Evaluation of a Prescription Strength 4% Hydroquinone/10% L-Ascorbic Acid Treatment System for Normal to Oily Skin

Suzanne Bruce MD[a] and JoAnne Watson DPM[b]
[a]Suzanne Bruce and Associates, PA, Houston, TX
[b]OMP, Inc., Long Beach, CA

ABSTRACT

Introduction: A 4% hydroquinone/10% L–ascorbic acid treatment system aims to treat early signs of photodamage in normal to oily skin and help prevent further photodamage. The system also contains vitamin E, witch hazel, aloe barbadensis leaf juice, penetration-enhancing ingredients, micronized zinc oxide, and octinoxate.
Methods: Patients with minimal or mild facial photodamage and hyperpigmentation, and normal to oily facial skin, used the treatment system for 12 weeks.
Results: Of 34 females enrolled, 30 completed. Median scores for the overall integrated assessment of photodamage, overall intensity of pigmentation, fine lines and wrinkles, tactile roughness, and laxity were significantly improved at week 12 compared with baseline. Furthermore, ≥90 percent of patients considered their skin was smoother, softer, more evenly toned, and more radiant, and 100 percent were satisfied with the overall appearance of their skin.
Conclusion: The treatment system can help to ameliorate early signs of photodamage in normal to oily skin.

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INTRODUCTION

Photodamage is a cumulative process and is best minimized or, ideally, prevented. Protecting the skin from ultraviolet light is the simplest and most effective method of preventing photodamage, but other approaches, such as the use of antioxidants, may also offer benefit. For skin that is already photodamaged, early intervention is advised not only to improve the appearance of the skin but also to encourage the adoption of adequate sun protection measures at a young age—thereby hopefully minimizing the need for further intervention later.

A variety of agents are used to reduce the manifestations of photodamage, including hydroquinone and L–ascorbic acid. An early intervention system containing prescription strength (4%) hydroquinone and 10% L–ascorbic acid has been developed to treat photodamage in youthful looking skin and prevent the development of further photodamage. The original version of this physician-dispensed early intervention system was designed for normal to dry skin and, more recently, a second version of the system has been developed for normal to oily skin.

A clinical study has been performed to evaluate the efficacy of this newer version of the 4% hydroquinone/10% L–ascorbic acid treatment system in individuals with normal to oily skin.

METHODS

Patients

Individuals were eligible for enrollment into this study if they had the following: a clinical diagnosis of minimal or mild facial photodamage and hyperpigmentation; type I or II Glogau photodamage classification; and a score of 1, 2, or 3 on the overall integrated assessment of facial photodamage and the overall intensity of facial pigmentation scale (Table 1). They were also required to have normal to oily facial skin and be between 18 and 40 years old. Newspaper advertisements approved by the institutional review board were used to recruit patients into the study.

Participants were required to refrain from the following during the study: the facial use of non-study topical products (including medications, moisturizers, sunscreens, and fragrances); the facial use of medicated make-up (except oil-free non-comedogenic make-up, mascara, eyeliner, eyeshadow, and lipstick were allowed if they were already being used before the study); facial procedures (including peels, facials, microdermabrasion, and injection of botulinum toxin type A or dermal fillers); and removal of facial hair (except plucking of eyebrows with tweezers was allowed). They were also required to be willing to avoid excessive sun exposure and refrain from using tanning booths.

TABLE 1.

