

The Use of Polyhydroxy Acids (PHAs) in Photoaged Skin

Pearl E. Grimes, MD; Barbara A. Green, RPh; Richard H. Wildnauer, PhD; Brenda L. Edison

The beneficial effects of alpha-hydroxyacids (AHAs) on skin were discovered by Drs. Van Scott and Yu in the early 1970s, including exfoliation, skin smoothing, and antiaging effects. A new generation of AHAs, called polyhydroxy acids (PHAs), was discovered that provide similar effects as AHAs but do not cause the sensory irritation responses that can limit the use of classical AHAs. PHAs have been found to be compatible with clinically sensitive skin, including rosacea and atopic dermatitis, and can be used after cosmetic procedures. PHAs provide additional humectant and moisturization properties compared with AHAs and can enhance stratum corneum barrier function, therefore increasing the skin's resistance to chemical challenge. Most PHAs also possess antioxidant properties. PHAs such as gluconolactone or lactobionic acid may be used in combination with other products, ingredients, or procedures such as laser and microdermabrasion to provide additional benefits to therapy or to enhance the therapeutic effect. Several studies were conducted in support of this, and methods and results are discussed. In summary, PHA-containing products were used in combination with retinoic acid in treating adult facial acne and were found to be well tolerated. PHAs plus retinyl acetate (provitamin A) in a cream base exhibited significant antiaging skin benefits such as skin smoothing and plumping. PHAs plus hydroquinone showed excellent improvement in antiaging and skin lightening parameters. Finally, PHA-containing products were shown to be compatible with African American, Caucasian, and Hispanic/Asian skin and provided significant improvements in photoaging in these populations.

Cutis. 2004;73(suppl 2):3-13.

Dr. Grimes is from the Vitiligo and Pigmentation Institute of Southern California, Los Angeles. Ms. Green, Dr. Wildnauer, and Ms. Edison are from NeoStrata Company, Inc, Princeton, New Jersey. Dr. Grimes reports no conflict of interest. Ms. Green, Dr. Wildnauer, and Ms. Edison are employees of NeoStrata Company, Inc.

The beneficial effects of alpha-hydroxyacids (AHAs) on skin prompted a new category of skin care products. Initially, when AHAs were discovered by Drs. Van Scott and Yu in the early 1970s, AHAs were used to treat severely dry skin and ichthyosis. AHAs were found to normalize irregular keratinization and thus alleviate these conditions.¹⁻⁵ Shortly thereafter, it was noted that AHAs had a profound effect in aiding to reverse the signs of aging. AHAs have been shown to provide beneficial effects to the skin such as exfoliation, skin smoothing, and antiaging effects.¹⁻⁸ However, AHAs also can cause sensory irritation such as stinging and burning.⁹

A new generation of AHAs, called polyhydroxy acids (PHAs), has been discovered that provide similar effects as traditional AHAs but do not cause the sensory irritation responses that can limit their use.¹⁰⁻¹³ PHAs also have been found to have additional benefits to skin compared with traditional AHAs. PHAs such as gluconolactone have a larger molecular structure than do AHAs; thus, PHAs are expected to be absorbed into the skin somewhat more gently and more gradually than traditional AHAs and without the usual stinging and burning associated with AHAs. Thus, PHAs have been found to be compatible with clinically sensitive skin, including rosacea and atopic dermatitis,¹⁰ and can be used after cosmetic procedures.¹⁴⁻¹⁵ Some of the other benefits of PHAs compared with AHAs include additional humectant and moisturization properties. Moreover, most PHAs possess antioxidant properties.^{5,12} PHAs also can enhance stratum corneum barrier function, increasing the skin's resistance to chemical challenge.¹⁶

As the discipline of dermatology evolves, there is an increasing interest in demonstrating the compatibility of various dermatologic products and the ability to use these products adjunctively with medications or procedures in physicians' offices. Also, the population of the United States is becoming more ethnically diverse, and questions regarding efficacy of products for all skin types are being posed more frequently.

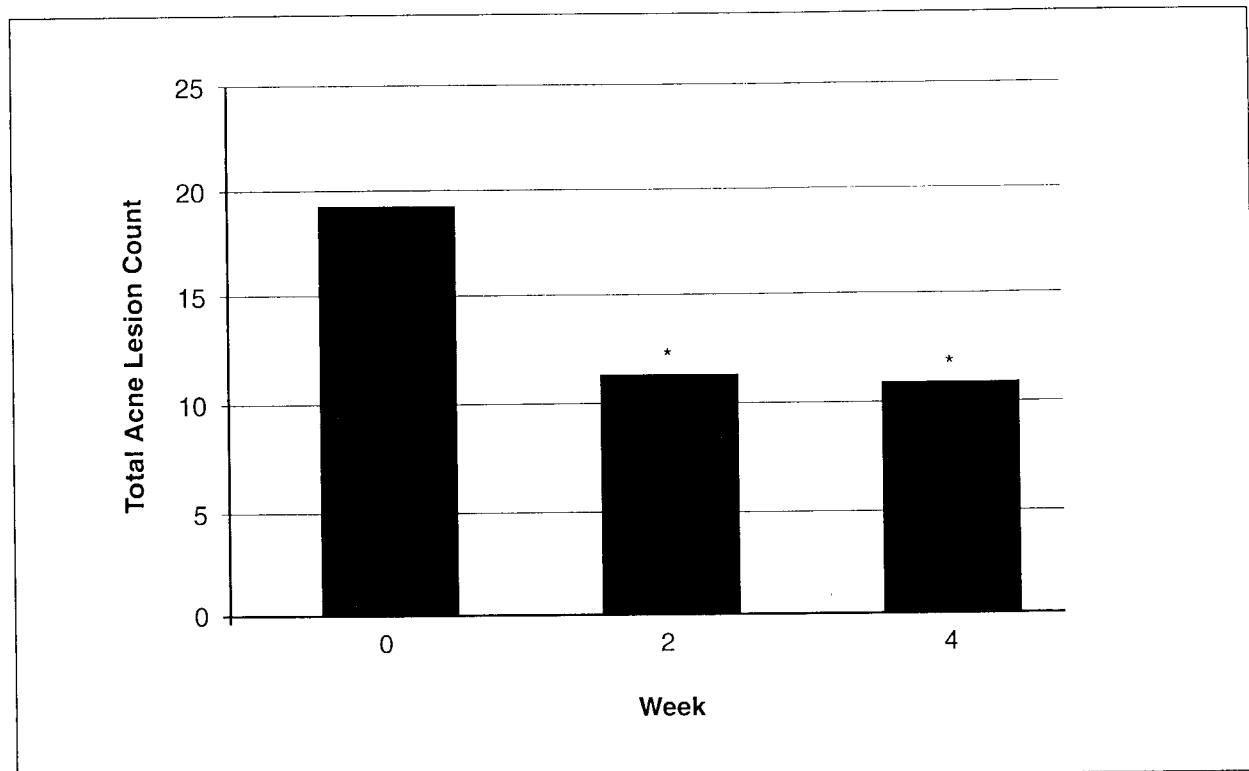


Figure 1. Total acne lesion counts in subjects using the combination therapy of tretinoin 0.1% gel and a poly-hydroxy acid regimen. Asterisk indicates statistically significant improvements vs baseline ($P \leq 0.05$).

Studies supporting the important beneficial properties of PHAs will be discussed, including PHAs' compatibility with retinoic acid, their effects when combined with other cosmetic and active ingredients, and their use in ethnic skin.

