
Assessment of adapalene gel for the treatment of actinic keratoses and lentigines: A randomized trial

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Background: Adapalene is a synthetic retinoid with an established clinical efficacy against acne and good local tolerability. Its effectiveness in the treatment of photodamaged skin has not been studied.

Objective: We sought to determine the safety and efficacy of adapalene gel in the treatment of actinic keratoses and solar lentigines.

Methods: In a prospective, 2-center, randomized, controlled, investigator-masked, parallel-group study, 90 patients with actinic keratoses and solar lentigines were treated daily with either adapalene gel (0.1% or 0.3%) or its vehicle gel for 4 weeks, followed by twice-daily applications, if tolerated, for up to 9 months.

Results: Of the 90 Caucasian patients (69 male, 21 female; mean age 63.1 years) who were enrolled into the study, 83 patients completed 9 months of treatment. With adapalene gel 0.1% and 0.3%, the mean number of actinic keratoses was reduced by 0.5 ± 0.9 (mean \pm SE) and 2.5 ± 0.9 , respectively. Whereas, with the vehicle gel, there was an increase of 1.5 ± 1.3 ($P < .05$). After 1 month of treatment, the patients who received adapalene had significant lightening of solar lentigines as compared with the patients who were treated with vehicle gel ($P < .05$). After 9 months, 57% and 59% of the patients had lighter lesions in the adapalene 0.1% and 0.3% groups, respectively, in comparison with only 36% in the vehicle group ($P < .05$). Histologic evaluations revealed improved cellular atypia and reduced epidermal melanin in adapalene-, as compared with vehicle-treated group. The differences, however, were not statistically significant. A retrospective evaluation of paired clinical photographs (before and after 9-month treatment) by 2 dermatologists who were treatment-blinded revealed significant improvement in wrinkles and other clinical features of photoaged skin with adapalene as compared with its vehicle.

Conclusion: Adapalene gel 0.1% and 0.3% were well tolerated and improved actinic keratoses, solar lentigines, and other features of photodamaged skin. (J Am Acad Dermatol 2003;49:83-90.)

Actinic keratoses are a common condition caused by excessive exposure to solar radiation, and represent one of several features of photodamaged skin. The histology of actinic ker-

atoses is distinct, with loss of orderly differentiation of epidermal keratinocytes from the basal cell layer to the stratum corneum, and morphologically anaplastic cells are frequently present.¹ The abnormal histology is thought by some to represent a premalignant state, and by others to be a nonaggressive, intraepidermal squamous cell carcinoma.²⁻⁴ Indeed, a high incidence of p53 tumor suppressor gene mutations in actinic keratoses is consistent with their association with cutaneous malignancy.⁵

Traditional treatments of actinic keratoses, such as cryotherapy and topical 5-fluorouracil,⁶ have targeted the individual lesions. Although effective, they are associated with risks of dyspigmentation, local skin irritation, ulceration, or a combination of these. In addition, their treatment approach is limited to established lesions and offers little or no benefit in the prevention of new lesions. Because actinic ker-

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atoses are a result of chronic sun exposure, the individual lesions arise on a background of photoaged skin, characterized clinically by fine and coarse wrinkling, brown spots (solar lentigines), blotchy dyspigmentation, and rough skin texture.^{7,8} Therefore, a therapeutic approach that will not only address actinic keratoses (both treatment and prevention), but also the other features of photoaging would be desirable.

Topical all-*trans*-retinoic acid (tretinoin) has been used to treat acne and, more recently, photoaging.⁹⁻¹¹ In addition to effacement of wrinkles, it can significantly improve clinical and microscopic manifestations of photoaging including solar lentigines.¹² Previous studies have also shown a beneficial effect of tretinoin in treating actinic keratoses.^{13,14} The mode of action of tretinoin is through activation of intranuclear retinoic acid receptors (RAR). Adapalene is a synthetic retinoid, which also activates RAR; however, with selectivity for RAR β and RAR γ .¹⁵ Topical adapalene has comparable efficacy with tretinoin in treating acne but with less potential for irritation.¹⁶ Thus, we hypothesized that topical adapalene might improve actinic keratoses and photoaging with less irritation than tretinoin. A 2-center randomized, placebo-controlled study was conducted to assess the efficacy of topical adapalene in the treatment of actinic keratosis and solar lentigines. Efficacy in treating other features of photoaging was also examined retrospectively through clinical photographs obtained during the study.

