

An Open Label Clinical Trial to Evaluate the Efficacy and Tolerance of a Retinol and Vitamin C Facial Regimen in Women With Mild-to-Moderate Hyperpigmentation and Photodamaged Facial Skin

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ABSTRACT

A 12-week open-label, single-center clinical usage trial was conducted to determine the effectiveness of a dual product regimen consisting of a 0.5% retinol treatment and an anti-aging moisturizer with 30% vitamin C in women with mild to moderate hyperpigmented and photodamaged facial skin. Clinical grading of several efficacy parameters, tolerability evaluations, subject self-assessment questionnaires, and digital photography were completed at baseline and at weeks 4, 8, and 12. A total of 44 women completed the study. Effective ingredients incorporated into the 0.5% retinol treatment included encapsulated retinol for a retinol concentration of 0.5%, bakuchiol, and Ophiopogon japonicus root extract. The anti-aging moisturizer with 30% vitamin C contained 30% vitamin C in the form of tetrahexyldecyl ascorbate (THD ascorbate), alpha-tocopheryl acetate (vitamin E) and ubiquinone (coenzyme Q10). The facial regimen produced a statistically significant decrease (improvement) in clinical grading scores for all parameters assessed at weeks 8 and 12 when compared with baseline scores. In addition, the majority of these parameters were improved at week 4. The test regimen was well-perceived by the subjects for various inquiries regarding facial skin condition, product efficacy, and product attributes. Several tolerability parameters were assessed with no statistically significant increase except for dryness. A statistically significant increase in clinical grading scores for dryness on the face occurred at weeks 4 and 8 when compared to baseline scores. The increase in dryness is expected when introducing a retinol product to a facial regimen and the dryness did not persist to the week 12 time point.

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INTRODUCTION

Facial skin becomes photodamaged and ages over time, showing signs such as fine lines and wrinkles, reduction in clarity and brightness of the skin, an increase in redness and hyperpigmentation, and increased visual and tactile roughness.[1] Fine lines and wrinkles arise due to the collagen breakdown and decreases in the amount of water held in the epidermis.[2]

A dual product regimen including a 0.5% retinol treatment and an anti-aging moisturizer with 30% vitamin C was developed to treat the skin on the face in order to improve the various signs of aging. The 0.5% retinol treatment contained 0.5% retinol encapsulated in porous microspheres. Use of retinol to improve photodamaged skin is well documented. Retinol has been shown to ameliorate ultraviolet (UV)-induced wrinkles, increase keratinocyte proliferation, induce the synthesis of new collagen in the dermis and inhibit the UV induction of matrix metalloproteinases (MMPs).[3-6]

The 2 major drawbacks of using retinol in a topical formulation are the lack of stability and the potential for irritation. The 0.5% retinol treatment incorporated retinol encapsulated in porous microspheres to counteract these drawbacks and enhance the stability and reduce the irritation.[7] Additionally, the encapsulation also allowed for a sustained release effect of the retinol.[8] The 0.5% retinol treatment also included bakuchiol and *Ophiopogon japonicus* root extract. Bakuchiol, a retinol-like functional compound, is a meroterpene phenol abundant in seeds and leaves of the plant *Psoralea corylifolia*.[9] Bakuchiol has broad-spectrum antioxidant properties.[9] It functions as an anti-aging compound through retinol-like regulation of gene expression and possesses anti-inflammatory, and antibacterial properties, among other positive effects.[9-13] In addition, Bakuchiol has been shown to have an activity enhancing and a stabilizing effect on retinol.[14] *Ophiopogon japonicus* root extract is hypothesized to improve and reinforce the barrier function of the skin, retaining its natural moisture.[15]

Vitamin C is known for its beneficial effects in treating aging skin.[16] The anti-aging moisturizer with 30% vitamin C contained 30% vitamin C in the form of tetrahexyldecyl ascorbate (THD ascorbate), an efficacious and stable form of vitamin C.[17] THD

ascorbate has demonstrated skin lightening effects[18] and antioxidant benefits, as well as protective effects in the presence of UVA radiation.[19] In addition, vitamin E was incorporated into the moisturizer for further antioxidant benefits. The anti-aging moisturizer with 30% vitamin C also contained coenzyme Q10, which has multiple known topical benefits including antioxidant, energizing, and wrinkle inhibitory effects.[20,21]

The test products containing these ingredients with known topical benefits should produce a statistically significant anti-aging result in this single-center clinical usage study.

