An Open-Label Study of the Efficacy and Tolerability of Microencapsulated Hydroquinone 4% and Retinol 0.15% With Antioxidants for the Treatment of Hyperpigmentation

Fran E. Cook-Bolden, MD; Saonjie F. Hamilton, BS

Hyperpigmentation describes areas of the skin with increased melanin content, when the pigmentation is darker than the healthy surrounding skin. Disorders of hyperpigmentation, such as melasma, postinflammatory hyperpigmentation (PIH), and solar lentigines, are common and pose a treatment challenge for all patients, particularly those with darker skin types whose melanocytes are more reactive to various stimuli. Although distressing when affecting the face and areas of the body that are difficult to conceal, disorders of hyperpigmentation can affect individuals from head to toe.

An innovative product containing microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants has improved hyperpigmentation disorders of the face based on disease severity, pigmentation intensity, lesion area, and colorimetric measurements. The objective of the current open-label study was to evaluate the efficacy and tolerability of microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants in individuals with Fitzpatrick skin types II through VI with hyperpigmentation of the face and/or body and to determine if this hydroquinone preparation was as effective on the body as it was on the face. Participants were treated twice daily for 12 weeks. Study evaluations were conducted at baseline and weeks 4, 8, and 12. Results from the efficacy assessments demonstrated that reductions in lesion size, darkness, and disease severity were significant as early as 4 weeks after treatment initiation and remained significantly reduced throughout the study (all P<.032). Furthermore, 63% of participants (12/19) had either marked improvement (defined as 75% overall improvement) or complete clearing (≥95% overall improvement) of their hyperpigmented lesions at the end of the 12-week treatment period. Reflectance spectrophotometer readings also were performed at each study visit and demonstrated a significant reduction in melanin content as early as week 4 (target A, P≤.001; target B, P=.002).

Cutis. 2008;81:365-371.

Accepted for publication September 6, 2007.

Dr. Cook-Bolden is from the Department of Dermatology, Columbia University College of Physicians and Surgeons, New York, New York, and The Skin Specialty Group, New York. Ms. Hamilton also is from The Skin Specialty Group.

The study was funded by SkinMedica, Inc.

Dr. Cook-Bolden is an investigator and speaker for SkinMedica, Inc. Ms. Hamilton reports no conflict of interest.

Correspondence: Fran E. Cook-Bolden, MD, 20 E 66th St, Suite 1A, New York, NY 10021 (research.cookbolden@gmail.com).

Hyperpigmentation disorders, such as melasma, postinflammatory hyperpigmentation (PIH), and solar lentigines, are distressing conditions that are often difficult to treat. Melasma is characterized by relatively symmetric brown or gray-brown patches on facial areas commonly exposed to the sun, particularly the cheeks, forehead, upper lip, and chin. Although most commonly found on the face,

melasma can affect other areas of the body. Causes of melasma include hormone exposure, familial disposition, photosensitizing medications, nutritional deficiency, and endocrine dysfunction. Exposure to UV radiation from the sun substantially increases the risk of developing melasma and exacerbates existing melasma.[1,2]

PIH is characterized by dark patches of pigmentation that develop because of trauma to the skin or an inflammatory process involving the skin and can appear anywhere on the body. Common causes include inflammatory diseases, such as psoriasis, eczema, allergic contact dermatitis, and acne; skin reactions to cosmetics or cosmetic procedures, such as chemical peels, laser skin resurfacing, waxing, and electrolysis; and any form of trauma.

The incidence of hyperpigmentation disorders is unknown, but they are particularly common among individuals with darker skin types.[1,3-6] Melasma predominantly occurs in women of childbearing age, but men also can be affected.[2,7,8] Although melasma may develop in individuals of all skin types, it is more prevalent among darker-skinned individuals (Fitzpatrick skin types IV–VI) living in areas with high UV light exposure.[1,4,5] There does not appear to be a gender predilection in PIH.