PATIENTS AND METHODS

A total of 90 consenting Caucasian patients were enrolled into this randomized, controlled, 2-center, investigator-masked, balanced parallel-group design study of 9 months duration. This study was reviewed and approved by each center's institutional review board before initiation.

Patients had to be between 18 and 85 years of age and have a minimum of 5 and a maximum of 25 visible actinic keratoses. There was no minimum number requirement for solar lentigines. The minimum size of individual actinic keratoses and solar lentigines for inclusion in the study was 2-mm diameter. However, those selected as target lesions for evaluation (maximum of 3 actinic keratoses and 3 actinic lentigines) were at least 5 mm in diameter.

None of the patients had received topical retinoids, alpha-hydroxy acids, or 5-fluorouracil during the 6 months before the study entry nor systemic retinoids, dermabrasion, or cosmetic operation during the previous year. In addition, none of the patients had used oral psoralen-UVA therapy for 2 months, cryotherapy for 1 month, or used topical

steroids for at least 2 weeks before the study. Patients with dark skin color (phototypes V and VI), and pregnant or lactating women were excluded, as were patients with a history of skin cancer in the previous 3 years, or any other condition that could have interfered with the study evaluation.

Patients were assigned to treatment with adapalene gel 0.1% (n = 30), adapalene gel 0.3% (n = 30), or vehicle gel (n = 30) (Galderma, Fort Worth, Tex) using a randomization procedure in blocks of 9. Each patient received a unique 4-digit number that distinguished the patients in each of the 2 treatment centers, which was randomized by a computer program (RANUNI, SAS Institute, Cary, NC). The investigators and patients were unaware of the group to which the patients had been assigned and the test materials were packaged identically in 45-g tubes in boxes with similar labels.

The treatment areas included the face above the jaw line, ears, and scalp. Patients were instructed to begin with a pea-sized amount of medication, but to apply enough to cover the entire treatment skin surface and to rub it in. The arms and backs of the hands were to be included if actinic keratoses and solar lentigines were not present in sufficient quantities on the face and scalp. A target area was identified for evaluation of solar lentigines. The adapalene gels or vehicle gel were applied once daily every evening approximately 20 minutes after washing. To allow the medication to penetrate and ensure maximum effectiveness, treatment application and the next washing of the treated areas were separated by several hours. If no significant skin irritation was present after 4 weeks, the drug application was increased to twice daily (morning and evening). Patients were treated for 9 months on an outpatient basis and were scheduled for 8 visits. At each visit after baseline (week 2, 4, 12, 18, 24, 30, and 36) the patients' response to treatment was assessed.

The primary efficacy variables measured the total lesion counts both before and after treatment, and the assessment of morphologic changes in target actinic keratoses (induration, scaling, and erythema evaluated on a scale of 0 [none] to 3 [severe]). In addition, the investigators' global assessment of improvement in actinic keratoses was included as an efficacy variable. Histologic changes in target lesions were also evaluated by biopsy specimens at one center (University of Michigan, Ann Arbor, Mich). A 2-mm punch biopsy specimen was taken under local lidocaine anesthesia from the base of 1 target actinic keratosis at baseline and at the final visit (week 36) or at the time of discontinuation if a patient withdrew from the study prematurely. If the

Table I. Patient demographics at baseline and patient flow

	Gel vehicle	Adapalene gel 0.1%	Adapalene gel 0.3%
Patients enrolled, No.	30	30	30
Sex, No. (%)			
Male	20 (67)	22 (73)	27 (90)
Female	10 (33)	8 (27)	3 (10)
Mean age, y (range)	64.6 (43-83)	61.7 (43-79)	63.1 (45-77)
Skin phototype, No. (%)			
I	5 (17)	5 (17)	1 (3)
II	21 (70)	18 (60)	21 (70)
III	1 (3)	5 (17)	4 (13)
IV	3 (10)	2 (6)	4 (13)
Patients completed, No.	28	28	27

original lesion was not large enough to accommodate the second biopsy specimen, a secondary lesion (preselected at baseline) was biopsied at the final visit. A 2-mm punch biopsy specimen was also taken at baseline, and at the final visit, from a treated but uninvolved area of skin (free of actinic keratoses or solar lentigines).

