An Efficacy Study of 3 Commercially Available Hydroquinone 4% Treatments for Melasma

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Melasma is a common disorder of hyperpigmentation typically characterized by relatively symmetric brown or gray-brown patches on sun-exposed facial areas. Treating melasma is challenging because of the prolonged time to response and the substantial relapse rate when therapy is discontinued.

The objective of this 12-week study was to compare the clinical efficacy and tolerability of 3 hydroquinone 4%–containing creams in the treatment of melasma. The 3 creams were cream A (microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants); cream B (hydroquinone 4% and retinol 0.3% with antioxidants); and cream C (fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%). This 2-arm, split-face, right-left bilateral, evaluator-blinded study compared cream A and cream B in treatment arm 1, and cream A and cream C in treatment arm 2.

Evaluator-blinded study assessments were conducted at baseline and weeks 4, 8, and 12. Results from treatment arm 1 demonstrated that at weeks 8 and 12, treatment with cream A showed statistically significant improvements over cream B in the efficacy assessments of overall disease severity (week 8, P=*.005; week 12,* P=*.028), lesion area (week 8,* P=*.005; week 12,* P=*.003), pigmentation intensity (week 8,* P=*.012; week 12,* P=*.012), and Melasma Area and Severity Index (MASI) score (week 8,* P=*.002; week 12,* P=*.012). Results from treatment arm 2 demonstrated that at weeks 4 and 8, treatment with cream A was similar to cream C in the efficacy assessments of overall disease severity, lesion area, pigmentation intensity, MASI score, and global evaluation of response to treatment. At week 12, cream A continued to demonstrate sustained improvements in each of the above efficacy assessments; however, cream C showed a decrease in improvement of these efficacy assessments because subjects were switched to placebo for the last 4 weeks of treatment. All 3 treatments were well-tolerated. These data confirm previous findings that the unique delivery system of microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants is safe and effective for use in treating melasma, and the data show that this novel nonsteroidal product should be considered when weighing long-term treatment options.*

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Melasma is a common disorder of hyperpigmentation typically characterized by relatively symmetric brown or gray-brown patches on facial areas exposed to the sun. It is an emotionally and therapeutically challenging disease because positive results may require months of treatment. 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]

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Figure 1. Subject from treatment arm 1 treated with cream A (microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants) at baseline (A), week 4 (B), and week 12 (C).

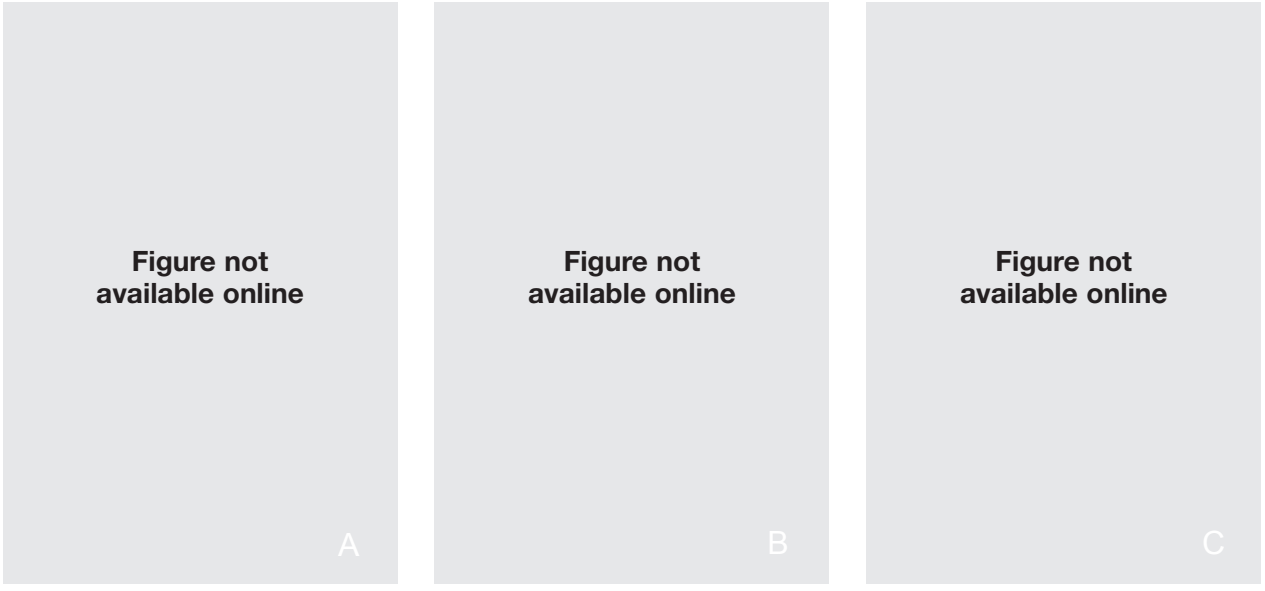

Figure 2. Subject from treatment arm 1 treated with cream B (hydroquinone 4% and retinol 0.3% with antioxidants) at baseline (A), week 4 (B), and week 12 (C).