Compatibility of a PHA Regimen With Topical Retinoic Acid

PHAs are used adjunctively with topical drug therapies for the treatment of inflammatory skin conditions including psoriasis, rosacea, acne, and seborrheic dermatitis; various hyperkeratotic conditions including xerosis and keratosis pilaris; fungal infections; and hyperpigmentation. PHAs also are used pretreatment and posttreatment for laser resurfacing.¹⁵⁻¹⁶

A study was conducted to determine the compatibility of a PHA regimen with topical tretinoin in the treatment of mild to moderate facial acne.¹⁷ Similar studies have shown compatibility of AHAs with tretinoin¹⁸⁻¹⁹ and maintained efficacy of the drug therapy when used in combination with AHAs to treat acne.²⁰ Skin care products that contain beneficial ingredients that can impart additional cosmetic benefits to the skin commonly are

combined with topical drug therapies. PHAs have been shown to exhibit similar cosmetic benefits to AHAs but are more gentle and nonirritating, thus perhaps making them a better alternative for use with retinoids.

This study was a single-center, 4-week, controlled-use study of the combination of a PHA skin care regimen with topical tretinoin. Product effects were compared statistically to baseline conditions. All products were provided in blinded packaging.¹⁷

Healthy men and women who exhibited mild to moderate facial acne were enrolled in the study. Subjects were excluded for use of the following: any acne therapy (including topical over-the-counter [OTC], topical prescription, or systemic medications) one month prior to the study; PHA or AHA products one month prior to the study; or topical retinoids within 3 months or oral retinoids within 6 months of study initiation.¹⁷

Test products were applied to the entire face in a controlled-use manner. Products contained the PHA gluconolactone and were applied in the morning and evening. In the morning, subjects washed their face with a cleanser containing gluconolactone 4% (pH 3.5) and applied a day lotion containing a sun

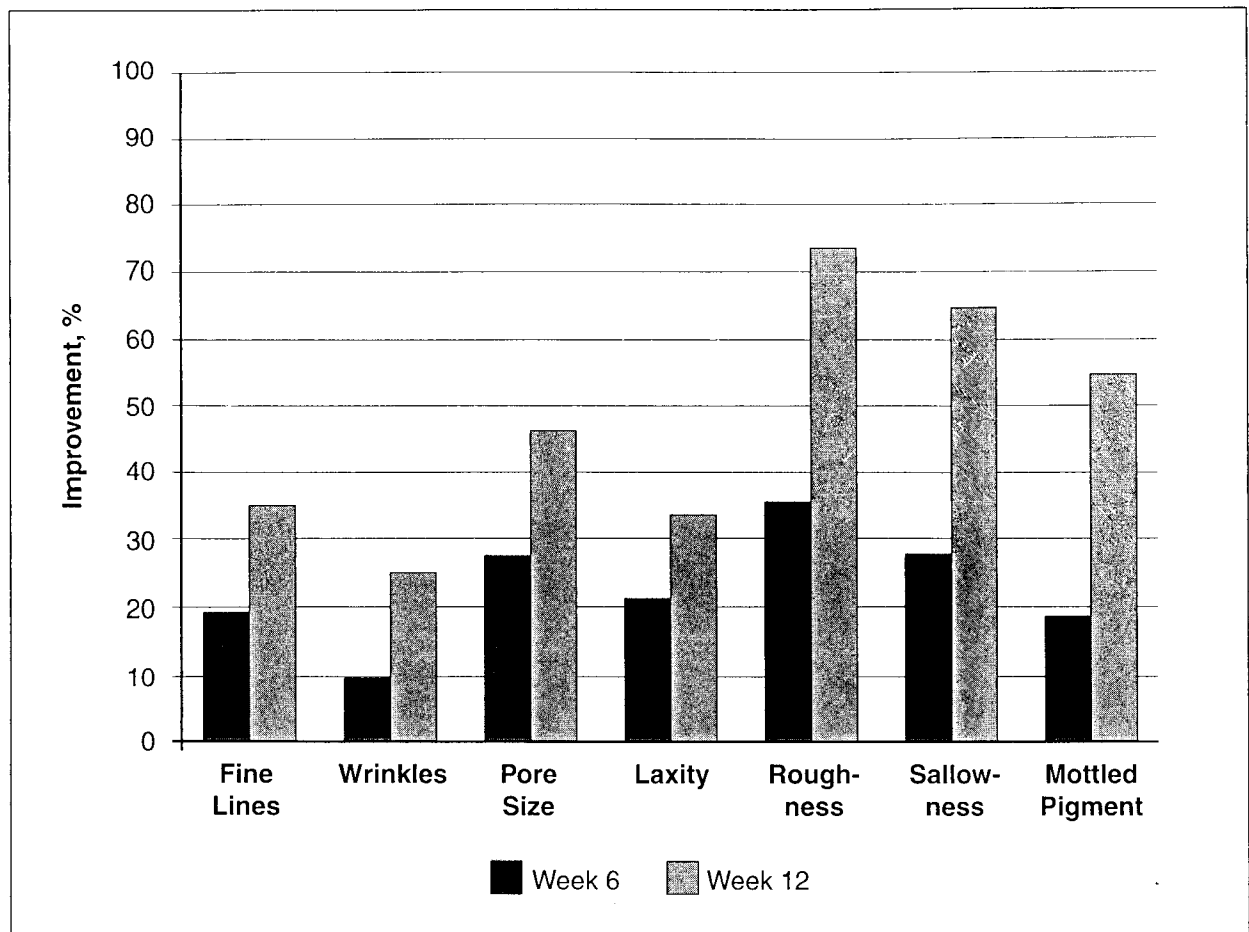


Figure 2. Percentage improvement in clinical grading of photoaging in subjects using polyhydroxy acid plus retinyl acetate (pro-vitamin A) cream. All attributes were significantly improved at weeks 6 and 12 vs baseline ($P < .05$).

protection factor (SPF) of 15 with gluconolactone 4% (pH 3.9); in the evening, subjects washed with the cleanser and applied a tretinoin 0.1% gel followed by application of a night cream with gluconolactone 15% (pH 3.3) over the tretinoin gel.¹⁷

Acne lesion counts for papules, pustules, open comedones, and closed comedones were conducted by a board-certified dermatologist. Total lesion counts represent the sum of the number of each type of lesion. In addition, the dermatologist conducted an assessment of objective irritation (dryness and erythema) and inquired about subjective irritation (itching, burning, stinging, tightness) using a 5-point scale (none, barely perceptible, mild, moderate, severe). Self-assessment also was conducted to gain consumer perception of efficacy and product tolerability.¹⁷

Twenty-seven subjects aged 19 to 54 years completed the study. Total acne lesion counts significantly decreased ($P \leq .05$) throughout the study

compared with baseline (Figure 1), and mean scores for both objective and subjective irritation remained minimal (less than "barely perceptible") after 4 weeks of product use.¹⁷

Self-assessment correlated with the dermatologic evaluation for improvement in the degree of acne and amount of skin oiliness; 92% and 100% of the subjects, respectively, believed their condition improved. In addition, more than 85% of the subjects reported that the test products, cleanser, day lotion with SPF 15, and night cream, which all contained gluconolactone, were compatible with the use of topical tretinoin.¹⁷

The PHAs have gained important clinical uses as a result of their ability to provide the benefits of AHAs but with additional gentleness and antioxidant characteristics resulting from the polyhydroxy molecule. The study indicates that tretinoin 0.1% gel in combination with a gluconolactone (a PHA) regimen is well tolerated when used in the treatment of acne.