Treating hyperpigmentation is challenging for both the clinician and the patient, and it often takes many weeks or months before any response is appreciated. For mild to moderate hyperpigmentation, hydroquinone-containing bleaching creams are widely used. Combination products containing hydroquinone (typically a 4% concentration) also are common treatments. These combination products frequently include agents such as tretinoin, retinol, glycolic acid, hyaluronic acid, vitamin C, ferulic acid, or corticosteroids (fluocinolone).

The approach of combining ingredients has produced impressive results. For example, the combination of tretinoin 0.05%, hydroquinone 4.0%, and fluocinolone acetonide 0.01% decreased melasma by 75% in one study.[9] While some manufacturers are focusing on various combinations, others are focusing on unique delivery methods. A novel formulation of hydroquinone 4% plus retinol was developed for the treatment of UV-induced dyschromia and discoloration such as melasma and PIH. This product entraps approximately 2.5% of the hydroquinone along with retinol into patented porous microspheres composed of methyl methacrylate/glycol dimethacrylate crosspolymers. The remaining hydroquinone is in free form. This microsphere delivery system provides gradual release of hydroquinone into the skin, which has been shown to minimize the side effects of skin irritation associated with hydroquinone use.[10] Two studies with this hydroquinone preparation demonstrated its efficacy when used on the face.[11,12]

Methods

Study Design—This 12-week open-label study examined the clinical efficacy and tolerability of microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants in individuals with mild to moderate hyperpigmentation of the face and/or body. The study medication was applied twice daily for 12 weeks. The study was approved by an institutional review board, and written informed consent and photographic release were obtained from each individual prior to participation.

Most study assessments were conducted at baseline and weeks 4, 8, and 12. However, the global improvement assessment was performed by the investigator at weeks 4, 8, and 12, and by the participant only at week 12. A participant questionnaire regarding overall satisfaction with treatment also was completed only at week 12.

Treatment Protocol—If participants had hyperpigmentation on both the face and body, the investigator was instructed to select a target area (either the face or body) at the baseline visit to follow for all clinical assessments at each of the 4 study visits. Participants were instructed to apply study medication to all areas of their face and/or body that were affected by hyperpigmentation twice daily (morning and evening) for 12 weeks, to record any missed doses in a participant diary, to use a sunscreen (minimum sun protection factor 30) at least daily, and to avoid sun exposure.

Inclusion and Exclusion Criteria—Individuals aged 18 years or older with Fitzpatrick skin types II through VI were included in the study. Participants had to be clinically diagnosed as having mild to moderate hyperpigmentation of the face and/or body. Exclusion criteria included use of hormone replacement or oral contraceptive therapy, or individuals who were pregnant or lactating. Individuals with any uncontrolled systemic disease, any concomitant disease that may interfere with the diagnosis and treatment of hyperpigmentation, or a known sensitivity to hydroquinone or sulfites also were excluded. Other exclusion criteria included the use of any form of bleaching creams including hydroquinone, glycolic acid, kojic acid, azelaic acid, tretinoin, retinol, or topical steroids within 4 weeks of study participation.

Efficacy Measurements—The study end points of lesion number, size, and darkness, as well as an evaluation of disease severity, were assessed at each of the 4 study visits. Each end point was scored based on a 5-point scale (0=clear, 1=almost clear,

2=mild, 3=moderate, 4=severe). A global improvement assessment was performed by the investigator at weeks 4, 8, and 12, and by the participant only at week 12. This assessment was scored according to a 5-point scale (0=no change or worsening, 1=slight improvement [25% overall improvement], 2=moderate improvement [50% overall improvement], 3=marked improvement [75% overall improvement], 4=complete clearing [≥95% overall improvement]). Also at the end of the study period (week 12), the participants completed a questionnaire regarding overall satisfaction with treatment. Satisfaction was rated as excellent (very satisfied), good (moderately satisfied), fair (slightly satisfied), or poor (not satisfied).

Reflectance spectrophotometer readings were performed to measure the pigmentation (melanin, erythema) of 2 targeted lesions and 1 adjacent area of normal skin at each study visit. For participants with melasma, a Melasma Area and Severity Index (MASI) score also was calculated at each study visit.