The pathology laboratory at the University of Michigan processed all biopsy specimens and the following parameters were evaluated in a blinded manner by a board-certified dermatopathologist (John T. Headington, MD, University of Michigan): stratum corneum (compact vs woven, parakeratosis, and thickness); epidermal thickness; granular cell layers; epidermal mucin; melanin; elastosis; cellular atypia; dermal inflammation; and the global evaluation of squamous intraepidermal neoplasia.

For solar lentigines, efficacy variables measured included assessment of color change, the total number of lesions before and after treatment, and investigators' global assessment of the overall improvement in lentigines. Skin safety variables (erythema, peeling, dryness, burning, and pruritus) were assessed by clinical examination at baseline and all scheduled visits, and evaluated on a scale of 0 (none) to 3 (severe). Spontaneously reported adverse events were recorded but hematology and biochemistry variables were not assessed during this study.

The planned sample size for this study was on the basis of estimates of reductions for total actinic keratosis lesion count that would be considered clinically meaningful. Using a 2-sided *t* test with $\alpha = 0.05$, inclusion of 25 patients per group would have resulted in at least 71% power for all pair-wise comparisons, with an estimated dropout rate of 20%. A total of 30 patients were enrolled in each treatment group.

Statistical analyses of actinic keratoses, solar lentigines, and skin safety variables were performed

using the Cochran-Mantel-Haenszel test. For change in number of actinic keratoses between treatment groups, 1-way analysis of variance with Tukey studentized range test was used. Target actinic keratosis lesion size, stratum corneum, and epidermal thickness were evaluated by analysis of variance, and the number of target actinic keratoses and new actinic keratoses on treated areas were analyzed by Fisher's exact test.

Photographic evaluation of photoaging

Standardized photographs were taken of 45 patients by a professional photographer at one center (University of Michigan) at baseline and after 3, 6, and 9 months of treatment. Lighting and positioning were standardized for each volunteer. Film was from the same emulsion lot and processed by a single professional laboratory. The photographs were evaluated retrospectively in a randomized, blinded fashion to assess the effects of the 3 treatments on photoaging characteristics (mottled hyperpigmentation, fine wrinkles, coarse wrinkles, rosy glow [healthy pink complexion], and global photoaging severity). Each parameter was graded for improvement on a scale of 0 to 6 similar to that published by Larnier et al.¹⁷ If there was no difference or worsening between before- and after-treatment photographs, then a score of 0 was given.

RESULTS

A total of 90 patients, 45 from each center, were included in the study and 83 patients completed 9 months of treatment. All patients presented with actinic keratoses and approximately 75% of patients also had at least 1 solar lentigo. All of the patients were Caucasian, with the majority (79%) having skin phototypes I and II. Only 1 patient in the adapalene 0.3% group discontinued because of skin irritation and the other 6 patients discontinued because of non-treatment-related events. Patient demographics

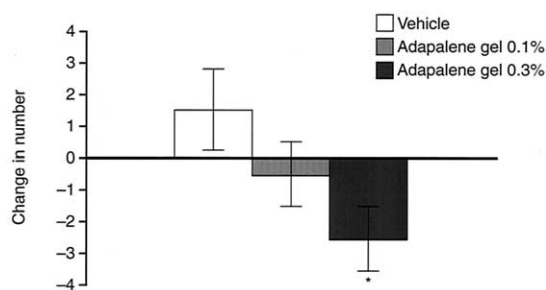


Fig 1. Change in number of actinic keratoses after 9 months of treatment with 0.1% adapalene gel, 0.3% adapalene gel, or vehicle gel. Bars and error bars indicate mean \pm SEM. * $P < .05$ versus vehicle.

at baseline are summarized in Table I. All patients were included in the intention-to-treat analysis, which compared baseline with results at end point (last available visit with efficacy data).

Actinic keratoses

The mean numbers of actinic keratoses in the 3 treatment groups were comparable. Differences in the total number of actinic keratoses from baseline to end of study for each group are summarized in Fig 1. With vehicle gel there was a net increase of 1.5 ± 1.3 (mean \pm SE) actinic keratoses after 9 months of therapy. With 0.1% and 0.3% adapalene gel, a mean reduction in numbers of actinic keratoses of 0.5 ± 0.9 and 2.5 ± 0.9 , respectively, was observed. The change in number of actinic keratoses between treatment groups was statistically significant ($P < .05$).