Investigator Efficacy Evaluations			
Overall Integrated Assessment of Facial Photodamage, Fine Lines and Wrinkles, Tactile Roughness, Laxity	**Overall Intensity of Facial Pigmentation**	**Global Response to Treatment**	**Change from Baseline in Lightness/Brightness of Facial Skin**
0 = None	0 = None No noticeable hyperpigmentation	Worse	Unchanged No detectable change from baseline evaluation
1 = Minimal	1 = Minimal Localized deposits of pigment	Unchanged No detectable improvement from baseline evaluation	Slight increase (~10%) in lightness/brightness
2 = Mild	2 = Mild Mild, diffuse deposits of pigment	Slight (~10%) improvement	Mild increase (~25%) in lightness/brightness
3 = Mild up to moderate	3 = Mild Mild, diffuse deposits of pigment	Mild (~25%) improvement	Moderate increase (~50%) in lightness/brightness
4 = Moderate	4 = Moderate Moderate, diffuse deposits of pigment	Moderate (~50%) improvement	Marked increase (≥ ~75%) in lightness/brightness
5 = Severe	5 = Marked Marked, dense deposits of pigment	Marked (~75%) improvement	—
—	6 = Severe Severe, dense deposits of pigment	Almost complete clearing (~90% improvement)	—
—	—	Complete clearing, no signs of hyperpigmentation (~100% improvement)	—

Exclusion criteria included: any past or present facial skin condition that might interfere with diagnosis or evaluation in the study; a requirement for the use of other drugs that might enhance hyperpigmentation (hormonal and gonadotropic hormones not to be initiated during the study); a history of increased pigmentation or contact dermatitis after using hydroquinone or tretinoin; known hypersensitivity to any ingredient in the treatment system; participation in activities involving excessive exposure to sunlight without wearing protective clothing; and facial sunburn at the baseline visit.

The following washout periods were required: 1 week for facial hair removal; 2 weeks for facial use of topical medications or bleaching products, photosensitizing medications or procedures, and UV light therapy or sunbathing; 3 weeks for facial use of topical tretinoin; 30 days for participation in an investigational drug or device study; 8 weeks for facial microdermabrasion; 12 weeks for chronic use of systemic steroids; 3 months for any drug with known potential for toxicity to a major organ; 6 months for acitretin, isotretinoin, methotrexate, photoallergic or phototoxic drugs, laser resurfacing, deep skin peels, or injection of botulinum toxin type A or dermal fillers; and 2 years for systemic retinoids.

All patients signed informed consent, and the protocol was approved by the relevant institutional review board.

Treatment Regimen

All patients were instructed to use the prescription strength hydroquinone/L–ascorbic acid treatment system for normal to oily skin (Obagi-C® Rx System, OMP, Inc., Long Beach, CA) for 12 weeks. This involved using a cleansing gel, balancing toner, clarifying serum, sunscreen SPF 30, and night cream (Table 2). The first application of the study treatment products was conducted at the end of the baseline visit under the supervision of the investigator or their designee, and the patients were provided with verbal and written instructions on how to apply the products (Table 2).

Outcome Measures

Patients were evaluated at baseline and weeks 4, 6, and 12. The investigator evaluated each patient's facial skin in terms of an overall integrated assessment of photodamage, the overall intensity of pigmentation, fine lines and wrinkles, tactile roughness, laxity, global response to treatment, and the change from baseline in lightness/brightness (Table 1).

At each post-baseline visit, the patients were instructed to complete a questionnaire which asked them to evaluate if the treatment system was easy to apply; their skin texture was smoother; their skin felt softer; their skin color tone was more even; their skin was more radiant; and they had a visible reduction in fine lines and wrinkles (Ta-

TABLE 2.

Prescription Strength Hydroquinone/L-Ascorbic Acid Treatment System*		
Components of Hydroquinone/ L-Ascorbic Acid System	**Frequency of Application**	**Application Instructions Given to Patients**
Cleansing gel	Twice daily	Mix a "quarter-sized" amount of the cleansing gel in the palm of your hand with lukewarm water to form a slight lather and gently rub over your entire face, avoiding the eyes. Rinse completely with lukewarm water and gently pat your face dry with a towel.
Balancing toner	Twice daily	Apply balancing toner to a cotton pad and apply to entire face, avoiding the eyes. Do not rinse. Allow the skin to dry.
Clarifying serum	Each morning	Apply a half dropperful of clarifying serum to the palm of your hand. Using your fingertips from the opposite hand, apply to entire face, massaging the serum gently into the skin, avoiding the eyes. Allow the skin to dry.
Sunscreen SPF 30	Each morning and as needed	Apply sunscreen evenly and generously to entire face, avoiding the eyes. Repeat after 2 hours if in the sun. Reapply as needed or after towel drying, swimming, or perspiring. Wash your hands thoroughly with soap and water after applying the treatment products.
Night cream	Each evening	Apply a "dime-sized" amount of the night cream onto the palm of your hand. Using your fingertips from the opposite hand, apply to entire face, avoiding the eyes. Wash your hands thoroughly with soap and water after applying the treatment products.

