A Method for Maintaining the Clinical Results of 4% Hydroquinone and 0.025% Tretinoin With a Cosmeceutical Formulation

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ABSTRACT

Facial dyspigmentation treatment is an unmet need in dermatology with increasing challenges due to the questionable safety of hydroquinone. This research examined a new OTC formulation containing hydroxyphenoxy propionic acid, ellagic acid, yeast extract, and salicylic acid on subjects who previously completed 12 weeks of treatment with 4% hydroquinone and 0.025% retinoic acid. The goal of this study was to evaluate the skin lightening and tolerability profile of a 20-week maintanence therapy with a cosmeceutical formulation during the summer months. 33 healthy subjects ages 25-60 years with moderate facial dyspigmentation defined as a score of 3 on a 5-point scale were enrolled. There was statistically significant improvement at week 20 in terms of even skin tone ($P<0.001$), spot intensity ($P<0.001$), spot size ($P<0.05$) and overall hyperpigmentation ($P=0.002$).

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INTRODUCTION

The treatment of facial dyspigmentation requires persistence and diligence on the part of the dermatologist and the patient. The current standard prescription therapy of 4% hydroquinone requires at least 3 months to obtain clinical results, but enhanced efficacy can sometimes be achieved by combining the 4% hydroquinone with 0.025% tretinoin.[7] There is some controversy as to how long subjects can safely use hydroquinone and the barrier damage induced by combination therapy can decrease patient compliance.[2] Further concerns regarding the safety of long-term hydroquinone use have been raised by both dermatologists and the FDA.[8] These concerns have led researchers to examine other options that might allow initial treatment with hydroquinone followed by maintenance therapy with a cosmeceutical formulation. Hydroquinone inhibits melanin production by inhibiting tyrosinase, the key enzymatic step in melanin production.[9] Its activity can be augmented by 0.025% tretinoin, which inhibits the transfer of melanin to keratinocytes, and also functions as a penetration enhancer for the hydroquinone through barrier degradation.[6] The barrier degradation accounts for much of the peeling, stinging, and burning some subjects experience with combination treatment. This research examined the use of a novel hyperpigmentation formulation on subjects who have previously completed 12 weeks of treatment with 4% hydroquinone and 0.025% retinoic acid. This formulation contained hydroxyphenoxy propionic acid, ellagic acid, yeast extract, and salicylic acid. These active ingredients were specifically chosen to target different layers of the skin for more comprehensive disruption of the pigment pathway and pigment distribution. In a previous study, it was established that the novel formula attained equivalent clinical benefits as 4% hydroquinone and 0.025% tretinoin.[1]

Hydroxyphenoxy propionic acid inhibits melanin production from cultured B16 cells without affecting melanocyte viability.[10] In addition, it inhibits melanosomes transfer to the keratinocytes. It is combined with ellagic acid, a naturally occurring compound found in fruits and berries, to block excess melanin production by inhibiting tyrosinase at the basal layer with an added function as an anti-inflammatory.[11,12] Yeast extract, derived from saccharmoyces cerevisiae, functions in the stimulation of lysosomal degradation of keratinocytes to speed melanin degradation and removal while stimulating fibroblasts in the dermis aiding the skin's resistance to formation of new pigment.[13] Finally, salicylic acid functions as a penetration enhancer, while also exfoliating the skin to aid in the desquamation of existing pigment containing keratinocytes.

The goal of this study was to evaluate the skin lightening and tolerability profile of a 20-week maintanence therapy with a cosmeceutical formulation during the summer months. The primary objective was to determine the ability of the cosmeceutical formulation to maintain the attained reduction in hyperpigmentation parameters and offer additional improvements in skin quality as measured by a validated investigator assessment.

METHODS

Thirty-three healthy subjects ages 25-60 years with moderate facial dyspigmentation defined as a score of 3 on a 5-point scale, with 5 indicating severe, were enrolled in this 20-week single center research study by Dermatology Consulting Services. Pregnant or nursing females were excluded. Following completion of an IRB-approved consent (Concordia Clinical Research Institutional Review Board, New Jersey), eligible subjects were requested to avoid excessive sun exposure and the use of artificial tanning methods. All colored cosmetics remained unchanged during the 20 weeks of the study. Subjects with any active facial dermatoses were excluded, as were those who possessed any hypersensitivity to any of the study product ingredients. All study participants were provided with a standardized cleanser and a SPF 30 sunscreen for daily use.

Subjects were selected based on previous use of 4% hydroquinone in combination with 0.025% tretinoin cream for a period of 12 weeks and instructed to discontinue the use of prescription combination. Following the cessation of hydroquinone and tretinoin, all subjects were provided with a cosmeceutical formulation for skin lightening (Advanced Pigment Corrector, SkinCeuticals, L'Oreal, New Jersey) to use twice daily. The goal was to determine if the cosmeceutical formulation could maintain the dyspigmentation improvement produced by the hydroquionone/tretinion prescription therapy.

