Open-Label Pilot Study of Alitretinoin Gel 0.1% in the Treatment of Photoaging

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Alitretinoin (9-cis-retinoic acid) is an FDA-approved topical therapy for the treatment of Kaposi sarcoma. Alitretinoin is a naturally occurring endogenous retinoid that binds to and activates all known intracellular retinoic acid receptor (RAR) subtypes α, β, and γ and retinoic X receptor (RXR) subtypes α, β, and γ. Photoaging of the skin is the result of accumulated exposure to solar UV radiation. Several topically applied retinoids have been proven clinically effective for treating the appearance of photoaging. Tretinoin and tazarotene, which have been shown to improve photodamaged skin, bind RAR subtypes only. The theoretic benefit of alitretinoin gel 0.1% (Panretin®) in the treatment of photoaged skin stems from the binding and activation of both RARs and RXRs, which promote the repair mechanisms in damaged skin.

The objective of this study was to evaluate the safety and efficacy of topical alitretinoin gel 0.1% in the treatment of photodamaged skin. The treatment was well tolerated by participants (N=20) and subjectively showed improvement of benign skin lesions (eg, seborrheic keratoses) and precancerous lesions (eg, actinic keratoses). Larger, blinded, controlled trials are needed to investigate the role of this novel retinoid in the treatment of photoaging.

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Photoaging of the skin is the result of accumulated exposure to solar UV radiation and is characterized by the appearance of superficial and deep wrinkles, mottled pigmentation, skin roughness, telangiectases, inelasticity, and easy bruisability. Histologically, photodamaged skin shows decreased and disorganized collagen in the upper dermis,[1,2] loss of normal dermal elastic fibers, and deposition of an amorphous elastic-containing material within the dermis.

Several topically applied retinoids have proven clinically effective for treating the appearance of photoaging.[3,4] Research has shown that topical tretinoin causes a reduction and more even distribution of melanin, leading to improvements in mottled hyperpigmentation and lentigines.[5] Within the epidermis, tretinoin temporarily stimulates proliferation of keratinocytes, resulting in increased shedding of corneocytes. Tretinoin also has been associated with the formation of a band of new collagen in the upper dermis.[6] Together, these functions result in smoothing of superficial wrinkles and increased skin firmness.

The benefits of retinoid therapy result primarily from activation of nuclear retinoid receptors and the subsequent gene activation and protein synthesis. The nuclear retinoid receptors can be divided into 2 groups: retinoic acid receptor (RAR) subtypes α, β, and γ and retinoic X receptor (RXR) subtypes α, β, and γ. RARs bind to their response elements as dimers. RXR is key for heterodimerization and the ultimate functioning of RARs.[7] Retinoic acid binds to retinoic response elements in DNA and then modulates transcription of specific genes.[8] Dimerization with RXR is required for RAR to effectively initiate gene promotion.[9] The molecular mechanisms by which retinoids benefit the repair of skin damage, and possibly counteract UV-related

damage, are largely unknown.[10] Wrinkles are associated with loss of collagen types I and III.[11]

All-*trans*-retinoic acid has been found to induce transforming growth factor β (TGF-β) in human skin. TGF-β is a peptide mediator that stimulates production of procollagen types I and III.[12] Skin treated with tretinoin is associated with the formation of a band of new collagen in the upper dermis. Thus, it can be concluded that the induction of TGF-β plays a role in the repair of photodamaged skin via retinoids by increasing collagen synthesis.[12,13]

This study presents the results of an evaluation of the safety and efficacy of alitretinoin gel 0.1% (Panretin®) in the treatment of photodamaged skin in 20 participants. There were several primary objectives for this pilot study: (1) to determine the efficacy of topical alitretinoin gel 0.1% in the treatment of photoaging, (2) to determine the incidence and duration of adverse events experienced with topical alitretinoin gel 0.1%, (3) to subjectively look at the effect on benign and premalignant skin lesions, and (4) to look for other effects of this novel retinoid.