Although melasma affects individuals of all skin types, it is more prevalent in darker-skinned individuals living in areas with high UV light exposure.[1,3-5] These individuals typically are classified as having Fitzpatrick skin types IV to VI.

For mild to moderate melasma, hydroquinone-containing bleaching creams are considered the gold standard. Multiple clinical studies have documented the efficacy of hydroquinone in the treatment of melasma.[2,6-9] Combination products containing hydroquinone (typically hydroquinone 4%) also are widely used because hydroquinone monotherapy formulations usually have low efficacy.[8] These combination products frequently include depigmenting agents such as tretinoin, retinol, glycolic acid, hyaluronic acid, antioxidants (to help stabilize the hydroquinone), or corticosteroids. An innovative hyperpigmentation disorder combination product containing microencapsulated hydroquinone 4% and retinol 0.15% with

antioxidants has been shown to significantly improve melasma and postinflammatory hyperpigmentation.[9] Significant improvements were reported in disease severity, lesion area, pigmentation intensity, and colorimetry measurements as early as 4 weeks of treatment ($P<.001$). Continued improvements were observed at each time point studied throughout the 12 weeks of treatment.[9]

A 2-arm, split-face, right-left bilateral, evaluator-blinded study was conducted to compare the clinical efficacy and tolerability of 3 different combination creams containing hydroquinone 4% in subjects with melasma.

METHODS

Study Design

This 12-week study of subjects with melasma examined the clinical efficacy and tolerability of 3 different hydroquinone 4%–containing combination creams (cream A, microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants; cream B, hydroquinone 4% and retinol 0.3% with antioxidants; cream C, fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%). This 2-arm, split-face, right-left bilateral, evaluator-blinded study compared cream A and cream B in treatment arm 1, and cream A and cream C in treatment arm 2. Cream A and cream B were applied twice daily for 12 weeks, and cream C was applied once daily for 8 weeks with a placebo replacing it for the last 4 weeks of treatment (at the time the study was performed, cream C labeling limited use to 8 weeks; labeling subsequently changed). Evaluator-blinded study assessments were conducted at baseline and at weeks 4, 8, and 12.

The study was approved by an institutional review board, and written informed consent and photographic release were obtained from each subject prior to participation in the study.

Treatment Protocol

The evaluator was blinded to medication use and medications were dispensed by a blinded source. Treatment arm 1 subjects were instructed to apply a designated amount of cream A to one side of the face and the same amount of cream B to the other side twice daily (morning and evening) for 12 weeks. Treatment arm 2 subjects were instructed to apply a designated amount of cream A to one side of the face twice daily (morning and evening) for 12 weeks. They also were instructed to apply an equal amount of cream C to the other side of the face once daily in the evening for 8 weeks. For the last 4 weeks, cream C was substituted with a placebo.

For both treatment arms, the side of the face to be treated with cream A was randomized to either the right or left side. To prevent cross contamination, subjects were instructed to wash their hands thoroughly between right- and left-side applications.

Inclusion and Exclusion Criteria—Subjects 18 years or older with Fitzpatrick skin types I through VI were included in the study. They had to be clinically diagnosed as having mild to moderate melasma that was relatively symmetric. Subjects were excluded from the study if they were taking hormone replacement or oral contraceptive therapy, were pregnant, or were lactating. Other exclusion criteria included the use of any form of bleaching creams including hydroquinone, tretinoin, retinol, glycolic acid, kojic acid, azelaic acid, or topical steroids within 4 weeks of study participation.

Efficacy Measurements

The study end points of overall disease severity, lesion area, and pigmentation intensity were assessed for each side of the face at each of the 4 visits. Overall disease severity was rated according to a 9-point scale (0=none and 8=severe). Lesion area and pigmentation intensity were rated according to a 6-point scale (0=none and 5=severe). Global evaluation of response to treatment was rated on a scale of 0 (worse) to 8 (completely cleared) and was performed at weeks 4, 8, and 12 to compare the overall appearance of treated areas to lesions at baseline.