"Finally, improvement in skin pigmentation continued after the prescription regimen was discontinued and application of cosmetic formulation ensued."

All efficacy and tolerability grading occurred on an ordinal 5-point scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe). The following parameters were evaluated: dark spot size, dark spot intensity, hyperpigmentation, visual and tactile smoothness, skin tone clarity, skin tone evenness, firmness, radiance, blotchiness, and overall appearance. Tolerability was also assessed on the same 5-point ordinal scale where the dermatologist investigator assessed erythema, edema, dryness, and peeling while the subjects assessed stinging, tingling, itching, and burning.

Bioinstrumentation was also performed at baseline, weeks 12 and 20 to evaluate the change in the skin moisturization after the hydroquinone/tretinoin combination was discontinued and the study skin lightening product was initiated. The bioinstrumentation consisted of corneometry measurements using a pin probe corneometer (Dermalab, Denmark). Digital frontal, right, and left photographs (Nikon, Canfield Scientific, New Jersey) were obtained at weeks 12 and 20.

RESULTS

Thirty-three of thirty-three subjects completed the study. No tolerability issues were noted by the investigator or the subjects with the study skin lightening preparation throughout the entire duration of the study. No adverse events or adverse experiences were reported.

An important finding attests to the moisturizing capabilities of the cosmeceutical formulation, which are not commonly observed with the hydroquinone/tretinoin combination and often lead to premature termination of the prescription therapy. The bio-instrumental analysis confirmed this outcome with corneometry measurements, which were statistically significantly increased at week 12 (P=0.043) and week 20 (P=0.004) as compared to baseline. In addition to the instrumental evaluation, differences in the skin smoothness were noted at week 12 after discontinuation of the hydroquinone/tretinoin combination as evident by the investigator rated statistically significant improvement (P<0.001) in visual smoothness and tactile smoothness. There was also a reduction in erythema (P=0.029), peeling (P=0.002), and dryness (P=0.003) at week 12, as compared to baseline, indicating better tolerability. All of these observations point to the superior moisturization properties of the study skin lightening product, which might result in enhanced patient compliance.

Further clinical efficacy was confirmed by additional improvement in skin quality as observed at week 20 of the study. There was continued statistically significant improvement in visual smoothness (P<0.05) and tactile smoothness (P<0.05) with a reduction in erythema, peeling, and dryness on week 20 as compared to the baseline assessment. Moreover, statistically significant improvement was seen in clarity (P=0.007), imperfections (P=0.005), radiance (P=0.001), and firmness (P=0.009). The improvement in all of these facial parameters was reflected in an overall highly statistically significant improvement at week 20 (P=0.001). The improvement in cosmetic attributes reflects the enhanced moisturization of the cosmeceutical formulation as compared to the prescription combination.

Finally, improvement in skin pigmentation continued after the prescription regimen was discontinued and application of cosmetic formulation ensued. There was statistically significant improvement at week 20 in terms of even skin tone (P<0.001), an assessment of overall skin color; spot intensity (P<0.001) and spot size (P<0.05), an assessment of the darkness of individual pigmented facial lesions; and overall hyperpigmentation (P=0.002; Figure 1). These observations are important as continued improvement in dyspigmentation was seen after discontinuation of the hydroquione/tretinoin combination.

FIGURE 1. The cosmeceutical skin lightening preparation continued to produce improvement for the 20-week duration of the study.