Safety Measurements—Tolerability to the study medications was assessed at each study visit using a 5-point scale evaluating the signs and symptoms of irritation including erythema, dryness, itching, stinging, and burning (0=none, 1=barely noticeable, 2=slight, 3=moderate, 4=severe). In addition, participants were queried at each study visit about any adverse events (AEs) they had experienced.

Statistical Analysis—Demographics and safety data are provided for the intention-to-treat population, which consisted of all participants, regardless of their exit status. All other data were analyzed for the per-protocol population, which consisted of all participants who completed the 12 weeks of treatment. Confidence intervals (95%) were determined based on a *t* distribution. For the efficacy variables (lesion number, size, darkness; disease severity; spectrophotometer reading; MASI score), analyses were performed using observed and change-from-baseline methodologies. *P* values were determined using a Wilcoxon signed rank test. For the other assessments (global improvement, participant questionnaire), *P* values, where applicable, were determined using both Wilcoxon signed rank and *t* tests.

Results

Twenty-one participants with either melasma or PIH (of the face and/or body) were enrolled in the study. Nineteen participants completed the study. Of 21 participants enrolled, 20 participants (95%) were women. Four participants (19%) were diagnosed with melasma and 17 participants (81%) were diagnosed with PIH. A total of 15 participants (71%) had mild disease at study entry, while 6 participants (29%) had moderate disease. The targeted areas for treatment were the face in 11 participants (52%) and the body in 10 participants (48%). The mean age of participants was 42.2 years (age range, 23.0–78.4 years). In all, 16 participants were black, 2 participants were white, 1 participant was Hispanic, 1 participant was Asian, and 1 participant was classified as other. Fitzpatrick skin

Participant Demographics and Baseline Characteristics

	n (%)
Gender	
Female	20 (95.2)
Male	1 (4.8)
Ethnicity	
Black	16 (76.2)
White	2 (9.5)
Hispanic	1 (4.8)
Asian	1 (4.8)
Other	1 (4.8)
Fitzpatrick Skin Type	
II	2 (9.5)
III	2 (9.5)
IV	6 (28.6)
V	8 (38.1)
VI	3 (14.3)
Hyperpigmentation Type	
Melasma	4 (19.0)
Postinflammatory hyperpigmentation	17 (81.0)
Disease Severity	
Mild	15 (71.4)
Moderate	6 (28.6)
Target Pattern of Hyperpigmentation	
Epidermal	16 (76.2)
Epidermal/dermal	5 (23.8)
Target Body Area	
Face	11 (52.4)
Body	10 (47.6)

