similar results were obtained in our study, after 12 weeks of once-daily topical application. Isotretinoin has been also used with success in combination with erythromycin.[7] To gain acceptance and usage, newer topical retinoids must demonstrate therapeutic advantages and less irritancy over retinoic acid. Few reports have compared the effectiveness of topical isotretinoin with that of retinoic acid.[3,8] Both drugs demonstrated the same degree of efficacy in treating acne, however, a much lower incidence and intensity of adverse events was reported with isotretinoin than with retinoic acid.

Adapalene is a synthetic retinoid that can affect keratinization and differentiation of epithelial tissue like all-*trans* retinoic acid, but offers the advantage of increased chemical and light stability, and high lipophilicity.[5] Adapalene also has anti-inflammatory activity. It has low flux through the skin and is maintained at high concentrations in the stratum corneum and hair follicles, which may enhance its effectiveness in treating acne.[9] In a number of studies adapalene appeared to be at least as effective as tretinoin 0·025% in the treatment of acne.[4,10,11] In one study adapalene performed significantly better in reducing noninflammatory and total lesion counts,[4] while in another study both types of lesions tended to decrease more rapidly with adapalene than with tretinoin.[10] In all cases, however, adapalene was much better tolerated than tretinoin and significant differences favouring adapalene were obtained in most of the tolerance and safety features investigated.

Our study is the first clinical trial to compare the effectiveness and tolerance of adapalene and isotretinoin in the treatment of acne. Both lesion counts and global assessment showed a better degree of efficacy with adapalene than with isotretinoin, although the difference between the two drugs was not significant. The greatest disadvantage of topical retinoid treatment for acne has been accompanying skin irritation. In various clinical trials involving tretinoin treatment, up to 90% of patients reported different degrees of skin discomfort.[12] Although isotretinoin is less irritating than tretinoin, almost 50% of isotretinoin patients experienced some degree of erythema, scaling and burning with pruritus.[1,3,8] When adapalene and

isotretinoin were compared, significantly lower mean scores were obtained with adapalene for these features, indicating that adapalene may begin a new era of treatment with low-irritant retinoids.

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