Alitretinoin gel is currently the only commercially available retinoid that binds and activates both RARs and RXRs (which promote the repair mechanisms in damaged skin), a theoretical benefit in the treatment of photoaged skin.

MATERIALS AND METHODS

This study was an open-label pilot study of alitretinoin gel 0.1%. Twenty healthy volunteers, aged 18 years or older, with clinical signs of photodamage on the face and dorsum of the hands, were enrolled in the study after providing informed consent. The University of Miami Medical Sciences Committee for the Protection of Human Subjects in Research approved the study.

Women of child-bearing potential underwent a urine pregnancy test before receiving the study medication. Women with positive pregnancy test results were excluded. Female participants were required to use a reliable form of birth control during the course of the study. Participants were asked to discontinue the use of topical medications to the treatment sites for 2 weeks before the study and could not have used oral or topical retinoids in the 4 weeks before the study. At the week-2 visit, participants were clinically and photographically assessed and then provided with alitretinoin gel 0.1%. Participants were instructed to apply the gel to their face and dorsum of their hands nightly for 14 weeks. Participants were given a mild soap and a generic sunscreen—both to be used daily—and a class V topical corticosteroid for skin redness, scaling, or itching, if needed.

Treatment sites were evaluated at day 0 and at weeks 2, 4, 8, and 16. At each visit, the unblinded investigator and study participant assessed 5 variables on both the face and dorsum of the hands: the appearance of telangiectases, solar lentigines and pigmentation, superficial wrinkles, deep wrinkles, and skin roughness. Each parameter was graded on a scale of 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe). Participants also were evaluated by the unblinded investigator for the presence of other UV-related lesions (eg, actinic keratoses) and benign skin lesions (eg, seborrheic keratoses). Participants were asked if they had noticed any other differences in their skin after using the medication. At each visit, the participants were asked if they

Statistical Evaluation of Participant Assessments Pretreatment (Week 2) Versus Posttreatment (Week 16)

Efficacy Variable	χ^2 Test	*P* Value
Face		
Telangiectases	0.400	.527
Solar lentigines and pigmentation	9.308	.002*
Superficial wrinkles	4.500	.034*
Deep wrinkles	2.667	.102
Skin roughness	4.455	.035*
Hand		
Telangiectases	1.923	.166
Solar lentigines and pigmentation	7.143	.008*
Superficial wrinkles	7.364	.007*
Deep wrinkles	3.600	.058
Skin roughness	10.000	.002*

*Significant.