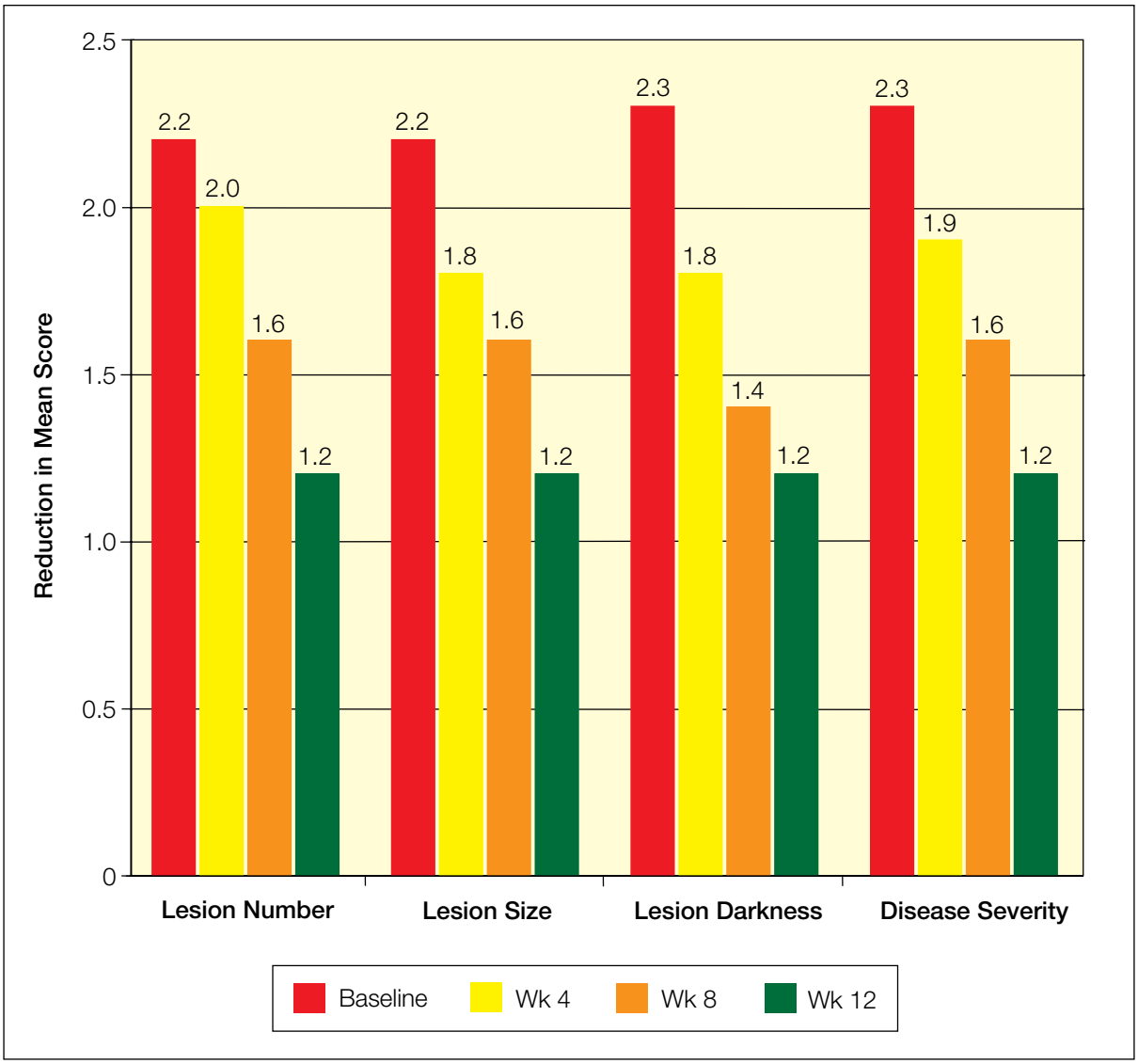

Figure 1. Mean scores at all study visits for lesion number, size, and darkness, as well as disease severity. Reductions in mean scores from baseline were statistically significant for lesion size, darkness, and disease severity as early as 4 weeks after treatment initiation and remained significantly reduced throughout the study (all $P<.032$). Lesion number also decreased by week 4 and significant reductions were noted at weeks 8 and 12 ($P\leq.001$). Each end point was scored based on a 5-point scale (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe).

types represented were type II (2 participants [9.5%]), type III (2 participants [9.5%]), type IV (6 participants [29%]), type V (8 participants [38%]), and type VI (3 participants [14%])(Table).

Treatment of the face and/or body with the microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants product produced improvement in all study end points. Results for the efficacy measurements of lesion size, darkness, and disease severity showed a statistically significant reduction in mean score from baseline that was observed as early as 4 weeks after treatment initiation (all $P<.032$)(Figure 1). Lesion number also decreased by week 4; significant reductions were noted at weeks 8 and 12 ($P\leq.001$).

The global improvement assessment was conducted by the investigator at weeks 4, 8, and 12. Improvements were noted as early as week 4 and progressed at each subsequent study visit. As assessed by the investigator, 63% of participants (12/19) had either marked improvement (defined as 75% overall improvement) or complete clearing (≥95% overall improvement) at the end of the 12-week treatment period. This finding was similar to the participant global improvement assessment (conducted at week 12); 53% of participants (10/19) assessed their own improvement as either marked or completely clear.