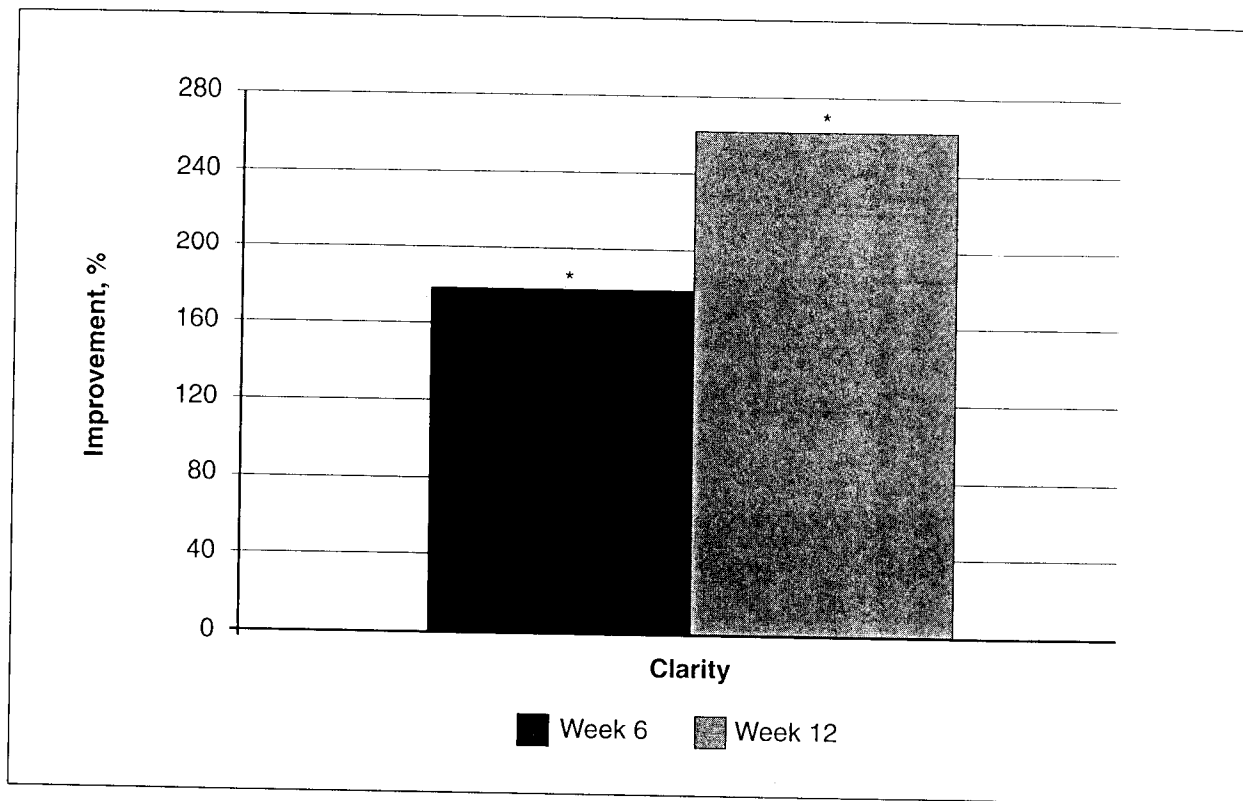


Figure 3. Percentage improvement in visual clarity in subjects using polyhydroxy acid plus retinyl acetate (pro-vitamin A) cream. Asterisk indicates significant improvements vs baseline ($P < .05$).

Effects of Ingredient Combinations With PHAs

Numerous combinations of PHAs with cosmetic and OTC ingredients exist; and there are strong rationales for many of these mixtures. PHAs have been used post-cosmetic procedure because they are very gentle to the skin, and they can complement the procedure by providing additional antiaging, antioxidant, and moisturizing benefits from homecare products. Some data suggest that combining AHAs or PHAs with drug substances can enhance the therapeutic effect more than when either ingredient is used alone.²¹ Two recent studies demonstrate the strong antiaging benefits of PHAs when combined with topical retinyl acetate (pro-vitamin A),²² and when combined in a regimen that included OTC-strength hydroquinone.²³

PHAs Plus Retinyl Acetate—This was a single-center, 12-week, controlled-use study.²² Statistical comparisons were made to baseline for facial evaluations. Product effects on skin thickness of the arm were compared statistically to an untreated control arm. All products were provided in blinded packaging.²²

Twenty-two healthy women aged 35 to 55 years with Fitzpatrick skin type I, II, or III who exhibited

moderate photodamage on the face completed the study. Visits were conducted at baseline and after 6 and 12 weeks of product use. There was a 3- to 5-day washout period prior to the study during which no topical products were applied to the face. Subjects were allowed to continue using their regular facial cleanser and glamour products.²²

Each woman applied the test cream 2 times daily to her face and 3 times daily to one forearm. The other arm served as an untreated control. The test cream contained gluconolactone 12% and retinyl acetate 1% (1% = 15,000 U/g)(pH 3.2).²²

Clinical grading was conducted for the following parameters: photoaging (fine lines, wrinkles, pore size, laxity, roughness, sallowness, mottled pigmentation, and clarity) using a 10-cm scale; objective irritation (erythema, edema, and dryness); and subjective irritation (stinging, burning, itching, tightness, and tingling). A 4-point scale (none, mild, moderate, severe) was employed for objective and subjective irritation grading. In addition, silicone replicas of the crow's-feet area were obtained with subsequent image analysis at baseline and 12 weeks. Total skin thickness measurements of both forearms were obtained via digital calipers²⁴ to