*Contains 4% hydroquinone, L-ascorbic acid, vitamin E, witch hazel, aloe barbadensis leaf juice, other penetration-enhancing ingredients, micronized zinc oxide, and octinoxate

TABLE 3.

Patient Efficacy Evaluations						
Treatment system is easy to apply?	**Skin is smoother? Skin feels softer? Skin appears more even toned? Skin appears more radiant?**	**Visible reduction in fine lines and wrinkles?**	**How improved is the overall appearance of your skin?**	**How would you rate this treatment system in terms of efficacy?**	**How would you rate this treatment system compared with other skin care treatments you have used in the past?**	**How satisfied are you with the overall appearance of your skin?**
Strongly agree	Strongly agree	Strongly agree	Extremely improved	Excellent	Excellent	Very satisfied
Somewhat agree	Somewhat agree	Somewhat agree	Very improved	Very good	Very good	Satisfied
Neutral	Neutral	Neutral	Moderately improved	Good	Good	Dissatisfied
Somewhat disagree	Somewhat disagree	Somewhat disagree	Just a little improved	Fair	Fair	Very dissatisfied
Strongly disagree	Strongly disagree	Strongly disagree	Not at all improved	Poor	Poor	–

ble 3). They were also asked to compare their baseline photograph (taken before they had started using the hydroquinone/L–ascorbic acid treatment system) with their current appearance (viewed in a hand mirror) before rating the following parameters: the efficacy of the hydroquinone/L–ascorbic acid treatment system; how the hydroquinone/L–ascorbic acid treatment system compared to previous skin care treatments they had used; and their satisfaction with the overall appearance of their skin (Table 3).

Statistical Analyses

Patients who discontinued early were excluded from the post-baseline efficacy analyses. For five of the investigator evaluations (overall integrated assessment of photodamage, overall intensity of pigmentation, fine lines and wrinkles, tactile roughness, and laxity), median values at each timepoint were compared with the baseline value using a signed-rank test. An α of $\leq .05$ was considered statistically significant.

RESULTS

Patients

Of 34 patients enrolled, 30 (88%) completed. Three discontinued due to mild facial adverse events and 1 withdrew voluntarily. The mean age of the patients was 32 years. The majority (88%) were Fitzpatrick skin type II–IV, with 82% being Caucasian, 12% Asian, and 6% black. In terms of the Glogau photodamage classification, 27% were type I, and 74% were type II.

Efficacy

At weeks 4, 6, and 12, respectively, the investigator evaluations showed that the proportion of patients showing at least a 1-grade improvement from baseline was: 7%, 47%, and 80% for the overall integrated assessment of photodamage; 30%, 60%, and 87% for the overall intensity of facial pigmentation; 10%, 30%, and 50% for fine lines and wrinkles; 57%, 87%, and 90% for tactile roughness; and 7%, 10%, and 33% for laxity (Figures 1–4). With each of these parameters, median scores showed significant improvements relative to baseline values: at all three timepoints for tactile roughness and overall intensity of pigmentation; at weeks 6 and 12 for the overall integrated assessment of photodamage and for fine lines and wrinkles; and at week 12 for laxity (Figures 1–4). In addition, at week 12, 90% of patients had achieved at least a moderate (~50%) global improvement and 87% had achieved at least a moderate (~50%) increase in lightness/brightness of the skin.