OBJECTIVES

This single-center study was conducted in order to assess the efficacy and tolerance of a dual-product regimen containing a 0.5% retinol treatment and an anti-aging moisturizer with 30% vitamin C when used over the course of 12 weeks by women with mild-to-moderate facial hyperpigmentation and photodamage. Clinical efficacy parameters included the following: 1) clarity/brightness; 2) fine lines; 3) evenness of skin tone (redness); 4) firmness; 5) global hyperpigmentation (mottled); 6) global hyperpigmentation (discrete); 7) overall photodamage; 8) radiance; 9) skin tone (color) evenness; 10) tactile smoothness; 11) visual smoothness; and 12) wrinkles. Tolerability parameters assessed included: erythema, dryness, scaling, burning, stinging, and itching. In addition, users completed self-assessment questionnaires to evaluate product efficacy and attributes.

MATERIALS AND METHODS

The efficacy and tolerance of the dual product regimen was assessed via clinical grading at baseline and at weeks 4, 8, and 12. Imaging procedures and self-assessment questionnaires were completed at these same timepoints.

The dual product regimen included a 0.5% retinol treatment and an anti-aging moisturizer with 30% vitamin C (containing 30% vitamin C in the form of THD ascorbate). In addition to encapsulated retinol, the 0.5% retinol treatment contained bakuchiol, and *Ophiopogon japonicus* root extract. In addition to the 30% THD ascorbate, the anti-aging moisturizer with 30% vitamin C also contained vitamin E and coenzyme Q10.

A total of 44 subjects (the per-protocol population) completed the 12-week clinical usage study. The demographic information is shown in Figure 1. Qualified subjects were between 35 to 60 years of age and exhibited mild-to-moderate global face hyperpigmentation and global face photodamage. Patients were not eligible if they had known allergies to facial skin care products, retinol products, moisturizers, or sunscreens, or if they were using any of several facial medications prior to study initiation.

Enrolled subjects were instructed to avoid application of any topical moisturizing products to the face for at least 2 days prior to the baseline visit. At the baseline visit they were then instructed to apply the anti-aging moisturizer with 30% vitamin C to the entire face once per day in the morning after cleansing. For the first 2 weeks of the study, subjects were instructed to apply the 0.5% retinol treatment every other evening to the entire face; subsequently, after the initial 2-week time period, they were instructed to apply the treatment every evening (or every other evening if irritation occurred). A basic sunscreen, Neutrogena UltraSheer® SPF 30, was instructed to be applied to the entire face if sun exposure was expected to occur for greater then 30 minutes for that day. Concerning study visits at the selected timepoints, subjects were instructed to remove all makeup at least 30 minutes prior to each scheduled clinic visit and to avoid applying other topical products to the face or eye area until after the visit.

Subjects were asked to avoid extended periods of sun exposure and all use of tanning beds for the study duration. In addition, they were instructed to wear protective clothing, including sunglasses, and to avoid sun exposure between 10 AM and 2 PM. They were asked to continue use of all regular brands of color cosmetics and makeup remover, but to avoid using any anti-aging products and beginning the use of any new facial products.

Clinical grading of efficacy parameters was performed at baseline and weeks 4, 8, and 12. The parameters were assessed globally using a modified Griffiths' 10-point scale[22] according to the following numeric definitions (half-point scores were used as necessary to improve accuracy of assessment): 0 = none (best possible condition); 1-3 = mild; 4-6 = moderate; and 7-9 = severe (worst possible condition). Figure 2 describes the parameters and possible assessment outcomes.

Tolerability evaluations were performed at baseline and weeks 4, 8, and 12 by assessing for signs and symptoms of erythema, dryness, and scaling, and by subject reporting of the degree of burning, stinging, and itching on the treatment area. For assessments of subjective irritation, subjects reported the degree of any parameters that they typically experienced when using a product similar to the test material(s) at the baseline visit. At post-baseline timepoints, subjects reported the degree of any of these symptoms they had experienced since the previous timepoint.

Digital photography was used to document each subject's condition using the VISIA CR photo-station (Canfield Imaging Systems, Fairfield, New Jersey) with a Canon Mark II 5D digital SLR camera (Canon Incorporated, Tokyo, Japan). A total of 3 full-face images were taken of each subjects (right side, left side, and center view).