In addition, the global assessment of improvement in actinic keratoses showed that adapalene gel 0.3% produced significantly greater global improvements in actinic keratoses in comparison with vehicle at 3 ($P < .05$), 6 ($P < .01$), and 9 ($P < .01$) months of treatment. There was also a statistically significant difference in global improvement with adapalene gel 0.1% versus vehicle at 1 and 6 months of treatment ($P < .05$). Overall, 62% ($P < .01$) and 66% ($P < .01$) of patients in the adapalene gel 0.1% and 0.3% groups, respectively, were considered to have shown clear, marked, or moderate improvement in actinic keratoses in comparison with only 34% of the patients treated with vehicle (Fig 2).

Solar lentigines

The numbers of solar lentigines counted at baseline were comparable among the 3 treatment groups, and the lack of significant differences persisted throughout the study. New solar lentigines on treated areas were reported in only 1 patient in the adapalene 0.3% group and 1 patient in the vehicle

group. New lesions in untreated areas were only reported in 1 patient in the vehicle group. Thus, there were no statistically significant differences between treatments with regard to new lesions in either treated or untreated areas. However, there were statistically significant differences in favor of adapalene gel 0.1% and 0.3% in comparison with vehicle for reduction in color of solar lentigines from 1 month to the end of study ($P < .05$). After 9 months of treatment, 57% and 59% of the patients had lighter lesions in the adapalene 0.1% and 0.3% groups, respectively, in comparison with only 36% in the vehicle group ($P < .05$) (Fig 3).

The global assessment of improvement in color of solar lentigines demonstrated that the 2 adapalene gel treatments were superior to vehicle gel. There were statistically significant differences ($P < .05$) in favor of both adapalene gel groups in comparison with vehicle intermittently throughout the study, with adapalene gel 0.1% superior to vehicle at 3 and 6 months, and adapalene gel 0.3% superior at 3 and 9 months. Overall, 59% and 65% of patients in the adapalene gel 0.1% and 0.3% groups, respectively, demonstrated global improvement in solar lentigines at end point in comparison with 43% in the patients who were vehicle-treated ($P < .05$). No statistically significant differences in global improvement in solar lentigines were observed between the active treatment groups.

Photoaging

Standardized photographs of patients' faces were taken from one study site (University of Michigan). Pretreatment and posttreatment photographs were available from 42 patients. Treatment- and time-(before or after) blinded evaluation of these photographs revealed improvements in several parameters of cutaneous photoaging with adapalene gel in comparison with vehicle treatment (Fig 4). The largest and most significant ($P < .05$) improvements with adapalene 0.1% and 0.3% in comparison with vehicle were seen in mottled hyperpigmentation (55%, 65%, and 25% of patients, respectively) and global appearance. Fine wrinkles and rosy glow (erythema) were also improved ($P < .05$). However, reduction in severity of coarse wrinkles was not significant.

Skin tolerability evaluations

Higher levels of erythema, peeling, dryness, burning, and pruritus were observed in the adapalene 0.3% and 0.1% groups in comparison with the vehicle group. However, all mean scores for these evaluations remained in the mild category throughout the study. No significant differences in