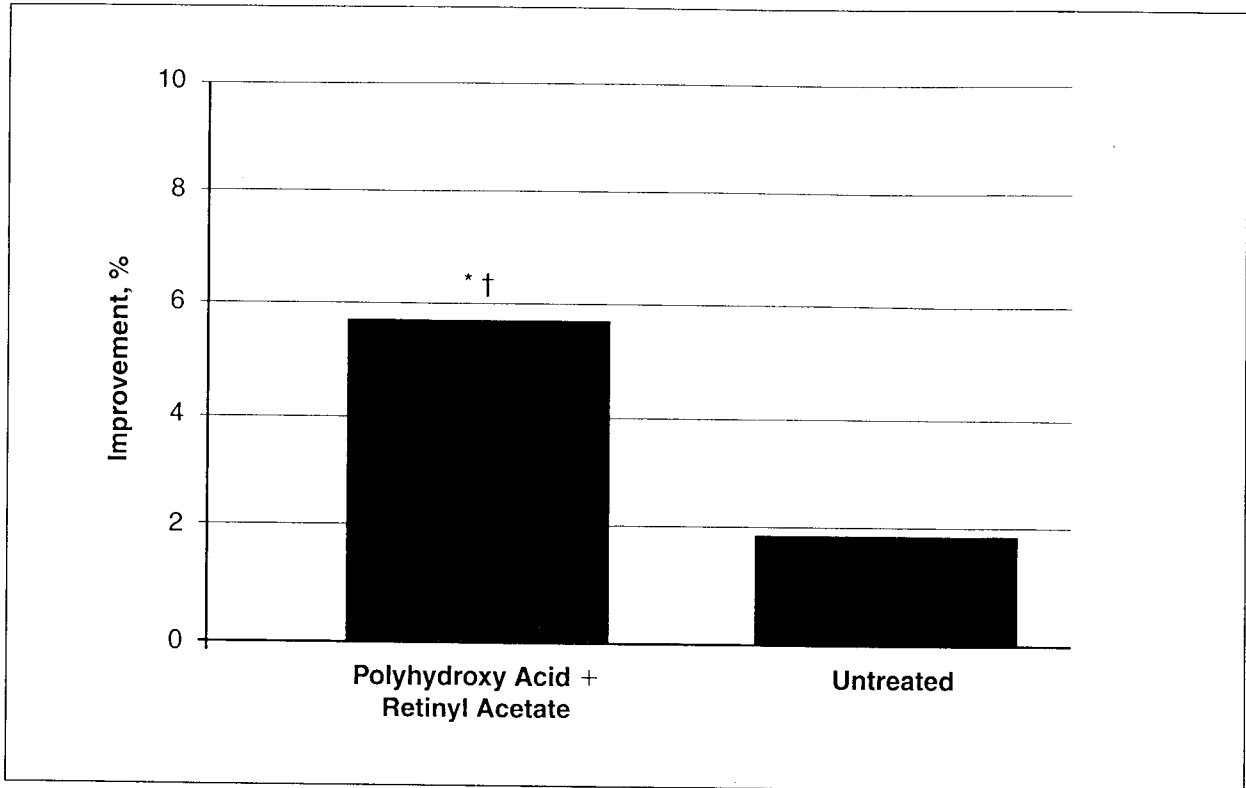


Figure 4. Percentage improvement in double skin thickness measurements in subjects using polyhydroxy acid plus retinyl acetate (pro-vitamin A) cream on one arm vs contralateral untreated control arm. Asterisk indicates significant improvement vs baseline ($P < .05$); dagger, significant improvement vs the untreated control ($P < .05$).

compare treated and untreated skin. Self-assessment also was collected to gain consumer perception of efficacy and product tolerance.²²

Data collected from clinical grading of photoaging and irritation were compared with baseline measurements using a paired *t* test at the $P \leq .05$ significance level. Mean percentage changes for aging parameters were calculated by averaging each subject's percentage change from baseline.²²

Clinical grading showed statistically significant improvement ($P < .05$) in all photoaging parameters at both 6 and 12 weeks. Fine lines improved by 36% and coarse wrinkles by 26% (Figures 2 and 3). Silicone replicas were analyzed and showed significant improvements in nearly all of the parameters representing the depth, number, and spacing of fine lines and coarse wrinkles (Rz, Ra, FNum, spacing, breadth, shadows, and NumWr), providing strong support for the clinical grading scores. In addition, 76% of the subjects self-assessed their skin to look and feel younger after just 2 weeks of product use. The irritation grading showed the product to be well tolerated at the recommended use of once daily.²²

Results of product use on the forearms showed a statistically significant increase ($P < .05$) in skin

thickness measurements at 12 weeks compared with the untreated control arm and baseline. The untreated control arm was not different from baseline (Figure 4).²² Increases in skin thickness are attributed to plumping of the skin, which is caused, in part, by increasing epidermal thickness and the amount of dermal glycosaminoglycans.²⁵ As a result, the texture/topography of the skin becomes smoother, with a corresponding reduced appearance of fine lines and wrinkles on the face.

PHAs Plus Hydroquinone—This single-center, 12-week, controlled-use study evaluated a PHA-containing skin-care regimen in conjunction with a skin-lightening product containing hydroquinone, kojic acid, gluconolactone, and lactobionic acid. Product effects were compared statistically with baseline conditions. All products were provided in blinded packaging.²³

Thirty-five healthy women aged 35 to 60 years with Fitzpatrick skin type I, II, or III who exhibited moderate photodamage on the face completed the study. Visits were conducted at baseline and after 6 and 12 weeks of product use. There was a 3- to 5-day washout period prior to the study during which no topical products were applied to the face.

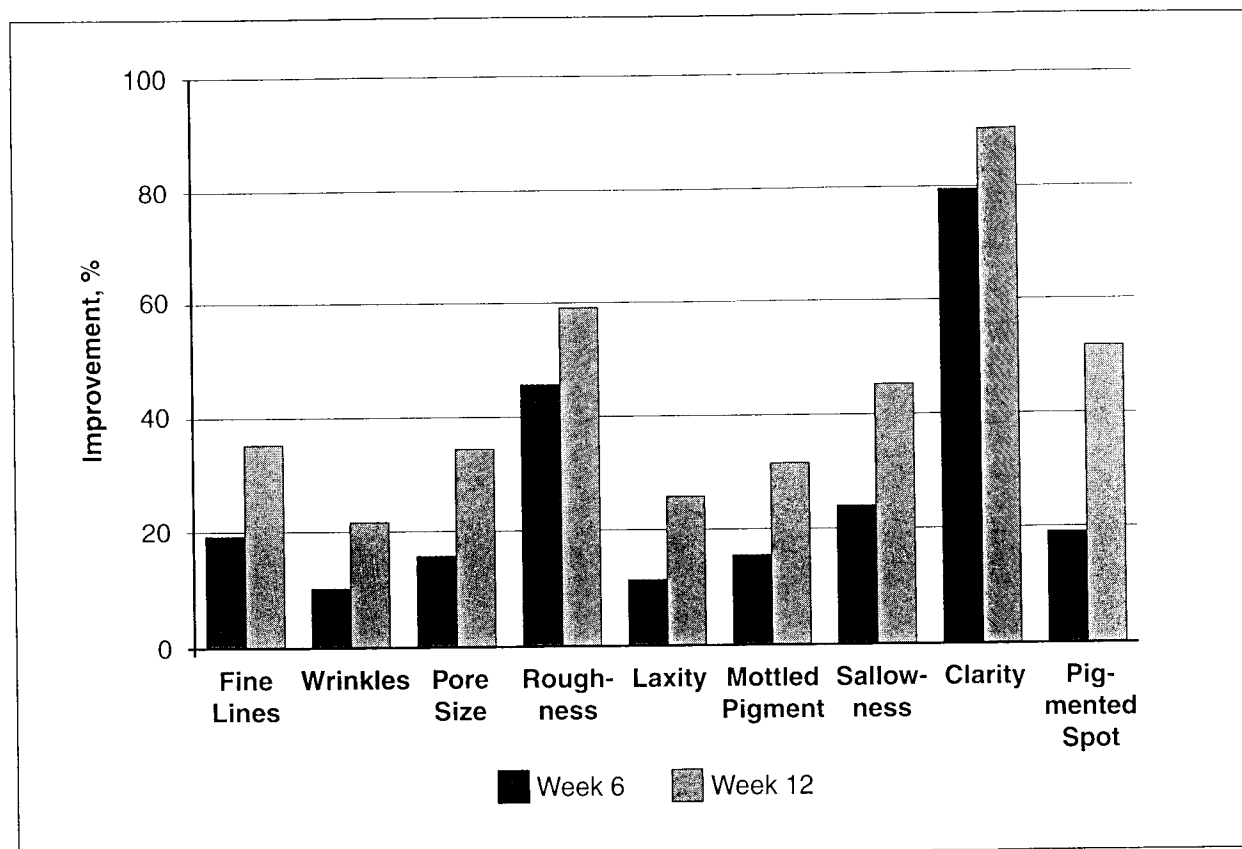


Figure 5. Percentage improvement in clinical grading of photoaging after 6 and 12 weeks of using a polyhydroxy acid and hydroquinone regimen. All attributes were significantly improved at weeks 6 and 12 vs baseline ($P \leq .05$).