A high proportion of patients strongly agreed or somewhat agreed that: their skin was smoother (93% at week 4, 97% at week 12); their skin felt softer (90% at week 4, 93% at week 12); the treatment system was easy to apply (90% at week 4, 93% at week 12); their skin had a more even color tone (76% at week 4, 90% at week 12); their skin appeared more radiant (87% at week 4, 90% at week 12); and there was a visible reduction in their fine lines and wrinkles (57% at week 4, 87% at week 12) (Figure 5). At weeks 4 and 12, respectively, 80% and 97% of patients considered the overall appearance of their skin to be at least moderately improved; 83% and 97% considered the efficacy of the treatment system to be excellent, very good, or good; and 86% and 100% considered the treatment system to be excellent, very good, or good when compared with other skin care treatments they had used previously.

Photographic documentation of the improvement in facial appearance attained in two patients is shown in Figure 6.

Patient Satisfaction

The proportion of patients who were satisfied or very satisfied with the overall appearance of their skin increased from 90% at week 4 to 100% at week 12.

Tolerability

Adverse events that were probably or definitely related to treatment were facial skin dryness (incidence of 32%), erythema (9%), peeling (9%), pruritus (6%), milia (6%), rash (3%), burning sensation (3%), contact dermatitis (3%), and acne (3%). All adverse events were mild and they were most likely to occur in the first week of treatment. Of the 25 reports of adverse events that were at least probably related to treatment, 16 occurred in the 1st week (5 dryness, 3 redness, 2 peeling, 2 milia, 1 rash, 1 pruritus, 1 contact dermatitis, 1 burning sensation), 5 in the 2nd week (4 dryness, 1 acne), 2 in the 4th week (dryness, pruritus), and 2 in the 5th week (dryness, peeling). Among these 25 reports of adverse events, 22 resolved during the study period (with continued, uninterrupted treatment). Two patients had adverse events that had not resolved by the end of the study (2 dryness, 1 peeling).

Three patients discontinued due to facial adverse events (dryness, erythema/pruritus/dryness/rash, and contact dermatitis, respectively). The other subjects did not reduce or interrupt dosing.

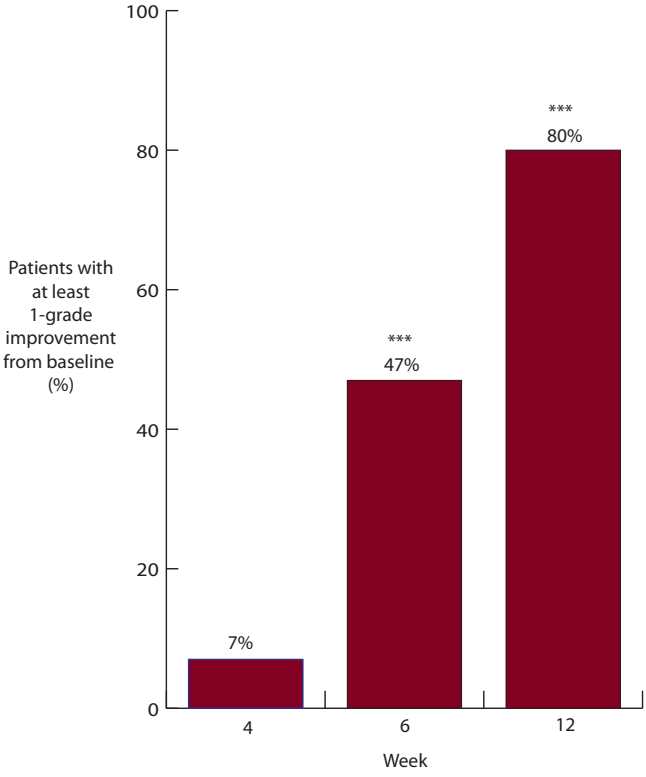
DISCUSSION

The results of this study show that use of the 4% hydroquinone/10% L–ascorbic acid treatment system is associated with improvements in the overall appearance of the skin as well as in multiple specific parameters (pigmentation, fine lines and wrinkles, tactile roughness, laxity, lightness/brightness, smoothness, softness, evenness of color tone, and radiance).