Baseline disease severity and treatment results at week 12 are presented in Figures 2 through 5. Figures 2

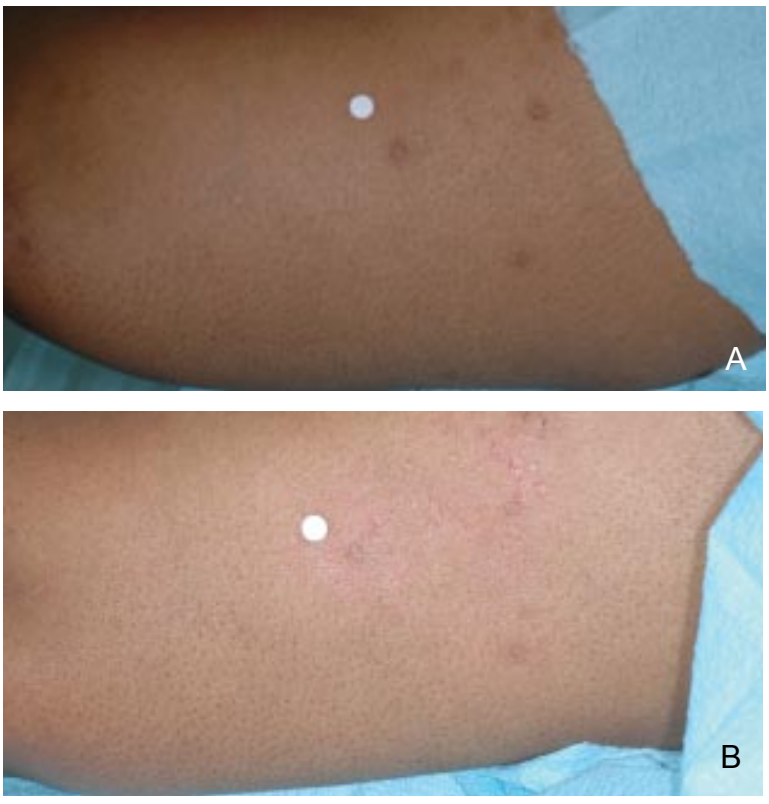

Figure 2. Postinflammatory hyperpigmentation on the arm at baseline (A) and after 12 weeks of treatment with microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants (B).

through 4 illustrate the face and body of participants treated for PIH, while Figure 5 demonstrates the effects of treatment in a participant with melasma.

As measured by spectrophotometer during the 12-week study, the mean melanin content in the target hyperpigmented macules decreased significantly by week 4 (target A: mean decrease=99, standard deviation [SD]=80 [$P \leq .001$]; target B: mean decrease=82, SD=99 [$P=.002$]). These decreases in means remained significant at week 8 (target A: mean decrease=139, SD=90 [$P<.001$]; target B: mean decrease=103, SD=99 [$P<.001$]) and week 12 (target A: mean decrease=170, SD=128 [$P<.001$]; target B: mean decrease=143, SD=101 [$P<.001$]). In contrast, the melanin content of normal skin was unchanged throughout the study period.

The hemoglobin content (erythema) in the target macules also decreased by week 4, with decreases in both macules becoming significant by week 12 (target A: mean decrease=31, SD=57 [$P=.026$]; target B: mean decrease=28, SD=49 [$P=.011$]). The hemoglobin content of normal skin decreased only slightly at week 4 and was relatively unchanged at each of the other study visits.