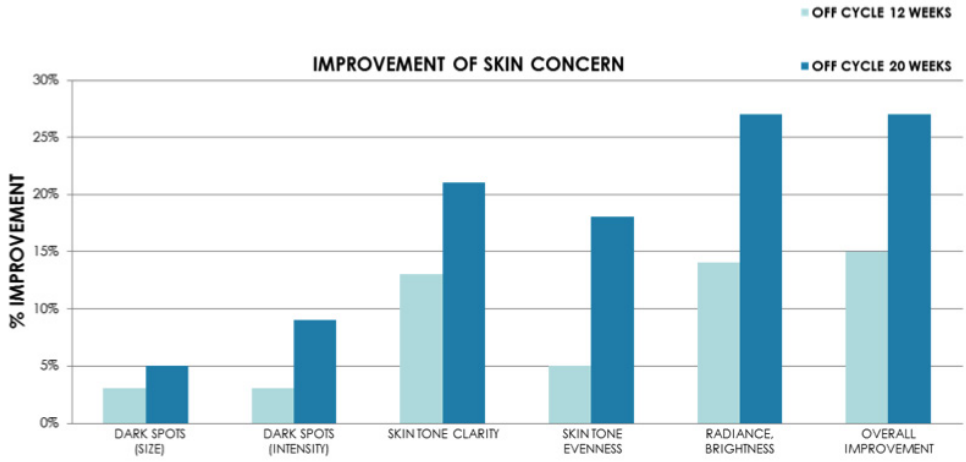
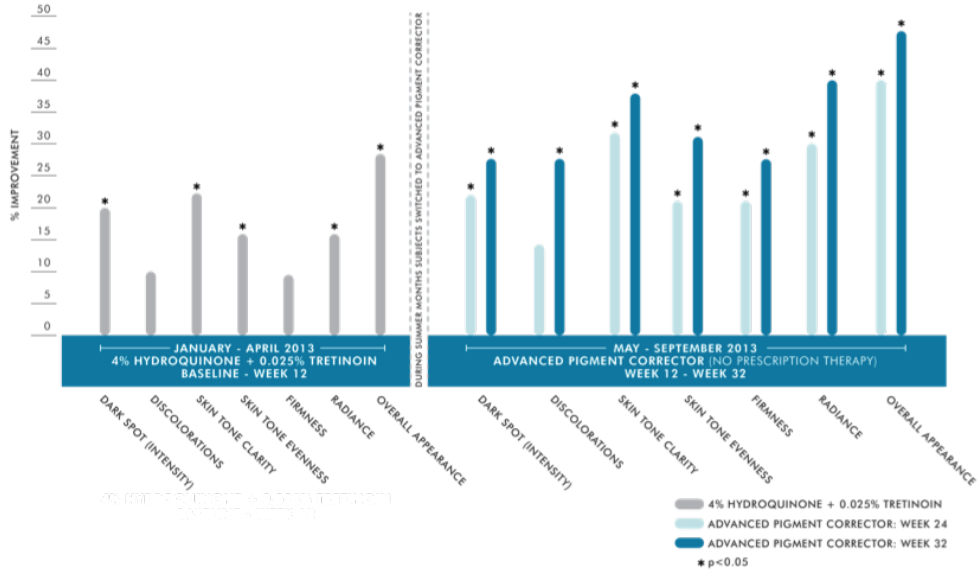


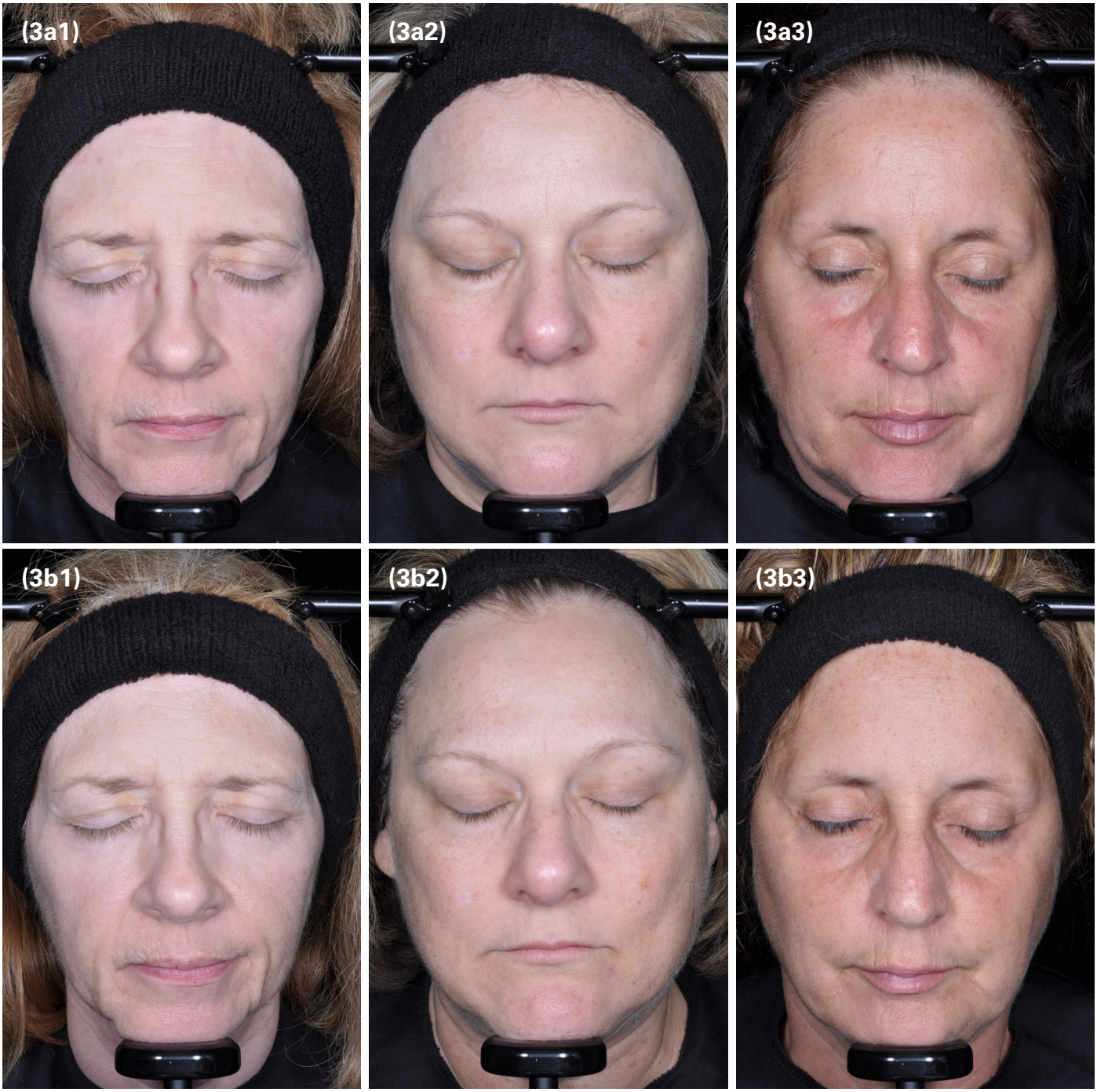
FIGURE 2. Pigment lightening prescription therapy with 4% hydroquinone/0.025% tretinoin can be maintained with a cosmeceutical formulation.