Importantly, 100 percent of the patients were satisfied or very satisfied with the overall appearance of their skin at the end of the study. This high rate of patient satisfaction is likely a reflection of the ease of application of the treatment system and the fact that the vast majority of patients observed improvements in their skin—at the end of the study, 97 percent reported the appearance of their skin to be at least moderately improved, 97 percent considered their skin was smoother, 93 percent considered their skin felt softer, 90 percent considered their skin was more evenly toned, 90 percent considered their skin was more radiant, and 87 percent reported a visible reduction in fine lines, and wrinkles. The high rate of patient satisfaction also likely reflects the fact that at the end of the study 100 percent of the patients considered the system was good, very good, or excellent compared with other treatments they had used previously.

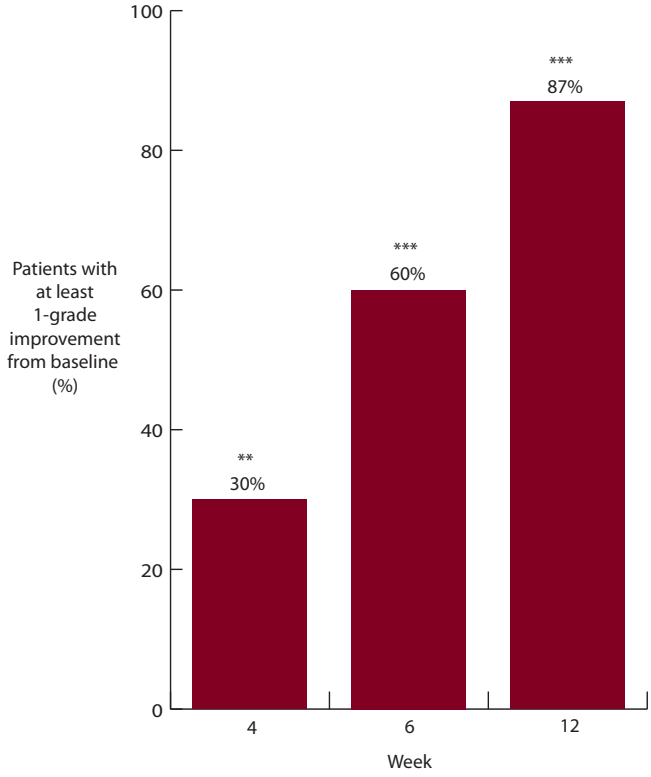
The favorable comparisons with other skin care treatments may also be partly attributable to the study product being a treatment system or "kit," a concept that has become very popular in dermatology in recent years, particularly in the treatment of acne. The popularity of such systems is thought to be at least partly due to their convenience in providing a complete skin care regimen which cares for the skin generally while also providing treatment for a specific condition such as photodamage (in this study) or acne. Importantly, another potential benefit of treatment systems is that they may enhance compliance[1] and, ultimately, this could enhance efficacy.

FIGURE 1. Overall integrated assessment of photodamage.