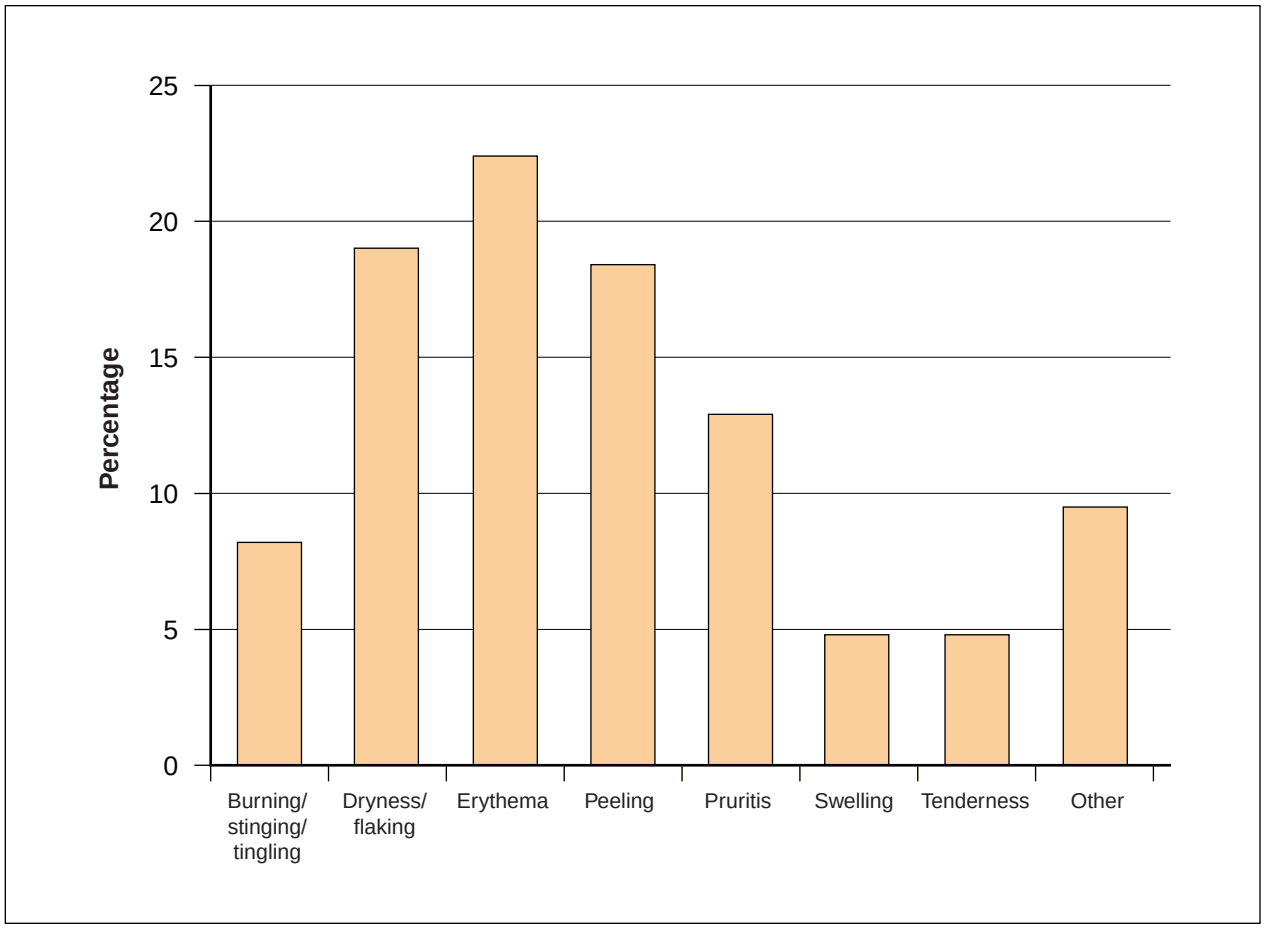

Figure 1. Percentage of total adverse events (N=147) reported by category. Several participants experienced the same adverse event more than once during the course of the study.

had experienced any adverse events that may have developed since starting the study medication. At day 0 and at week 16, study participants completed a visual analog scale (VAS) to assess the cosmetic appearance of treatment sites. The participants also completed a VAS at week 16 to assess adverse events related to the study medication.

At each visit, participants were photographed in a standardized manner with a Canfield photography system, which is able to consistently and reproducibly photograph the areas in question, maintaining the same degree of light and distance. Three views of the face were taken, as well as a single-view of the dorsum of the hands.

RESULTS

Twenty-five volunteers with photodamage were screened for this pilot study, and 20 subjects were enrolled. Participants ranged in age from 48.5 to 67.3 years (mean age, 56.9 years). Six participants (30%) were men, and 14 participants (70%) were women. Fifteen participants (75%) reported their race or ethnicity as white, 4 (20%) as Hispanic, and 1 (5%) as other. Eighteen participants (90%) completed the study, and 2 (10%) were lost to follow-up.

Efficacy

Unblinded Investigator Assessment—Pretreatment (week 2) and posttreatment (week 16) investigator assessment results were compared using the Friedman test of significance to assess overall treatment response. All parameters were found to be significantly different ($P<.05$) at week 16 compared with week 2, except for telangiectases on the face and hand and deep wrinkles on the hand.