Subjects were allowed to continue using their regular facial cleanser and glamour products.²³

The therapeutic regimen included a cleanser with gluconolactone 4% (pH 3.4); a skin lightener with gluconolactone 5%, lactobionic acid 5%, kojic acid 3%, and hydroquinone 2% (pH 3.9); a day lotion with SPF 15 with gluconolactone 4% (pH 3.9); and a night cream with gluconolactone 15% (pH 3.3). Products were applied in the morning and evening as follows: subjects washed their face with the cleanser, applied the skin lightener to pigmented areas, and then applied the appropriate moisturizer to the entire face.²³

Clinical grading was conducted for the following parameters: photoaging (fine lines, wrinkles, pore size, laxity, roughness, sallowness, mottled pigmentation, and clarity) using a 10-cm scale; skin lightening in a selected area of hyperpigmentation; objective irritation (erythema, edema, and dryness); and subjective irritation (stinging, burning, itching, tightness, and tingling). A 5-point scale with half-point increments (equal, slightly, moderately, markedly, and extremely darker) was

employed to grade skin lightening compared with surrounding skin; and a 4-point scale (none, mild, moderate, severe) was used for objective and subjective irritation grading.²³

In addition, pinch recoil was conducted in this study. Pinch recoil has been correlated to skin elasticity and is a measure of the time it takes for the skin to recover (recoil) after mechanical distortion (pinching).²⁶ Photographs were taken to capture the changes in skin condition. Self-assessment also was collected to gain consumer perception of efficacy and product tolerance.²³

Data collected from clinical grading of photoaging, skin lightening and irritation were compared with baseline measurements using a paired *t* test at the $P \leq .05$ significance level. Mean percentage changes were calculated by averaging each subject's percentage change from baseline.²³

The therapeutic regimen showed significant improvement for clinical grading ($P \leq .05$) at both 6 and 12 weeks for all photoaging attributes. The targeted pigmented spot showed a 52% improvement (Figure 5), and mean scores showed an improvement

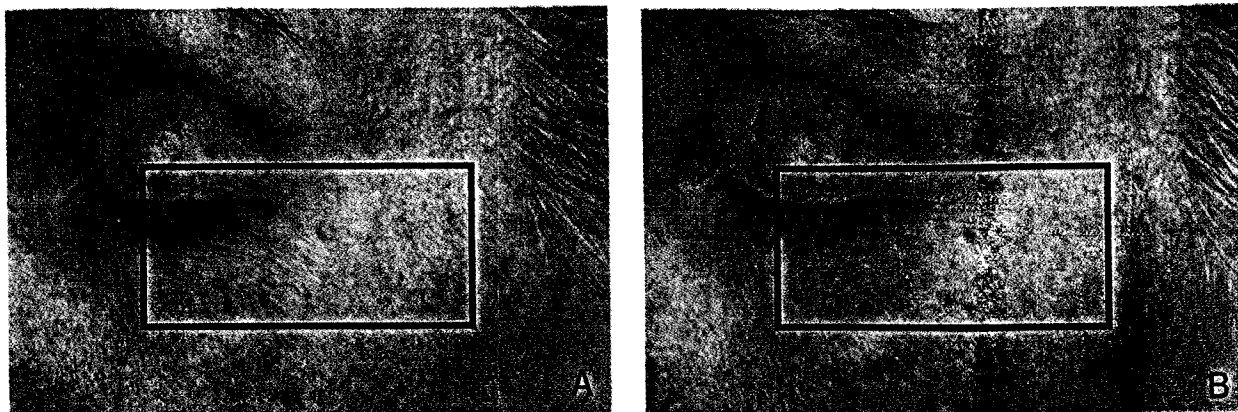


Figure 6. Before (A) and after (B) a 6-week therapeutic regimen containing polyhydroxy acids and hydroquinone. Improvements are noted in the appearance of fine lines in the under-eye area and in the lightening of pigmentation.

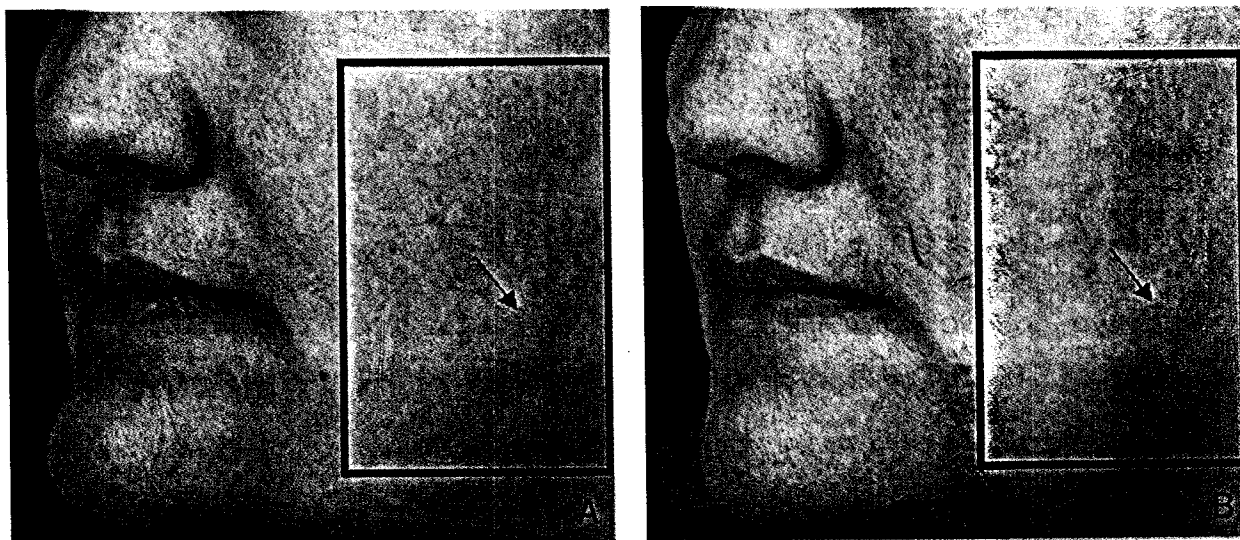


Figure 7. Before (A) and after (B) a 12-week therapeutic regimen containing polyhydroxy acids and hydroquinone. Improvements are noted in melasma.

of an entire grade after 12 weeks (from moderate to slight pigmentation, on average). In addition, 83% of the subjects self-assessed their pigmentation spot as being lighter at 12 weeks. Seventy-four percent of the subjects also noticed improvement in skin elasticity after 12 weeks. Pinch recoil, as a measure of skin elasticity, also was significantly improved ($P \leq .05$) from baseline after 6 and 12 weeks, thus providing further support for the clinical grading and consumer perception.²³

The therapeutic regimen was very well tolerated. Objective and subjective irritation was low overall, and subjects reported significant improvements in facial tightness at week 12.

Photography showed a smoothening in skin texture, especially in diminishing the appearance of fine lines and wrinkles in the eye area. Notable

improvements also were seen both in the lightening of dark spots and in skin clarity (Figures 6 through 9).