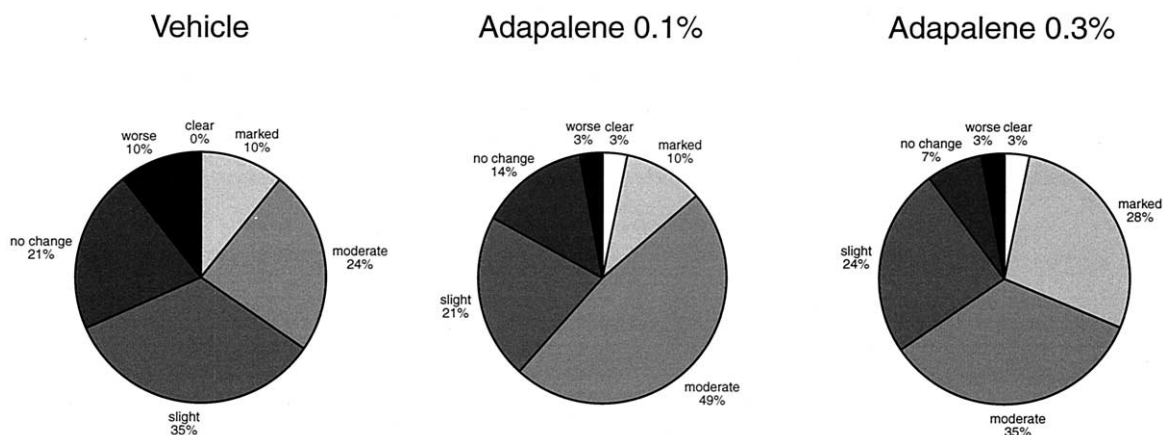


Fig 2. Investigators' overall global assessment of improvement in actinic keratoses after 9 months of treatment with 0.1% or 0.3% adapalene gel, or vehicle gel. Proportion of patients who achieved moderate or marked improvement, or clearing of actinic keratoses with each concentration of adapalene (0.1% gel = 62%; 0.3% gel = 66%) was significantly greater than with vehicle (34%) ($P < .01$). There were no significant difference between 0.1% and 0.3% adapalene in their ability to improve actinic keratoses.

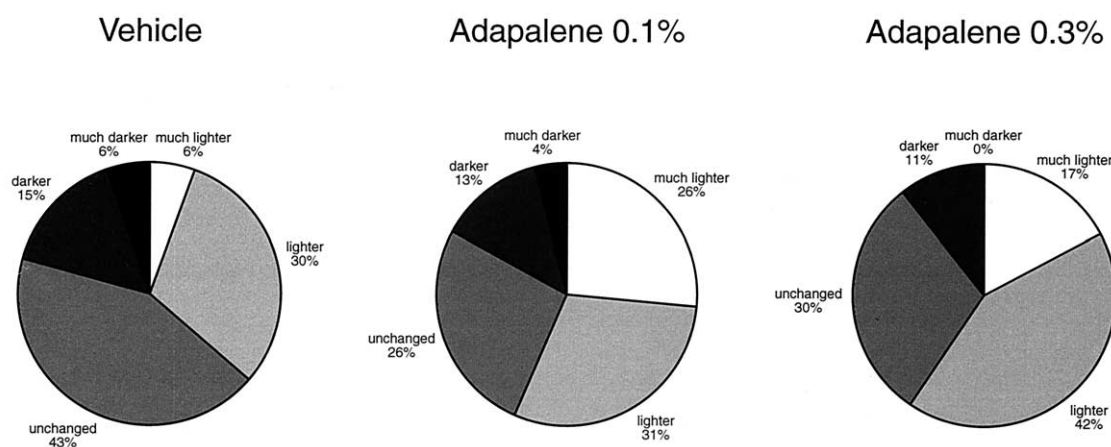


Fig 3. Investigators' overall global assessment of improvement in solar lentigines after 9 months of treatment with 0.1% or 0.3% adapalene gel, or vehicle gel. As compared with vehicle, adapalene caused significant lightening of hyperpigmented lesions. Among patients given 0.1% and 0.3% adapalene gel, 57% and 59%, respectively, achieved "much lighter" or "lighter" improvement in solar lentigines, as compared with 36% among those given vehicle gel ($P < .05$).

skin tolerability evaluations were noted between the 2 active treatment groups.

Histology

All 45 patients at one center (University of Michigan) had actinic keratoses biopsied at baseline and 36 of them had evaluable biopsy specimens from both the baseline and final visits (15 and 12 in the adapalene 0.1% and 0.3% groups, respectively, and 9 in the vehicle group). No statistically significant

differences were noted between the treatments for changes in the histology of the biopsied actinic keratoses. The evaluation for atypia and squamous intraepidermal neoplasia were similar with slight improvements in the adapalene-treated groups but no improvements in the vehicle group. There was a trend for the granular cell layers in patients who were adapalene-treated to increase more than those in the vehicle group and there was also a greater increase in mucin in the patients who were ada-