Subjects completed a self-assessment questionnaire on facial skin condition, product efficacy, and product aesthetics at baseline and at weeks 4, 8, and 12.

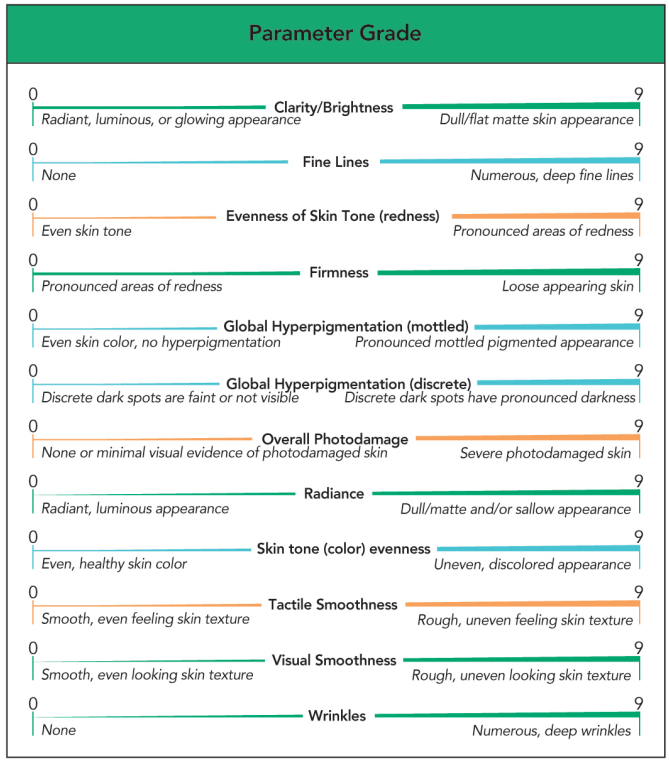
FIGURE 1. Demographic information for subjects completing 12-week study.

Demographic Information

Demographics of Enrolled Subjects (Per-Protocol Population)

	All Subjects
N	44
Age (Years)	
Mean	51.1
Standard Deviation	6.9
Minimum	35
Median	53.0
Maximum	60
	N (%)
Sex	
Female	44 (100)
Ethnicity/Race	
Asian	7 (15.9)
Hispanic or Latino	4 (9.1)
White	33 (75.0)
Fitzpatrick Skin Type	
II	21 (47.7)
III	22 (50.0)
IV	1 (2.3)

FIGURE 2. Parameter grading scale used by expert grader during clinical grading efficacy.



The per-protocol population was the primary population for all statistical analyses and included all subjects who received treatment and completed the study according to protocol.

The mean of the change from baseline (defined as post-baseline value minus baseline value) was estimated at post-baseline timepoints. The null hypothesis that the mean change from baseline was 0 was tested using the Wilcoxon Signed Rank Test. All statistical tests were 2-sided at significance level $\alpha = 0.05$. Statistical analyses were performed using SAS software version 9.30 series (SAS Statistical Institute).

RESULTS

Clinical Grading of Efficacy Parameter

Use of the 0.5% retinol treatment and the anti-aging moisturizer with 30% vitamin C produced a statistically significant decrease (improvement) in clinical grading scores for all parameters assessed at weeks 8 and 12, including: clarity/brightness, fine lines, evenness of skin tone (redness), firmness, global hyperpigmentation (mottled and discrete), overall photodamage, radiance, skin tone (color) evenness, tactile smoothness, and visual smoothness and wrinkles at weeks 8 and 12 when compared with baseline scores. There was also a statistically significant decrease (improvement) in clinical grading scores for many parameters at the week 4 timepoint, including: clarity/brightness, fine lines, evenness of skin tone (redness), global

hyperpigmentation (mottled and discrete), skin tone (color) evenness, tactile smoothness, and visual smoothness compared with baseline scores. After 12 weeks of twice daily use:

- 79% of subjects showed an improvement in clarity/brightness with an average improvement of 9.4%
- 100% of subjects showed an improvement in fine lines with an average improvement of 15.5%
- 72% of subjects showed an improvement in evenness of skin tone (redness) with an average improvement of 10.7%
- 86% of subjects showed an improvement in firmness with an average improvement of 10.3%
- 75% of subjects showed an improvement in global hyperpigmentation (mottled) with an average improvement of 9.9%
- 77% of subjects showed an improvement in global hyperpigmentation (discrete) with an average improvement of 11.0%
- 90% of subjects showed an improvement in overall photodamage with an average improvement of 10.5%
- 100% of subjects showed an improvement in radiance with an average improvement of 13.0%
- 77% of subjects showed an improvement in skin tone (color) evenness with an average improvement of 12.4%
- 90% of subjects showed an improvement in tactile smoothness with an average improvement of 13.6%
- 75% of subjects showed an improvement in visual smoothness with an average improvement of 9.3%
- 86% of subjects showed an improvement in wrinkles with an average improvement of 10.4%

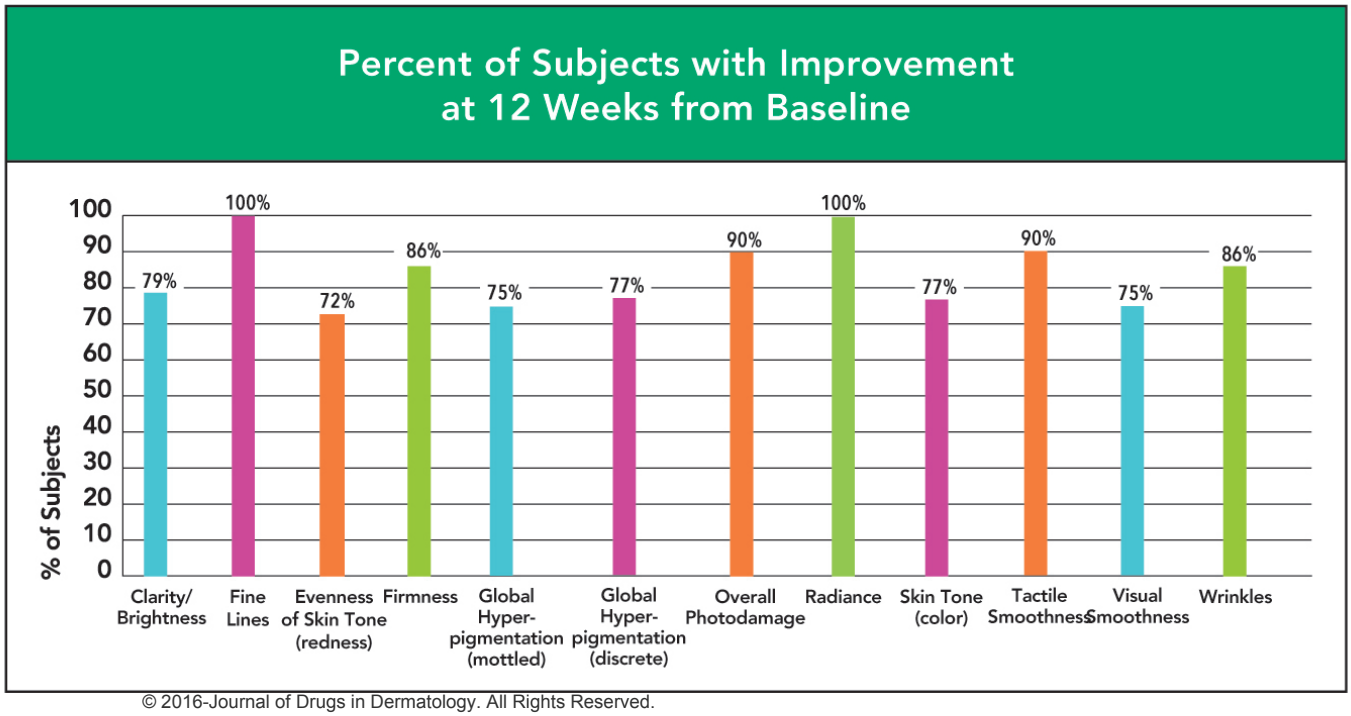
Tolerability Evaluations

Use of 0.5% retinol treatment and anti-aging moisturizer with vitamin C resulted in a statistically significant increase (worsening) in clinical grading scores for dryness on the face at weeks 4 (15% of subjects) and 8 (13% of subjects) compared with baseline scores. However, this change did not persist to the week 12 timepoint, and an increase in dryness is expected when introducing a retinol product to a facial skin care regimen. No statistically significant changes from baseline were detected for erythema, scaling, burning, stinging, or itching at weeks 4, 8, and 12.