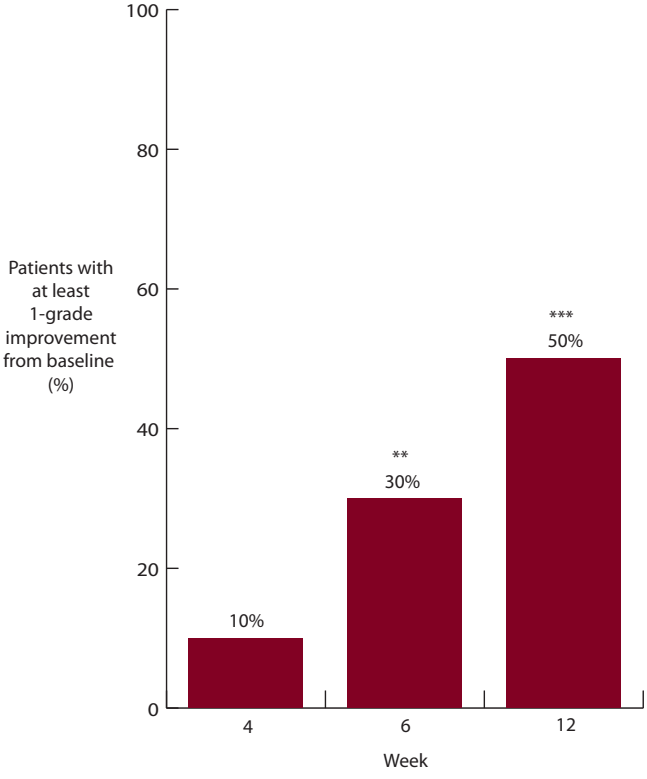
*** P≤.001 for median score versus baseline

FIGURE 2. Overall intensity of facial pigmentation.



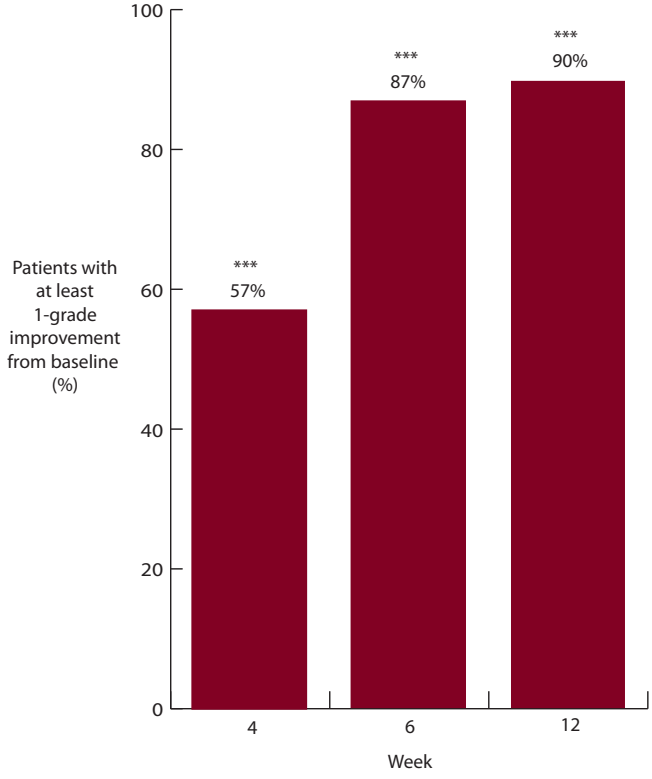
** P≤.01, *** P≤.001 for median score versus baseline

FIGURE 3. Fine lines and wrinkles.



** P≤.01, *** P≤.001 for median score versus baseline

FIGURE 4. Tactile roughness.



*** P≤.001 for median score versus baseline

FIGURE 5. Patient ratings at week 12.