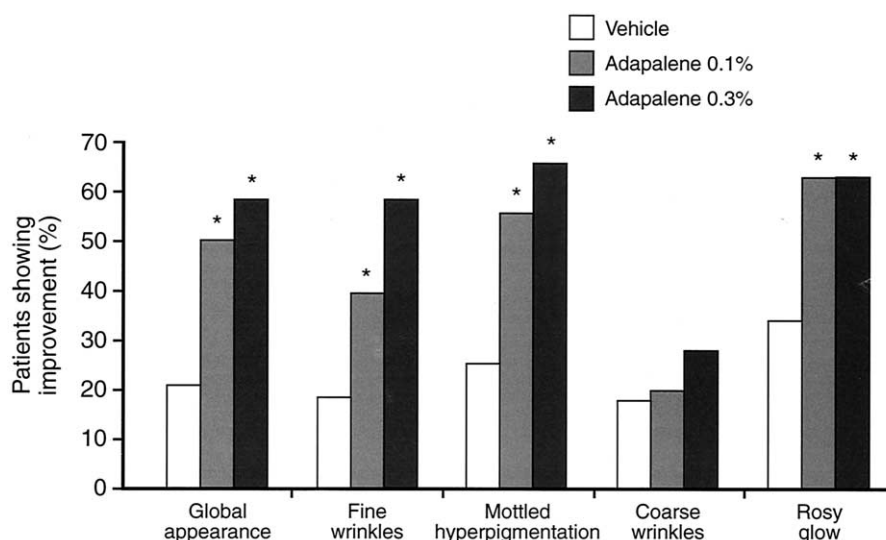


Fig 4. Percentage of patients with improvement in clinical features of photoaged skin after 9 months of treatment with 0.1% adapalene gel, 0.3% adapalene gel, or vehicle gel. Clinical photographs from baseline and at end of treatment were evaluated retrospectively in a randomized and blinded fashion. N = 42, * $P < .05$ versus vehicle.

palene-treated, especially in the 0.3% group. No changes in parakeratosis, elastosis, stratum corneum thickness, or epidermal thickness were observed and there was no change in dermal inflammation in the adapalene-treated groups, although a mild decrease was observed in the vehicle group. Diffuse epidermal melanin was decreased in both adapalene-treated groups and was unchanged in the vehicle group.

Adverse events

No potentially serious adverse events were considered related to adapalene gel 0.1% or 0.3% treatment. Three patients were discontinued from the study for medical reasons. One 45-year-old male patient in the adapalene 0.3% group was withdrawn because of a diagnosis of contact dermatitis. He was patch tested with the active and vehicle treatments, both of which were negative for allergic contact dermatitis. A 70-year-old male patient in the adapalene 0.3% group, who was legally blind in 1 eye, was concerned for his vision. He withdrew because of dryness he experienced in both eyes, although considered unlikely to be related to treatment. Another 70-year-old male patient assigned to vehicle treatment had a fatal myocardial infarction that was considered definitely unrelated to study treatment. Mild to moderate dermatitis was the most frequently reported adverse event and it occurred in 40% and 25% of the patients in the adapalene 0.1% and 0.3% groups, respectively, and in 9% of patients who were vehicle-treated.

DISCUSSION

Topical application of adapalene gel 0.1% and 0.3% was well tolerated and improved actinic keratoses and lentigines. In addition, retrospective evaluation of clinical photographs revealed that adapalene gel also improved signs of photoaging, particularly mottled hyperpigmentation and fine wrinkles, during a treatment period of 9 months' duration.

Adapalene gel use resulted in a modest reduction in the number of actinic keratosis in a dose-dependent manner, whereas vehicle gel led to an increase in number. Reliably counting actinic keratoses in clinical studies has always been a challenge. A recent study that formally addressed the validity of this method of ascertaining actinic keratoses found that the counts can be unreliable even when performed by experienced dermatologists; however, improvement in reliability can be achieved by discussions among the investigators.¹⁸ Such preparation took place for the current study. Furthermore, by specifying the minimum size requirement (≥ 2 mm) in the inclusion criteria, a more uniform population of actinic keratoses was evaluated. Lastly, by selecting larger actinic keratoses (≥ 5 mm) as target lesions and assessing their clinical features more critically, end points other than lesion counts were evaluated. In fact, the global assessment of improvement in actinic keratoses supported the trend observed in lesion number with the 0.3% adapalene gel group demonstrating the highest proportion (66%) of pa-

tients with moderate improvement or better (marked improvement and clear). In this study, the protocol did not require patients to use sunscreen. Rather, they were told to continue with their routine practice of sunscreen use. The slight increase in the mean number of actinic keratoses in the vehicle group most likely reflects nonregimented use of sunscreens and is in agreement with a previous study¹⁹ where regular sunscreen use reduced number of actinic keratoses.