Self-Assessment Questionnaires

A statistically significant proportion of subjects responded favorably to all skin condition inquiries included in the self-assessment questionnaire. In addition, a statistically

FIGURE 3. Percent of subjects that showed an improvement in various parameters at the week 12 time point compared to baseline during a 12-week study using dual product regimen consisting of a 0.5% retinol treatment and an anti-aging moisturizer with 30% vitamin c.



significant proportion of subjects responded favorably regarding the efficacy of the test product. Specifically, after 12 weeks:

- 90% of subjects thought their skin texture was improved
- 93% of subjects felt that their skin tone appeared more even
- 72% of subjects thought their brown spots were less noticeable
- 93% of subjects felt that their face looked more radiant or brighter
- 75% of subjects thought their skin was less red in color
- 90% of subjects thought the fine lines on their skin were less noticeable
- 88% of subjects felt the wrinkles on their face were less noticeable
- 90% of subjects thought their skin looked and felt more healthy
- 86% of subjects felt their skin looked younger and firmer
- 86% of subjects reported that their skin felt more moisturized
- 93% of subjects though the appearance of their skin was improved overall.

A statistically significant proportion of subjects reported positively regarding the product aesthetics by week 12. Specifically:

- 86% of subjects felt that that the products moisturized their skin
- 90% of subjects thought that the products' scent was pleasant
- 93% of subjects felt that the products' texture was pleasant
- 93% of subjects thought that the products did not leave an unpleasant after-feel
- 95% of subjects felt that applying the products was a pleasant experience
- 93% of subjects thought that the products were mild and did not irritate the skin
- 86% of subjects reported that they would like to purchase the products

Adverse Events

Overall, 13 subjects experienced a total of 30 non-serious adverse events (AEs) that were deemed to be definitely related to the product regimen. These included exfoliation (n=12), erythema (n=7), burning sensation (n=6), pruritus (n=2), pain of skin (n=1), dry skin (n=1), and tenderness of skin (n=1). All of the symptoms are expected reactions to the use of retinol product. All AEs were mild-to-moderate, and all resolved with time as skin became acclimated to 0.5% retinol treatment or with modified use of the test material.

"The combination of these effective ingredients are thought to result in an improvement in the signs of aging around the facial skin."

DISCUSSION

Overall, the results of this open-label, single-center clinical usage trial indicate that the use of the dual product regimen (0.5% retinol treatment and anti-aging moisturizer with 30% vitamin C) was effective in improving aged facial skin when used over the course of 12 weeks by women with mild-to-moderate facial hyperpigmentation and photodamage. The facial regimen produced a statistically significant decrease (improvement) in clinical grading scores for all parameters assessed including: clarity/brightness, fine lines, evenness of skin tone (redness), firmness, global hyperpigmentation (mottled), global hyperpigmentation (discrete), overall photodamage, radiance, skin tone (color) evenness, tactile smoothness, visual smoothness, and wrinkles at weeks 8 and 12 when compared with baseline scores. In addition, the majority of these parameters also were improved at week 4.

Of note, the 0.5% retinol treatment test product contained encapsulated retinol, which enhances stability, reduces irritation, and allows for sustained released of retinol onto the skin for optimal efficacy of the product.[7,8] It also included bakuchiol, a broad-spectrum antioxidant which has a stabilizing and an efficacy boosting effect on retinol,[9-14] as well as *Ophiopogon japonicus* root extract to enhance skin barrier function and increase the skin's own natural moisturizing factor.[15] The anti-aging moisturizer with 30% vitamin C (THD ascorbate) works with retinol to improve antioxidant and anti-aging activity.[17-19] The anti-aging moisturizer with 30% vitamin C also contained vitamin E and ubiquinone (coenzyme Q10), antioxidants, which reduce free radical formation.[15] The combination of these effective ingredients are thought to result in an improvement in the signs of aging around the facial skin. This study appears to positively support this hypothesis, as illustrated by the photos shown in Figures 4 and 5.

FIGURE 4. Treatment of aging skin with retinol and vitamin C facial regimen at baseline and after 12 weeks.