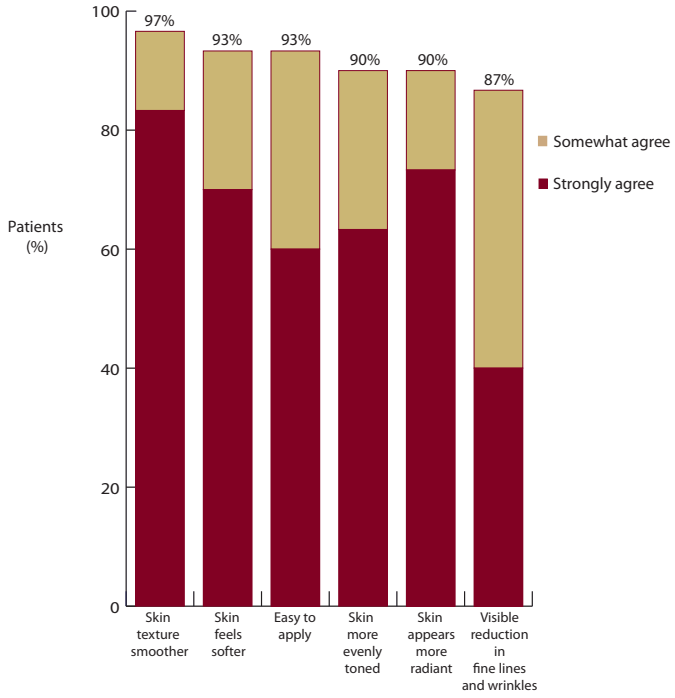
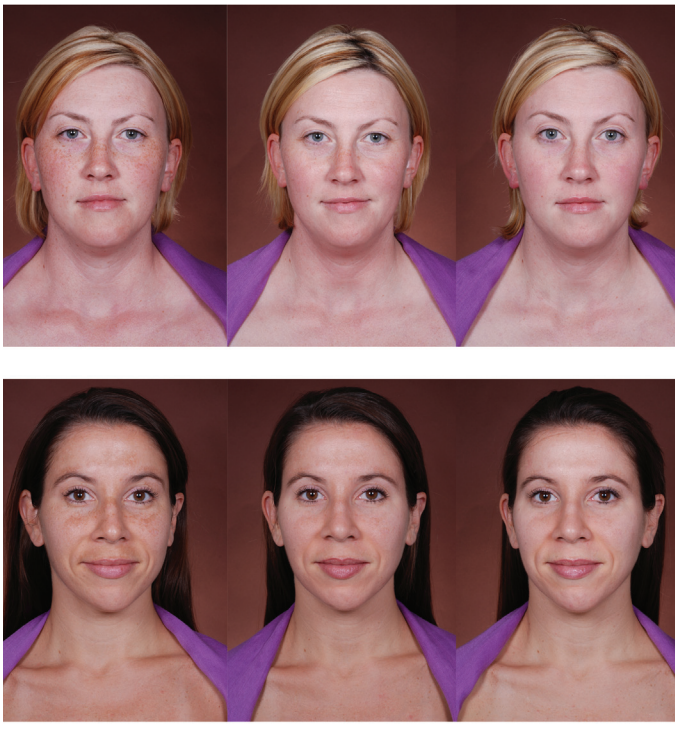


FIGURE 6. Clinical improvement associated with use of the 4% hydroquinone/10% L-ascorbic acid treatment system for normal to oily skin.



Hydroquinone has been the gold standard for the treatment of hyperpigmentation for more than 50 years and is believed to reduce the production of melanin by inhibiting the enzyme tyrosinase.[2] In the United States and Canada, formulations of hydroquinone with a concentration of up to 2% can be sold over-the-counter without a prescription and formulations up to 4% are available with a prescription. Due to their higher concentration, the 4% prescription formulations are more efficacious, and quicker to show their effects, than the over-the-counter formulations.[2]

There are multiple advantages of using L–ascorbic acid in conjunction with hydroquinone. First, it may enhance the penetration, and hence efficacy, of hydroquinone.[2] Second, as an antioxidant, L–ascorbic acid offers protection against free radicals produced after exposure to ultraviolet light and can therefore help prevent the development of further photodamage.[3-5] Third, L–ascorbic acid is essential for collagen biosynthesis and reduces melanin synthesis by inhibiting tyrosinase—mechanisms of action which may help reduce fine lines and wrinkles, and dyspigmentation, respectively.[6,7]

Vitamin C is an unstable molecule that readily oxidizes when exposed to light or air and must be formulated appropriately to ensure adequate stability, bioavailability, and effectiveness—as factors such as the pH of its formulation can influence its efficacy.[8-11] The importance of appropriate formulation is demonstrated by the results of an in vitro study using human skin which showed greater L–ascorbic acid stability, and greater delivery of bioavailable L–ascorbic acid to the viable layers of the skin, with an optimized formulation containing 10% L–ascorbic acid and 4% hydroquinone than with a leading competitor formulation containing 20% L–ascorbic acid.[11] A more than 10-fold greater absorption of L–ascorbic acid was evident with the optimized formulation compared with the competitor product.[11] (The optimized formulation in the Agahigian study is the clarifying serum used in the version of the hydroquinone/L–ascorbic treatment system for individuals with normal to dry skin.)