The mechanism by which adapalene might improve actinic keratoses is currently unknown, and addressing this issue was not within the limit of this clinical study. Because actinic keratoses are considered as a precursor or, indeed, a form of squamous cell carcinoma, it is possible that mechanisms by which systemic retinoids prevent squamous cell carcinomas of the head and neck²⁰ are similar in topical retinoid-mediated improvement of actinic keratoses. In this regard, topical tretinoin's ability to prevent UV induction of cJun may be relevant.²¹ In normal human skin in vivo, cFos is constitutively expressed, whereas cJun is minimally detectable. UV irradiation does not affect level of cFos expression in human skin, however, it markedly induces cJun protein, which can then heterodimerize with cFos, forming a complete, active AP-1 transcription factor.²¹ The importance of AP-1 in mediating carcinogenic transformation of papillomas has been demonstrated.²² In human squamous cell carcinomas, cJun expression is increased (Gary J. Fisher, PhD, oral personal communication). As to how tretinoin blocks UV induction of cJun is currently unknown; however, it is speculated to involve RAR activation. Because the most common RAR in human skin is RAR γ ,²³ and adapalene is RAR γ -selective, it is predicted that adapalene may possess an anti-cJun action, similar to tretinoin, in UV signaling. The gene for cellular retinoic acid binding protein-II is regulated by RAR and is expressed in human skin.²³ Similar to tretinoin, topically applied adapalene markedly enhances the level of cellular retinoic acid binding protein-II messenger RNA expression,²⁴ indicating its ability to activate RAR in human skin in vivo. The ability of topical adapalene to reduce the number of actinic keratoses also implies that it may chemoprevent the subsequent development of squamous cell carcinoma. A formal demonstration of this point would involve a clinical study design incorporating more patients and a longer duration of observation. Only from such a study can the true safety of using adapalene for an extended length of time be determined. To date, most adapalene use has been for treatment of acne, which has limited duration of use. Even so, it is promising that significant side effects

have not been recorded with adapalene use since it first became available more than 5 years ago.

This study also demonstrated that, in comparison with vehicle, adapalene gel 0.1% and 0.3% produced statistically significant lightening in color of solar lentigines. Similar results have been observed with topical tretinoin.¹² This retinoid effect was thought to be related, in part, to inhibition of induced melanogenesis²⁵ and an increase in epidermal keratinocyte hyperproliferation (evidenced by thickened epidermis). Histologic results from our study indicate that its effect on melanogenesis may be a more important factor. Although skin biopsy specimens were obtained from actinic keratoses and not from lentigines, there were no statistically significant differences between the treatment groups, even in epidermal thickness. Thus, the lightening of lentigines by adapalene must involve processes other than a simple increase in keratinocyte transit time through the epidermal layer and consequent removal of melanin, and indirectly suggests an inhibitory action of adapalene on melanogenesis. In the current study, individuals with dark skin color (phototypes V and VI) were not included. However, our findings on adapalene and pigmentation suggest a possibility of skin color reduction in this group of patients with its chronic use. In a longer (40-week) clinical study of tretinoin in African-American patients with postinflammatory hyperpigmentation, preferential lightening of hyperpigmented areas occurred without clinically obvious reduction in patients' normal uninvolved skin color.²⁶ Topical adapalene is expected to have a similar effect. Certainly, substantial clinical experience from acne treatment indicates that gross skin lightening or undesirable dyspigmentation does not occur with adapalene.

In addition to improvements in actinic keratoses and lentigines, topical adapalene also improved other clinical features of facial photodamage. It is important to emphasize that this study design focused on actinic keratoses and lentigines, and not on wrinkles. Therefore, the clinical severity of photoaging in our study patients was less severe than in those typically targeted in trials of treatment for photoaging. Thus, assessment of improvement in photoaging was more difficult. Nevertheless, consistent with the fact that adapalene improves 2 distinct clinical features of photodamage (actinic keratosis and lentigines), retrospective blinded evaluation of clinical photographs revealed that fine wrinkles and dyspigmentation associated with photoaging also improved with adapalene. Thus, topical use of adapalene is associated with some improvement in many features of photodamaged human skin including actinic keratoses, solar lentigines, and photoag-

ing. It had been previously postulated that retinoid irritancy is related to efficacy.²⁷ However, results of a large clinical study,²⁸ and data from the current adapalene study provide convincing evidence to the contrary. Both gel formulations of adapalene were well tolerated when applied once or twice daily. Their use was not associated with severe cutaneous irritation or dermatitis, however, were both successful in improving actinic keratoses, actinic lentigines, and wrinkles associated with photoaged skin. Thus, topical adapalene has the potential to be used as a comprehensive antiphotodamage therapy.

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