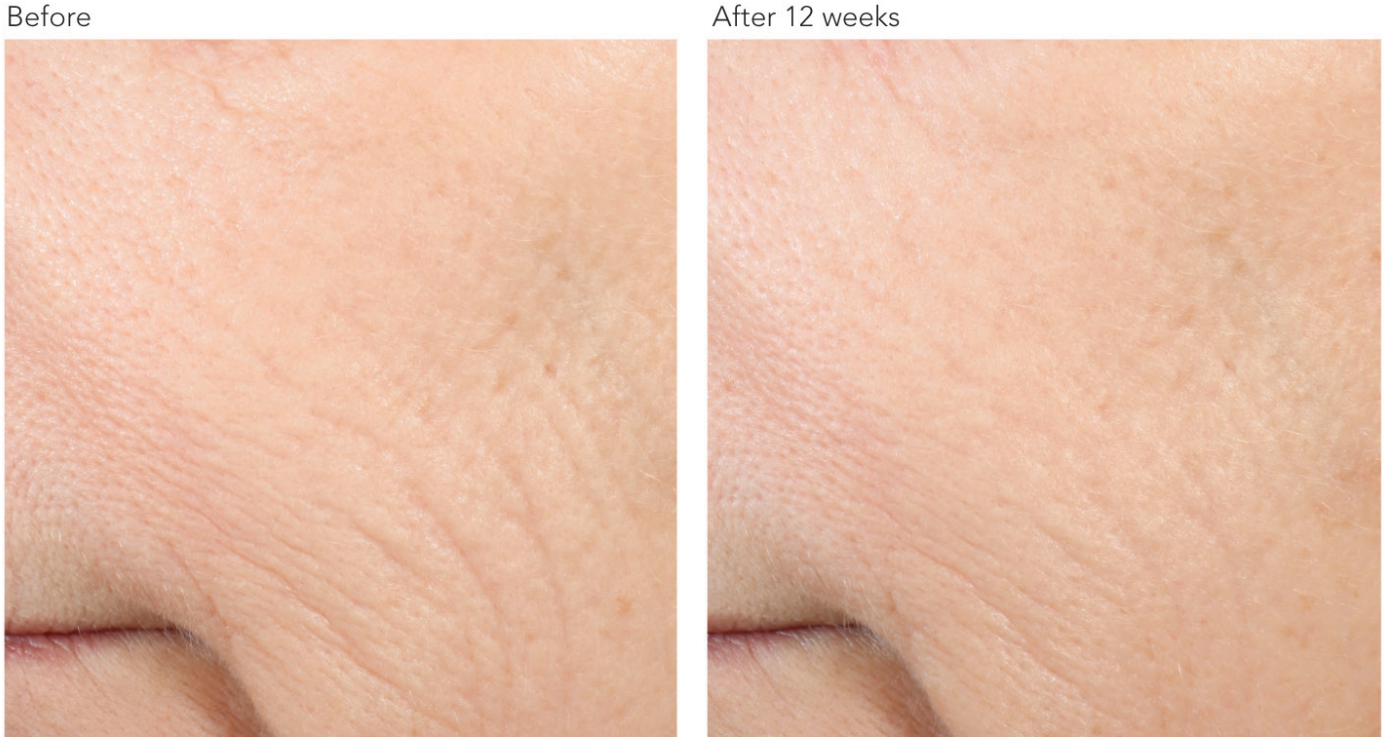
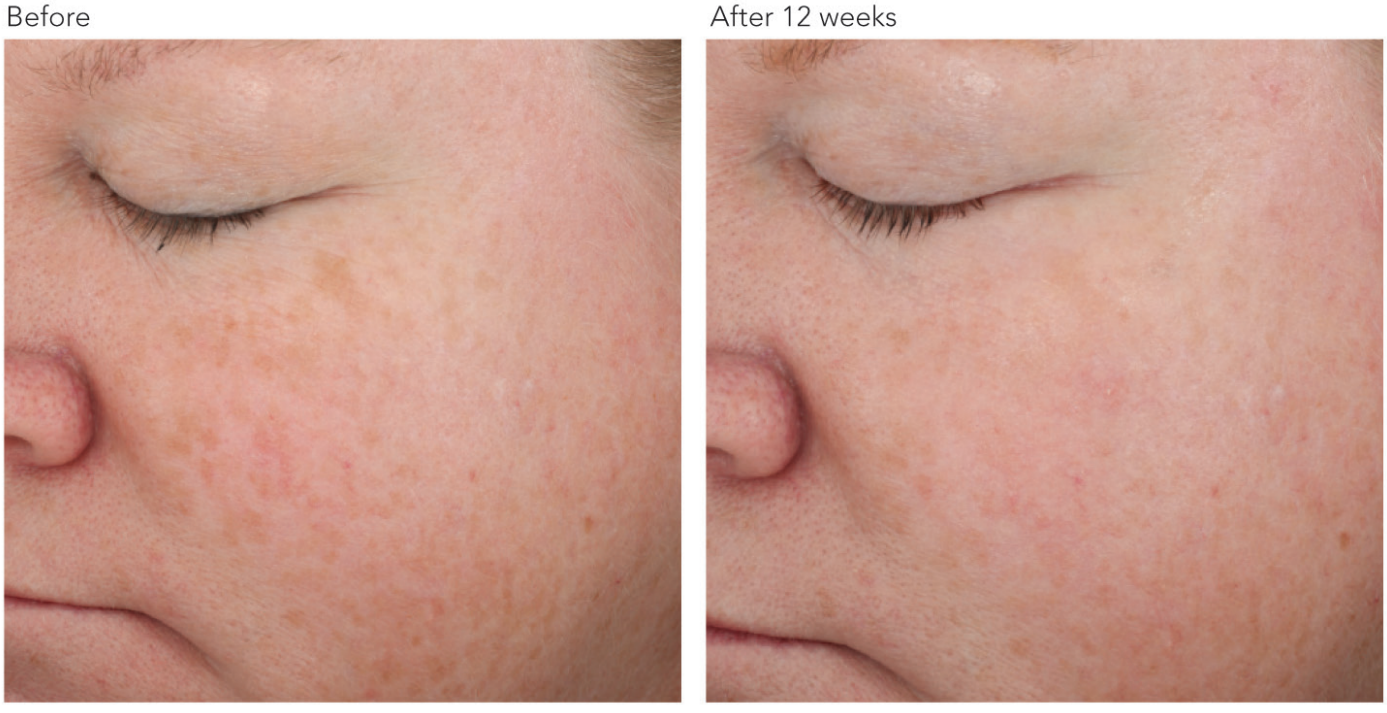