In addition, a Melasma Area and Severity Index (MASI) score was calculated at each visit, and reflectance spectrophotometer readings were performed to measure the pigmentation (melanin, erythema) of both targeted facial lesions and an adjacent area of healthy skin at each visit.

Tolerability Measurements

Signs of skin irritation such as dryness, erythema, oiliness, and peeling in combination with symptoms of skin irritation such as burning and pruritus were recorded at each visit after initiation of the study medications. Any adverse events experienced also were recorded at each visit. A 6-point scale (0=normal and 5=severe) was used to assess any signs or symptoms of irritation.

Statistical Analysis

Statistical tests were 2-sided and interpreted at a 5% significance level. Comparisons between baseline and each follow-up visit (for each side of the face) were performed using a paired *t* test.

RESULTS

The study enrolled 36 subjects with melasma. Fourteen subjects (all women) were enrolled in treatment arm 1, and 22 subjects (21 women, 1 man) were

Figure 3. Subject from treatment arm 2 treated with cream A (microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants) at baseline (A), week 4 (B), and week 12 (C).

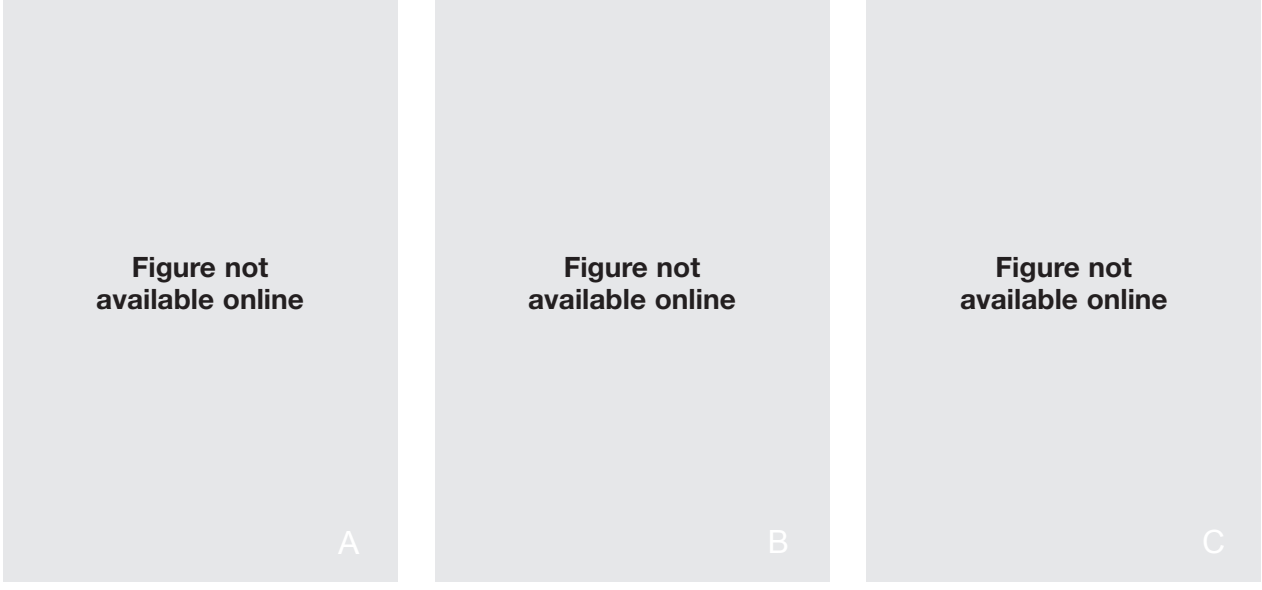

Figure 4. Subject from treatment arm 2 treated with cream C (fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%) at baseline (A) and week 4 (B), with a placebo replacing cream C for the last 4 weeks of treatment (week 12)(C).

enrolled in treatment arm 2. For all data analysis conducted in this study, the number of subjects was 14 in treatment arm 1 and 21 in treatment arm 2, for a total of 35 subjects (1 subject from treatment arm 2 was dropped from all analyses because of noncompliance). The mean age of subjects was 51.4 years in treatment arm 1 and 44.6 years in treatment arm 2. Of the subjects enrolled in treatment arm 1, 7 (50%) were black, 1 (7%) was white, and 6 (43%) were Hispanic; in treatment arm 2, 4 (19%) were black, 1 (5%) was white, and 16 (76%) were Hispanic. In treatment arm 1, 1 (7%) subject had Fitzpatrick skin type III, 6 (43%) had type IV, and 6 (43%) had type V. The skin type is not available for 1 subject in treatment arm 1. In treatment arm 2, 3 subjects (14%) had Fitzpatrick skin type III, 9 (43%) had type IV, and 9 (43%) had type V.