The combination of PHAs with other topical dermatologic ingredients into one product formulation provides added benefits, as well as simplicity of use for the patient. This, in turn, may enhance compliance and gives the physician better control over the patient's use of the product at home. Thus, a better result for both physician and patient may be achieved.

PHA Use in Ethnic Skin

Typically, antiaging studies are conducted on fair-skinned individuals (Fitzpatrick I, II, or III); therefore, little information exists on the efficacy and tolerance of antiaging products in darker skin types. A study comparing 3 groups of patients with skin color ranging from

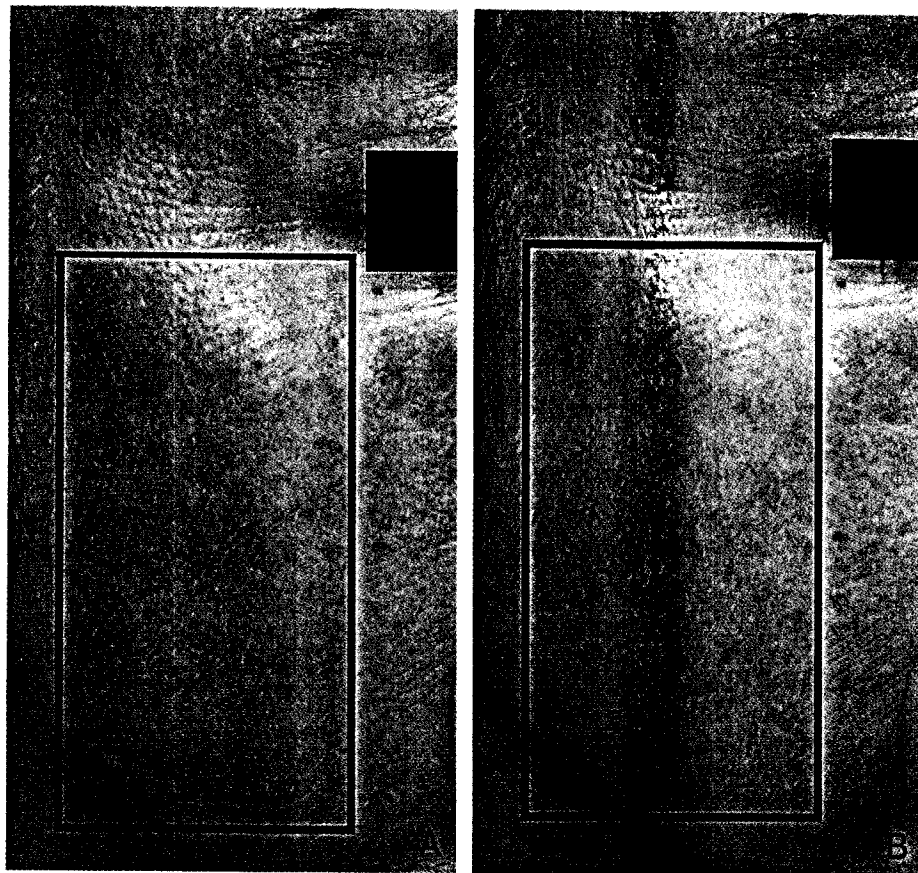


Figure 8. Before (A) and after (B) a 12-week therapeutic regimen containing polyhydroxy acids and hydroquinone. Improvements are noted in hyperpigmentation.

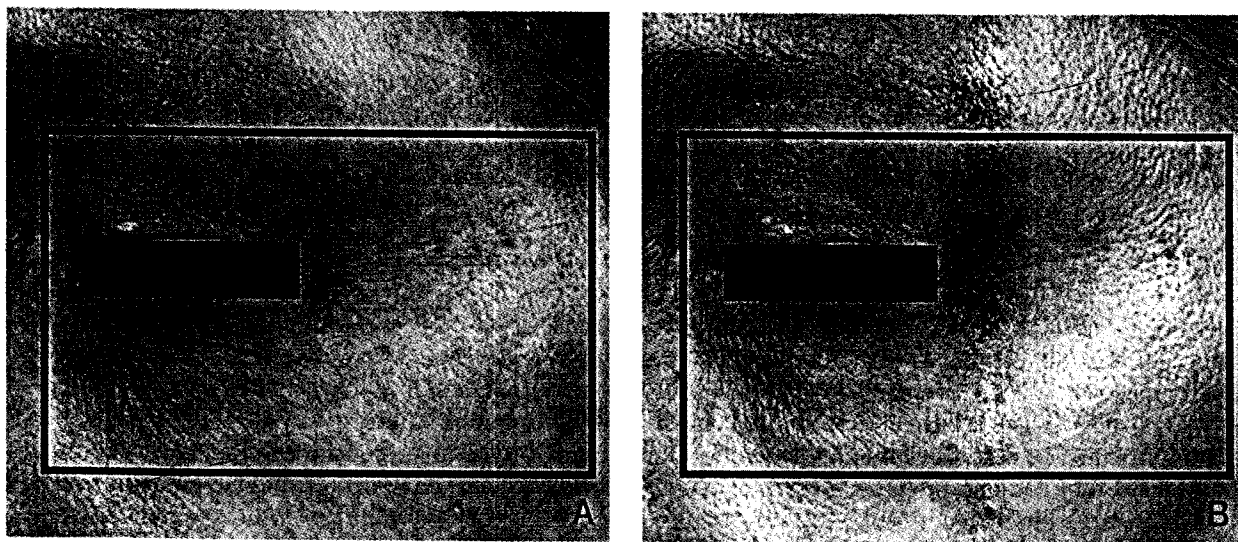


Figure 9. Before (A) and after (B) a 12-week therapeutic regimen containing polyhydroxy acids and hydroquinone. Improvements are noted in clarity and appearance of fine lines and wrinkles.

light to dark was conducted to assess their response to application of a PHA-containing regimen.¹⁴

This was a single-center, 12-week, controlled-use regimen study. Product effects were compared statistically with baseline conditions. Products were provided in blinded packaging. Healthy women aged 35

to 65 years with moderate facial photodamage were enrolled in the study. The 3 ethnic groups assessed were African Americans (n=18), Caucasians (n=19), and Hispanic (n=9)/Asian (n=6). Visits were conducted at baseline and after 2, 6, and 12 weeks of product use. There was a 2-day washout period prior to the