FIGURE 5. Treatment of aging skin with retinal and vitamin C facial regimen at baseline and after 12 weeks.



A worsening in dryness was observed in 15% and 13% of the subjects at week 4 and week 8 respectively, although this improved by week 12. No statistically significant changes from baseline were detected for erythema, scaling, burning, stinging, and itching at any timepoint. A total of 13 subjects experienced 30 non-serious AEs, which were classified as definitely related to

use of the test materials. The increase in dryness and frequency of AEs is typical for introducing a retinol product to a facial skin care regimen, and the majority of the AEs were resolved with time as the skin became acclimated to regular application of retinol. Some AEs were resolved after modifying the use of the test materials. Additionally, the tolerability of the product was deemed favorable when noting the self-assessment questionnaire results of 72% and 86% of the subjects agreeing that "My skin feels more moisturized" and 81% and 93% of the subjects agreeing that "Overall, the products were mild and did not irritate my skin" at week 8 and week 12, respectively.

The test regimen was well-perceived by the subjects under the conditions of this test for various inquiries regarding facial skin condition, product efficacy, and product attributes. After 12 weeks of usage, 86% of subjects indicated desire to purchase the products.

A limitation of this study includes the lack of a control product.

CONCLUSION

A 12-week single-center clinical usage study was conducted to test a 0.5% retinol treatment and an anti-aging moisturizer with 30% vitamin C in 44 women with mild-to-moderate hyperpigmentation and photodamaged skin. The facial regimen produced a statistically significant decrease (improvement) in clinical grading scores for all parameters assessed including clarity/brightness, fine lines, evenness of skin tone (redness), firmness, global hyperpigmentation (mottled), global hyperpigmentation (discrete), overall photodamage, radiance, skin tone (color) evenness, tactile smoothness, visual smoothness, and wrinkles at weeks 8 and 12 when compared with baseline scores. In addition, the majority of these parameters were also improved at week 4. Moreover, as indicated by responses on the self-assessment questionnaire, the subjects believed in the efficacy of the product and were interested in purchasing it. Digital photography further supported these results. The study illustrated that the combination of efficacious ingredients in each product and using the products in a dual regimen provided a broad anti-aging effect with good tolerability. These results provide medical professionals with information that may benefit patients seeking treatment for hyperpigmentation or photodamaged facial skin.

DISCLOSURES

This study was 100% sponsored by Revision Skincare. The authors have no conflicts of interest to declare.

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