In addition to 4% hydroquinone and 10% L–ascorbic acid, the treatment system used in the study presented here also contains vitamin E, witch hazel, aloe barbadensis leaf juice, other penetration-enhancing ingredients, and sunscreens. Vitamin E is included as it is believed to act synergistically with vitamin C,[4-6,12] and witch hazel and aloe barbadensis leaf juice are both reported to possess anti-inflammatory activity.[13-15] In addition, witch hazel has been reported to have potential anti-aging effects, with potent scavenging activity against active oxygen[16] and suppression of UV-induced erythema.[15] Ingredients included in the treatment system to enhance skin penetration include sodium lauryl sulfate, ethanol, and propylene glycol. And the two sunscreens included are broad spectrum sunscreens—micronized zinc oxide (a physical sunscreen) and octinoxate (a

chemical sunscreen)—which aim to prevent the development of further photodamage by minimizing the exposure of the skin to UV light.

The tolerability of the system was generally good. Only mild adverse events were reported, the most common of which was facial skin dryness (occurring in 32% of patients). However, it is possible that dryness would occur less frequently in clinical practice when, free from the constraints of the clinical trial protocol, patients would be able to use a moisturizer as needed.

CONCLUSION

The investigator evaluations show that the system offers reductions in fine lines and wrinkles, tactile roughness, intensity of pigmentation, and laxity together with an increase in the lightness/brightness of the skin. In addition, the patients considered that the system was easy to apply and resulted in smoother skin, softer skin, more even color tone, more radiant skin, a visible reduction in fine lines and wrinkles, and an improvement in the overall appearance of their skin.

Overall, the results of this study demonstrate that the prescription strength hydroquinone/L–ascorbic acid treatment system can be valuable as an early intervention strategy against photodamage in individuals with minimal or mild photodamage and hyperpigmentation. It is also suitable for patients who are not ready for retinoid therapy or more aggressive anti-aging regimens.

DISCLOSURES

Dr. Bruce has received grants as an investigator for Actavis, Inc., Allergan, Inc., Cipher Pharmaceuticals, Inc., Contura International A/S, Dow Pharmaceutical Sciences, Inc., Fibrocell Science, Inc., Galderma R & D, Inc., Graceway Pharmaceuticals, LLC, Incyte Corporation, Intendis, Inc., Isolagen Technologies, Inc., Novartis Pharmaceutical Corporation, Nycomed US, Inc., Obagi Medical Products, Inc., Paddock Laboratories, Inc., Peplin, Inc., Perrigo Company, Revance Therapeutics, Inc., Schering-Plough Corporation, Solta Medical, Inc., Spear Pharmaceuticals, Inc., Stiefel Laboratories, Inc., Teva Pharmaceuticals, Inc., Tolmar, Inc., and Warner Chilcott Ltd. She has also received honoraria as a consultant for Allergan, Inc., Merz Aesthetics, Inc., Obagi Medical Products, Inc., SkinMedica, Inc., Solta Medical, Inc., and TRIA Beauty, Inc. Dr. Watson is an employee of, and holds stock and stock options in, OMP, Inc.

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ADDRESS FOR CORRESPONDENCE

Suzanne Bruce MD
1900 St. James Place
Suite 600
Houston, TX 77056
Phone:.....(713) 796-9199
Fax:.....(713) 627-1782
E-mail:.....sbruce@sba-skincare.com