Participant Assessment—Participants assessed the appearance of the same 10 efficacy variables at each study visit. Comparison at week 2 and week 16 of the participant questionnaire responses found significant decreases in solar lentigines and pigmentation ($P=.002$), superficial wrinkles ($P=.034$), and skin roughness ($P=.035$) on the face (Table).

No significant decrease was seen in telangiectases or deep wrinkles on the face. On the hands, significant decreases also were seen in solar lentigines and pigmentation ($P=.008$), superficial wrinkles ($P=.007$), and skin roughness ($P=.002$). No significant decreases were seen in telangiectases or deep wrinkles on the hands.

In addition to the questionnaire assessments completed at each visit, participants completed a 10-cm VAS scale, rating their satisfaction with the overall appearance of their skin at day 0 and at the week-16 exit visit; the scale ranged from 0 (not satisfied) to 10 (very satisfied). Skin satisfaction scores for the 17 participants for whom these ratings were available increased significantly, from a mean score of 2.568 before treatment to a mean score of 6.382 at the exit visit ($P<.001$), showing a higher satisfaction with their skin appearance at the end of the study compared with the beginning of the study.

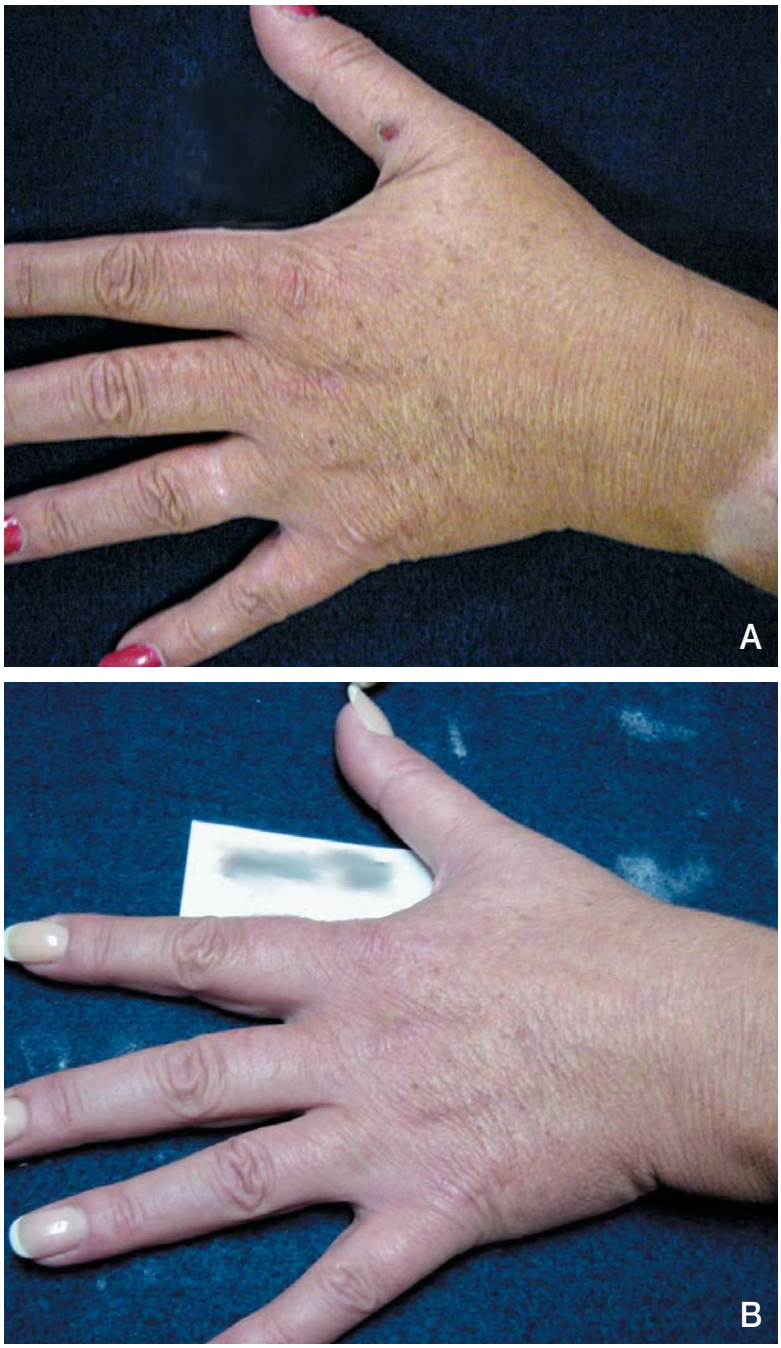

Figure 2. Before (A) and after 14 weeks of treatment (B) with alitretinoin gel 0.1%.

Safety

Adverse Events—In this pilot study, participants were treated topically with alitretinoin gel 0.1%. Two participants were lost to follow-up; the remaining participants completed the study. A total of 147 adverse events were reported by 20 study participants. Treatment-related adverse events were localized to the skin and within the parameters of the risks listed on the consent form.

A total of 130 adverse events (88.4%) were *definitely* related to the study drug. This number included 12 cases of burning, stinging, or tingling on application; 28 cases of dryness/flaking; 32 cases of erythema; 27 cases of peeling; 16 cases of pruritus; 7 cases of swelling; 7 cases of tenderness; and 1 event classified as "other." Four adverse events (2.7%) were *probably* related to the study drug, including 1 case of erythema of the antecubital fossa, 1 case of pruritus of the neck, and 2 cases of pruritus of the antecubital fossa. No adverse events were *possibly* related to the study drug. The remaining 13 events (8.8%) were *not* related to the study drug. There were no serious adverse events experienced by participants during the course of the study. The percentages of each adverse event are shown in Figure 1.