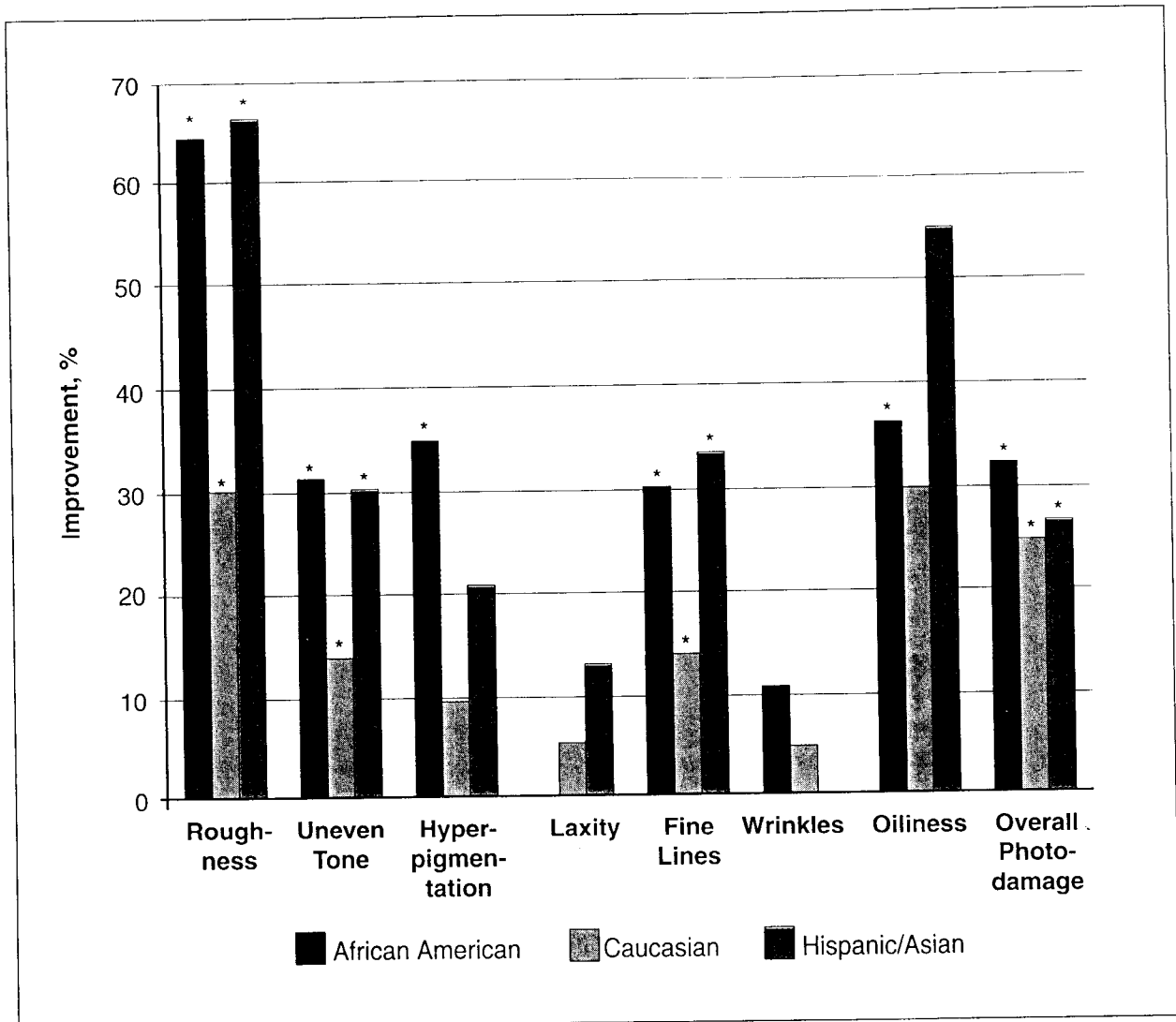


Figure 10. Percentage improvement in clinical grading of photoaging after 12 weeks of using a polyhydroxy acid regimen. Asterisks indicate significant improvement vs baseline ($P \leq 0.05$).

study during which no topical products were applied to the face. Patients were allowed to continue using their regular facial cleanser and glamour products.¹⁴

The regimen included a foaming cleanser with gluconolactone <1% (pH 3.8); a day lotion with SPF 15 with gluconolactone 4% (pH 3.9); and a night cream with gluconolactone 8% (pH 3.8). Patients washed their face with the cleanser twice daily followed by application of the appropriate moisturizer to the entire face.¹⁴

A board-certified dermatologist assessed the following parameters using a 5-point scale (none, mild, moderate, marked, severe): photoaging (roughness, uneven tone, hyperpigmentation, laxity, fine lines, wrinkles, oiliness, and overall photo-

damage); objective irritation (erythema, edema, dryness, and overall irritation); and subjective irritation (stinging, burning, and itching). Self-assessment also was collected to gain patient perception of efficacy and product tolerance.¹⁴

Data collected from clinical grading of photoaging and irritation were compared with baseline measurements using a paired *t* test at the $P \leq 0.05$ significance level. Mean percentage changes for photoaging parameters were calculated by averaging each patient's percentage change from baseline.¹⁴

Patients in all 3 groups showed significant improvements ($P \leq 0.05$) in the clinical grading of many of the photoaging parameters assessed (Figure 10). Women in the darker-skinned groups, however, seemed to exhibit greater improvements

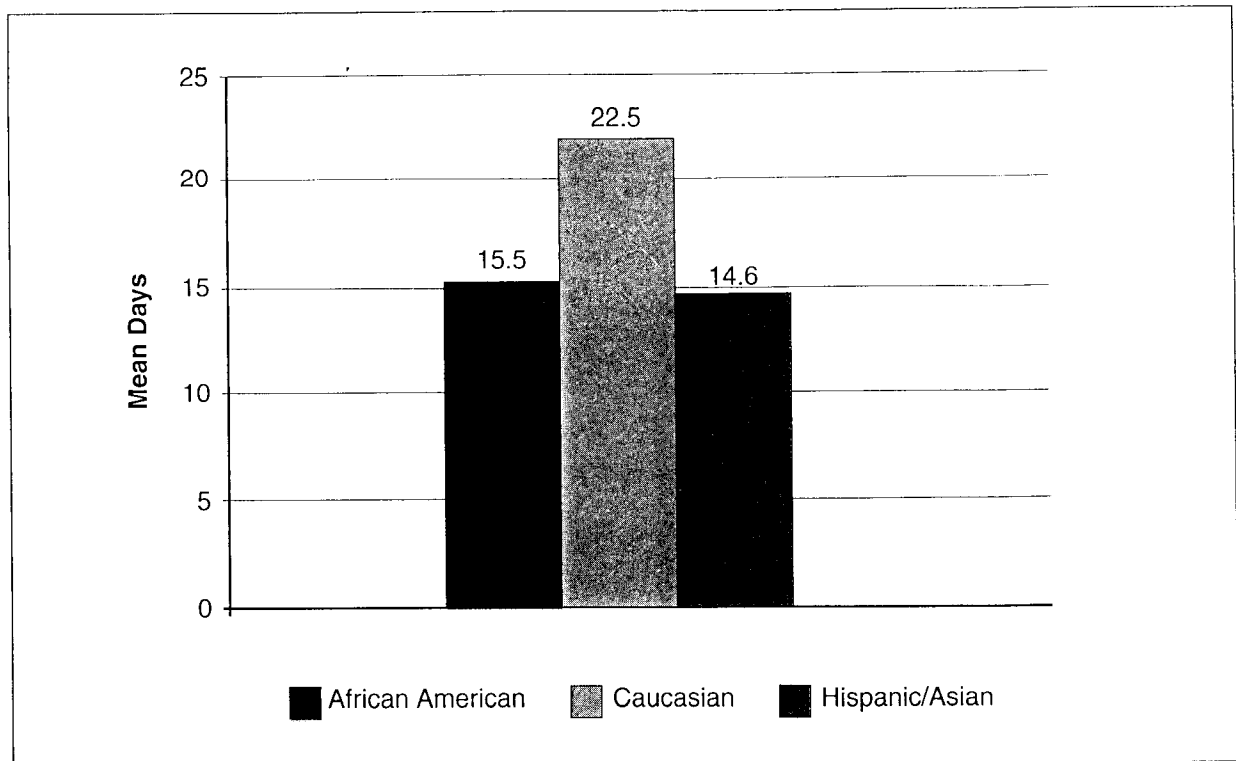


Figure 11. Patient self-assessment of the number of days to younger-looking skin with the use of a polyhydroxy acid regimen.