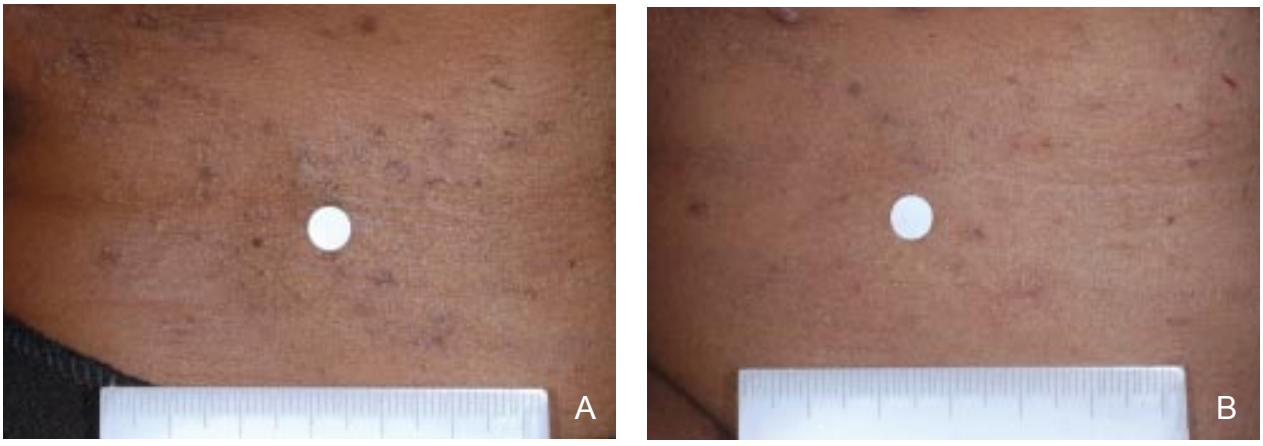

Figure 3. Postinflammatory hyperpigmentation on the neck at baseline (A) and after 12 weeks of treatment with microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants (B).

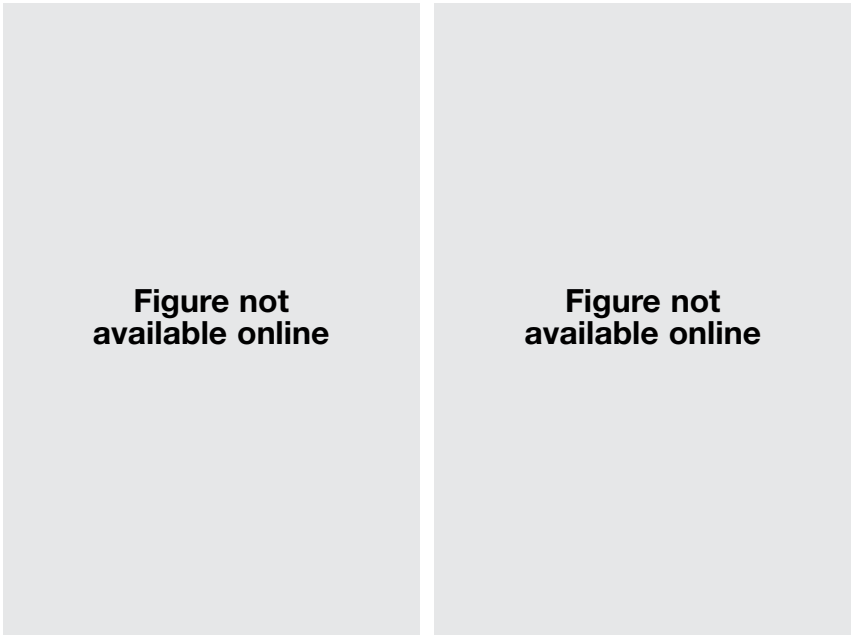

Figure 4. Postinflammatory hyperpigmentation on the face at baseline (A) and after 12 weeks of treatment with microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants (B).

Figure 5. Melasma on the face at baseline (A) and after 12 weeks of treatment with microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants (B).

Four participants diagnosed with melasma were enrolled in the study and were treated with the microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants product. The mean MASI score for the 4 participants with melasma decreased throughout the study from baseline (MASI=7.2) through week 12 (MASI=1.2); however, none of the changes from baseline proved to be statistically significant, which may be attributed to the small number of participants being treated for melasma (n=4).

At week 12, participants completed a questionnaire that used a 4-point scale to assess their overall satisfaction with the treatment. In all, 84% of participants (16/19) rated their satisfaction with treatment as either excellent (very satisfied) or good (moderately satisfied), while 11% of participants (2/19) rated their satisfaction as fair (slightly satisfied) and only 1 participant (5%) rated his/her satisfaction as poor (not satisfied). Participants had favorable comments about the cosmetic properties of the product, with most participants responding that it had a pleasing texture and consistency, absorbed quickly, had a nongreasy feel, was moisturizing, and did not clog pores. Most participants (84% [16/19]) stated that they would continue to use the product, if needed.