At the exit visit, participants were asked to rate the side effects of using the gel on a 10-cm VAS scale. A score of 0 indicated that treatment was not tolerable, while a score of 10 indicated that treatment was tolerable. The mean rating given by the 18 participants for whom these data were

available was 7.34. This is equivalent to a neutral to tolerable rating.

COMMENT

Alitretinoin gel 0.1% is a novel retinoid that has unique effects due to its actions on RARs and RXRs. This open-label pilot study found alitretinoin gel 0.1% to be effective and well tolerated in the treatment of photodamaged skin. Based on both unblinded investigator and participant assessments, 14 weeks of topical treatment with alitretinoin gel 0.1% was found to significantly improve solar lentigines and pigmentation, superficial wrinkles, and skin roughness on the face and hands ($P<.05$). The investigator also noted subjective improvement of seborrheic keratoses and actinic keratoses. Previous studies of retinoids have shown that dyspigmentation, surface roughness, and superficial wrinkles consistently and significantly improved with topical retinoid therapy.[14] Indeed, our results are consistent with these findings. Figure 2 shows noticeable photodamage before treatment with alitretinoin gel 0.1% and noticeable improvement of photodamage after 14 weeks of treatment.

In our study, although there was a high incidence of treatment-related adverse events, most were generally neutral to tolerable and confined to treatment sites. The most frequent adverse events were erythema, dryness, peeling, and pruritus, which are often seen in patients using retinoids and have been referred to as *retinoid dermatitis*. The retinoid dermatitis in this study was surprisingly less than that seen when alitretinoin gel 0.1% is used for Kaposi sarcoma. This is likely because in Kaposi sarcoma, the medication is used under occlusion. The investigators believe that the gel formulation of this medication may have contributed to the dryness seen. A cream formulation, which is more hydrating, may have resulted in fewer adverse events.

CONCLUSION

In this pilot study, alitretinoin gel 0.1% was safe and associated with improvements in photodamaged skin on the face and dorsum of the hands. The local irritation that occurred was consistent with that found in most topical retinoids and was reasonably tolerated by the participants. Larger, blinded, controlled studies are needed to assess the role of alitretinoin gel 0.1% compared with other topical retinoids in the treatment of photoaging.

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