In the statistical analysis of all clinical efficacy assessments in this study, the change from baseline was evaluated at weeks 4, 8, and 12 for the

sides of the face treated with cream A versus the sides of the face treated with cream B in treatment arm 1, compared to the sides of the face treated with cream C in treatment arm 2. Results from treatment arm 1 demonstrated that at weeks 8 and 12, treatment with cream A (microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants) showed statistically significant improvements over cream B (hydroquinone 4% and retinol 0.3% with antioxidants) in the efficacy assessments of overall disease severity (week 8, $P=.005$; week 12, $P=.028$) and MASI score (week 8, $P=.002$; week 12, $P=.012$). Statistically significant improvements with cream A compared with cream B also were seen with lesion area (week 8, $P=.005$; week 12, $P=.003$) and pigmentation intensity (week 8, $P=.012$; week 12, $P=.012$). At week 4, both creams in treatment arm 1 (cream A and cream B) showed similar results in all efficacy assessments (no significant differences between the 2 treatments), and creams A and B both demonstrated significant improvements over baseline in overall evaluation of disease severity, pigmentation intensity, and MASI score as early as 4 weeks of treatment ($P<.05$ for all). With respect to the reflectance spectrophotometer readings of melanin and erythema and the global evaluation of response to treatment, there were no significant differences between treatment with cream A and cream B at any of the time points (weeks 4, 8, or 12).

Results from treatment arm 2 demonstrated that at weeks 4 and 8, treatment with cream A was similar to cream C (the triple-combination cream) in the efficacy assessments of overall disease severity, lesion area, pigmentation intensity, MASI score, and global evaluation of response to treatment. Both treatments showed statistically significant improvements over baseline in these assessments as early as week 4 and continuing at week 8 ($P<.05$ for all). At week 12, cream A continued to demonstrate sustained improvements in each of the above efficacy assessments; however, cream C showed a decrease in improvement of these efficacy assessments because subjects were switched to placebo for the last 4 weeks of treatment.

Analysis of evaluator and subject tolerability assessments were performed as direct comparisons between the sides of the face treated with cream A and the sides of the face treated with cream B (or cream C) at each visit. Figure 1 shows the cream A–treated side of the face of a subject in treatment arm 1, and Figure 2 shows the cream B–treated side of the same subject. Figures 3 and 4 depict the cream A– and cream C–treated sides of the face, respectively, of a subject in treatment arm 2.

No significant differences between the 3 creams were found in any of the tolerability parameters assessed by the investigator. All 3 treatments were well-tolerated, with a few isolated incidences of mild to moderate dryness, erythema, and peeling reported by subjects from all 3 treatments (A, B, C). No other adverse events were reported. Only 2 subjects discontinued from the study for reasons unrelated to the use of the study medications.

COMMENT

Because the treatment of hyperpigmentation often can require long-term strategies to maintain positive results, considerations regarding safety, efficacy and tolerability are key factors when selecting a topical therapy. With combination products containing hydroquinone 4% becoming more widely used, formulations are being developed to achieve greater efficacy for the treatment of melasma while maintaining long-term tolerability. Previous studies suggested the need for long-term maintenance therapy for melasma.[10] This finding is further demonstrated in this study by the rapid recurrence that was observed in the cream C–treated subjects after they discontinued hydroquinone and began using placebo at week 8.

Data presented in this article demonstrate that as early as 4 weeks after the initiation of treatment, a novel non–steroid-containing hydroquinone 4% product showed increased or comparable efficacy to other hydroquinone 4% combination products in regard to the study assessments performed. Results from treatment arm 1 demonstrated that cream A was statistically significantly better than cream B for a variety of efficacy parameters, which is noteworthy because both cream A and cream B contained similar components. However, in cream A, hydroquinone and retinol were microencapsulated into porous microspheres that gradually released their contents into the skin. This novel formulation may account for the significant improvements seen in skin treated with cream A versus cream B. Of particular significance are the similar efficacy results observed with cream A and cream C in treatment arm 2 of this study. Because cream C is steroid containing and cream A is not, these findings should be particularly important because of the potential adverse effects of long-term steroid treatment, such as telangiectasia, acne, acne rosacea, and atrophy.

These data confirm previous findings that microencapsulated hydroquinone 4% and retinol 0.15% with antioxidants is safe and effective for use in treating melasma, and the data show that this novel

nonsteroidal product should be considered when weighing long-term treatment options, especially as an alternative to long-term use of hydroquinone formulations that contain topical steroids.

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