In summation, the bio-instrumental analysis, skin quality improvements, and continued reduction in unwanted pigmentation all confirm the complementary benefits offered by the cosmeceutical regimen when used following the recommended 12-week use of the prescription hydroquinone/tretinoin combination. As exemplified in this study, the increased skin quality and dyspigmentation benefits offered by this novel formula exhibit an excellent addition when utilized post-prescription therapy to maintain the clinical outcomes.

However, it is also worthwhile to examine the efficacy of the entire treatment regimen combining the 12 weeks of prescription therapy with the 20 weeks of cosmeceutical therapy as compared to initial baseline, when the use of 4% hydriquinone and 0.025% tretinoin was first initiated. Statistically significant improvement was seen from baseline in clarity (P<0.001), even skin tone (P=0.005), spot intensity (P=0.006), radiance (P<0.001), firmness (P<0.001), and overall skin appearance at week 32 as compared to initial administration of 4% hydroquinone and 0.025% tretinoin. By this time, the subjects had completed 12 weeks of prescription therapy followed by 20 weeks of cosmeceutical therapy. It is interesting to note that spot size (P<0.05), spot intensity (P=0.006), hyperpigmentation (P<0.05), and even skin tone (P=0.005) continued to improve with the cosmetic for-

FIGURE 3. Figure 3 shows the images of 3 subjects following the completion of 12 weeks of 4% hydroquinone/0.025% tretinoin treatment qhs (3a1, 3a2, 3a3). The result has been maintained at week 32 after 20 weeks of treatment with the cosmeceutical formulation (3b1, 3b2, 3b3).



mulation even after the tretinoin/hydroquinone combination had been stopped (Figure 2). This means the cosmetic formulation can be used to maintain and continue pigmentation improvement after prescription therapy has been discontinued for a comprehensive solution to treat subjects without the negative consequences of interrupting their treatment regimen (Figure 3).

DISCUSSION

Pigment lightening is an important worldwide appearance need that is challenging for the dermatologist. The main prescription pigment treatment is 4% hydroquinone with no new prescription pigmentation products in the FDA approval pipeline. Concerns about the safety of hydroquinone

have created opportunities for more customized pigmentation treatment. Our initial study confirmed that the use of this novel cosmeceutical formulation is as effective as this gold standard of prescription hyperpigmentation therapy.[1] This research took our initial findings a step further by examining the efficacy of maintenance treatment for 20 weeks with a hydroxyphenoxy propionic acid, ellagic acid, yeast extract, and salicylic acid cosmetic formulation during the summer months, the most difficult time to treat hyperpigmentary disorders. This cosmeceutical product was specifically formulated to target different cutaneous layers in order to provide a comprehensive approach for melanin removal from the skin and prevention of new pigment formation without seasonal limitations. The cosmetic formulation improved skin feel and appearance while maintaining the pigment lightening results achieved with the hydroquinone/tretinoin combination. Surprisingly, the improvement in pigmentation actually continued after the discontinuation of prescription and lasted throughout the entire duration of the 20-week study.

This research examined a method for combining pharmaceuticals with cosmeceuticals. The combination achieved statistically significant improvement in pigmentation that persisted for 20 weeks. This methodology may be the future of dermatology care for appearance related issues, attesting to the possible synergy between the cycled use of prescription and cosmeceutical regimens.

DISCLOSURES

Zoe Diana Draelos, MD, performed this work at her research facility as part of a research grant from SkinCeuticals, a division of L'Oreal. The remaining authors are employees of L'Oreal.

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