Treatment with the microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants product was well-tolerated by all 21 participants. In fact, the mean severity scores for the signs and symptoms of erythema decreased during the study period. Erythema scores decreased from a mean of 2.3 (slight to moderate) at baseline to 1.2 (barely noticeable to slight) at week 12. Similar decreases were seen for dryness throughout the study. The mean scores for itching, stinging, and burning remained virtually unchanged during the study, with scores at baseline and week 12 of approximately 0 (no signs or symptoms).

A total of 6 participants reported AEs during the study, including contact dermatitis (2), excoriation (1), acneform eruption (1), headache (1), and sinusitis (1). Only one of the contact dermatitis AEs was deemed to be possibly related to the study drug, while the other 5 AEs were recorded as not related. Two participants discontinued from the study because of AEs: one to contact dermatitis (possibly related) and the other to acneform eruption (not related). All other participants completed the study.

Comment

The data presented here augment the results from 2 prior clinical studies with a novel nonsteroid-containing microencapsulated hydroquinone 4% product. In the current study, the microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants product continued to demonstrate a favorable safety and tolerability profile for participants being treated on the face and, for the first time, on the body. Positive and statistically significant efficacy results in the end points of lesion size, darkness, disease severity, and spectrophotometer readings were seen as early as 4 weeks after initiation of treatment and continued for the duration of the study period. Global improvement at week 12 was assessed by the investigator and the participants to be either marked or completely clear in most cases.

The main difference between this study of microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants and the previous 2 studies was the inclusion of hyperpigmentation treatment on the face as well as the body. These clinical findings are noteworthy in that PIH may be more difficult to treat on nonfacial areas because of increased skin thickness, with the possibility of deeper dermal deposition of melanin and persistence of the PIH lesions on the body. The importance of these results is that this combination product provides an option for clinicians in the treatment of hyperpigmentation on the body.

These data confirm and enhance previous findings that microencapsulated hydroquinone 4% and retinol with antioxidants is effective and safe for use in the treatment of hyperpigmentation in various skin types on the face as well as the body.

REFERENCES

1. Pathak MA, Fitzpatrick TB, Kraus EW. Usefulness of retinoic acid in the treatment of melasma. *J Am Acad Dermatol*. 1986;15(4, pt 2):894-899.
2. Freedberg IM, Eisen AZ, Wolff K, et al. *Fitzpatrick's Dermatology in General Medicine*. 5th ed. New York, NY: McGraw-Hill; 1999.
3. Halder RM, Grimes PE, McLaurin CI, et al. Incidence of common dermatoses in a predominantly black dermatologic practice. *Cutis*. 1983;32:388, 390.
4. Grimes PE. Melasma. etiologic and therapeutic considerations. *Arch Dermatol*. 1995;131:1453-1457.
5. Sanchez NP, Pathak MA, Sato S, et al. Melasma: a clinical, light microscopic, ultrastructural, and immunofluorescence study. *J Am Acad Dermatol*. 1981;4:698-710.
6. Alaluf S, Atkins D, Barrett K, et al. Ethnic variation in melanin content and composition in photoexposed and photoprotected human skin. *Pigment Cell Res*. 2002;15:112-118.
7. Vazquez M, Maldonado H, Benmaman C, et al. Melasma in men. a clinical and histologic study. *Int J Dermatol*. 1988;27:25-27.
8. Sialy R, Hassan I, Kaur I, et al. Melasma in men: a hormonal profile. *J Dermatol*. 2000;27:64-65.
9. Taylor SC, Torok H, Jones T, et al. Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. *Cutis*. 2003;72:67-72.
10. Embil K, Nacht S. The Microsponge Delivery System (MDS): a topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. *J Microencapsul*. 1996;13:575-588.
11. Grimes PE. A microsponge formulation of hydroquinone 4% and retinol 0.15% in the treatment of melasma and postinflammatory hyperpigmentation. *Cutis*. 2004;74:362-368.
12. Grimes PE. An efficacy study of 3 commercially available hydroquinone 4% treatments for melasma. *Cutis*. 2007;80:497-502.