in the photoaging parameters overall compared with women in the Caucasian group. Physician assessment at baseline showed patients with darker skin to have more severe hyperpigmentation and uneven skin tone than patients in the lighter-skinned group. Thus, it seems that greater improvements were observed in the pigmentation irregularities that started in a worsened condition. Conversely, the Caucasian group was assessed at baseline to exhibit the most severe condition for surface textural parameters such as fine lines. The African American and Hispanic/Asian groups, however, showed greater improvement in surface textural condition even though they started with a less severe condition. Thus, the more severe pigmentation irregularities improved to a greater extent than the more severe textural conditions. This seems to correlate with the location of the condition—conditions originating in the epidermis, such as hyperpigmentation, should respond more quickly and more easily to topical products than conditions that have their origin in the dermis, as is the case with fine lines and skin laxity.¹⁴

The PHA regimen was well tolerated by all ethnicities. Objective irritation was low, and there was no subjective irritation reported after 12 weeks of product use. Self-assessment of product effects and

skin compatibility support the clinical data. Mean scores indicate that patients rated improvements in photodamage and product compatibility with their skin from good to excellent. Self-assessment results also showed that after approximately 2 to 3 weeks of product use, patients reported that their skin looked younger (Figure 11). It is interesting to note that women in the Caucasian group reported the longest time to younger-looking skin. This is in agreement with the clinical grading. The data show that this finding was apparent both to the physicians and patients in this study.¹⁴

Conclusion

The gentleness of PHAs, along with their moisturizing abilities and antioxidant effects, make them a solid choice for use on any skin type. They may be used in combination with other products, ingredients, or procedures to provide additional benefits to therapy or to enhance therapeutic effect.

This article discusses various aspects of PHA combinations and assesses their compatibility and efficacy. The combination of tretinoin and gluconolactone-containing products was well tolerated in treating adult facial acne.

Combinations of ingredients and regimens including retinyl acetate (pro-vitamin A) and hydro-

quinone were shown to be effective in providing anti-aging benefits to the skin. The gluconolactone and retinyl acetate combination cream exhibited significant skin benefits including skin smoothing and plumping and was assessed through a variety of methods. The therapeutic regimen of PHAs (gluconolactone and lactobionic acid) and hydroquinone showed excellent improvements in antiaging and skin lightening parameters. The regimen was well tolerated and was well received by the study participants as evidenced by positive self-assessment. Finally, gluconolactone-containing products were shown to be compatible with skin of various ethnicities and were shown to provide significant improvements in photoaging in these populations.

These studies collectively support the use of PHAs to provide antiaging benefits either when used alone, regardless of skin type or ethnicity, or in combination with therapeutic products or ingredients.

REFERENCES

1. Van Scott EJ, Yu RJ. Hyperkeratinization, corneocyte cohesion, and alpha hydroxy acids. *J Am Acad Dermatol.* 1984;11:867-879.
2. Van Scott EJ, Yu RJ. Alpha-hydroxy acids: procedures for use in clinical practice. *Cutis.* 1989;43:222-228.
3. Van Scott EJ, Yu RJ. Alpha hydroxy acids: therapeutic potentials. *Canadian J Dermatol.* 1989;1:108-112.
4. Van Scott EJ, Yu RJ. Hydroxy acids: past, present, future. In: Moy R, Luftman D, Kakita L, eds. *Glycolic Acid Peels.* New York, NY: Marcel Dekker; 2002:1-14.
5. Yu RJ, Van Scott EJ. Alpha-hydroxy acids: science and therapeutic use. *Cosmet Dermatol.* Oct 1994;7(suppl):12, 14, 16-20.
6. Bergfeld W, Tung R, Vidimos A, et al. Improving the cosmetic appearance of photoaged skin with glycolic acid. *J Am Acad Dermatol.* 1997;36:101-103.
7. Leyden JJ, Lavker RM, Grove G, et al. Alpha hydroxy acids are more than moisturizers. *J Geriatr Dermatol.* 1995;3(suppl A):33A-37A.
8. Rendon MI, Okan G. The use of alpha hydroxy acids in xerosis and photoaging. In: Moy R, Luftman D, Kakita L, eds. *Glycolic Acid Peels.* New York, NY: Marcel Dekker; 2002:115-139.
9. Smith W. Hydroxy acids and skin aging. *Cosmet Toilet.* 1994;109:41-48.
10. Bergfeld WF, Remzi BK, Green B, et al. An evaluation of the gluconolactone sensitive skin care products. Poster presented at: 56th Annual Meeting of the American Academy of Dermatology; February 27-March 4, 1998; Orlando, Fla.
11. Bernstein EF, Green BA, Edison B, et al. Poly hydroxy acids (PHAs): clinical uses for the next generation of hydroxy acids. *Skin Aging.* 2001;suppl:4-11.
12. Yu RJ, Van Scott EJ. Hydroxycarboxylic acids, N-acetylamino sugars, and N-acetylamino acids. *Skinmed.* 2002;2:117-122.
13. Green B, Tseng C, Wildnauer R, et al. Safety and efficacy of a gluconolactone (polyhydroxy acid) containing regimen on sensitive skin and photodamage following controlled consumer use. Poster presented at: 57th Annual Meeting of the American Academy of Dermatology; March 19-24, 1999; New Orleans, La.
14. Data on file. Princeton, NJ: NeoStrata Company, Inc; 1999.
15. Petratos MA. Drug therapies and adjunctive uses of alpha-hydroxy and polyhydroxy acids. *Cutis.* 2000;66:107-111.
16. Berardesca E, Distanto F, Vignoli GP, et al. Alpha hydroxy-acids modulate stratum corneum barrier function. *Br J Dermatol.* 1997;137:934-938.
17. Data on file. Princeton, NJ: NeoStrata Company, Inc; 2001.
18. Kligman A. Results of a pilot study evaluating the compatibility of topical tretinoin in combination with glycolic acid. *Cosmet Dermatol.* Oct 1993;6:28-32.
19. Kligman A. Compatibility of a glycolic acid cream with topical tretinoin for the treatment of the photo damaged face of older women. *J Geriatr Dermatol.* 1993;1:179-181.
20. Weiss JS, Shavin JS. An evaluation of the compatibility of tretinoin cream 0.05% and a glycolic acid 8% solution for acne-prone skin. *Cosmet Dermatol.* Oct 1996;9:26-38.
21. Yu RJ, Van Scott EJ. Additives enhancing topical actions of therapeutic agents. US Patent 5 665 776. September 9, 1997.
22. Data on file. Princeton, NJ: NeoStrata Company, Inc; 2000.
23. Data on file. Princeton, NJ: NeoStrata Company, Inc; 2002.
24. Green BA, Edison BL, Wildnauer RH, et al. Lactobionic acid and gluconolactone: PHAs for photoaged skin. *Cosmet Dermatol.* Sept 2001;14:24-28.
25. Ditre CM, Griffin TD, Murphy GF, et al. Effects of alpha-hydroxy acids on photoaged skin: a pilot clinical, histologic, and ultrastructural study. *J Am Acad Dermatol.* 1996;34:187-195.
26. Appa Y, Asuncion BS, Stephens TH, et al. A six month clinical study to evaluate the long term efficacy and safety of an alpha hydroxy acid lotion. Poster presented at: 54th Annual Meeting of the American Academy of Dermatology; February 10-15, 1996; Washington, DC.