Treating Epidermal Melasma With a 4% Hydroquinone Skin Care System Plus Tretinoin Cream 0.025%

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We sought to evaluate the efficacy and tolerability of treating melasma using a 4% hydroquinone skin care system, including a proprietary cleanser, toner, 4% hydroquinone, exfoliation enhancer, and sunscreen, plus tretinoin cream 0.025%. Together these products offer not only treatment of melasma but also a complete skin care regimen. Twenty participants with mild or moderate epidermal melasma with Fitzpatrick skin types III to VI were instructed to use the hydroquinone skin care system and tretinoin cream for 12 weeks.

Melasma severity, melasma pigmentation intensity, and melasma area and severity index (MASI) score were significantly reduced from week 4 onward relative to baseline (P≤.01). The proportion of participants who felt embarrassed or self-conscious about their skin very much or a lot declined from 80% (16/20) to 20% (4/20) between baseline and week 12. Similarly, the proportion of those who made very much or a lot of effort to hide their skin discoloration declined from 90% (18/20) to 37% (7/19). In total, 85% (17/20) of participants were satisfied with the overall effectiveness of the study treatment. Three participants had adverse events probably related to treatment (dryness, erythema, peeling, and stinging sensation). The 4% hydroquinone skin care system plus tretinoin cream 0.025% is effective and well-tolerated in the treatment of melasma.

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Melasma is symmetric facial hypermelanosis characterized by patches of light brown or gray-brown macules on sun-exposed skin. It occurs most commonly in women, especially those living in areas of intense sunlight.[1] The misconception that melasma is merely a cosmetic nuisance has resulted in underdiagnosis and undertreatment.[2] However, the condition can cause great distress and can have substantial negative effects on the emotional well-being, social life, and quality of life (QOL) of patients.[3]

Several factors may be involved in triggering melasma, including genetic influences, pregnancy, UV light, oral contraceptives, phototoxic drugs, and antiseizure drugs.[4] Because exposure to UV light appears to be one of the most important triggers,[5] a broad-spectrum sunscreen should always be part of any depigmenting treatment regimen; its inclusion has been proven to enhance the effectiveness of treatment.[6] Hydroquinone is the most effective topical bleaching agent approved by the US Food and Drug Administration for the treatment of melasma.[4] It reduces the synthesis of melanin by inhibiting tyrosinase activity and also may be involved in the degradation of melanosomes and melanocytes.[4] Tretinoin also is effective in the treatment of melasma.[5,7,8] Tretinoin may enhance the penetration of hydroquinone through the stratum corneum, protect hydroquinone from oxidation, and facilitate pigment removal by accelerating keratinocyte turnover.[9]

Although both hydroquinone and tretinoin are effective in treating melasma,[10-12] a disadvantage

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of monotherapy with either agent is the prolonged treatment time required before meaningful results are achieved. For example, it has been reported that it may take 24 weeks to achieve notable improvement with tretinoin treatment.[8] With combination therapy, meaningful improvements can be achieved more rapidly.

We sought to evaluate the efficacy and tolerability of treating melasma using a 4% hydroquinone skin care system plus tretinoin cream 0.025%, which not only treats melasma but also provides a complete skin care regimen including protection from UV light.

Methods

Participants—Female patients were eligible to enroll in the study if they met the following inclusion criteria: mild or moderate epidermal melasma, confirmed with Wood lamp examination; minimal to marked intensity of melasma pigmentation; cutaneous melanosis that had been stable over the preceding 3 months; Fitzpatrick skin types III to VI; and aged 25 to 65 years.

Participants were required to be willing to refrain from the following throughout the study: facial use of nonstudy topical products including medications, moisturizers, sunscreens, fragrances, and medicated makeup, though oil-free noncomedogenic makeup, mascara, eyeliner, eye shadow, and lipstick were allowed; facial procedures including chemical peels, facial microdermabrasion, laser resurfacing, nonablative laser, light or radiofrequency treatment, and injection of dermal fillers or botulinum toxin type A; facial hair removal, except plucking of eyebrows with tweezers, which was allowed; and use of systemic retinoids, methotrexate, photoallergic drugs, phototoxic drugs, and photosensitizing drugs. Sunbathing, the use of tanning booths, and the facial use of tanning products also were prohibited; participants were required to wear appropriate protective clothing when exposed to the sun. Participants taking oral contraceptives or hormonal replacement therapy were required not to alter their treatment during the study.

Exclusion criteria included the following: history or presence of any facial skin condition that might interfere with diagnosis or evaluation during the study; known hypersensitivity or allergy to sulfites or ingredients in the study treatment products, including parabens and aloe; history of increased pigmentation and/or contact dermatitis with prior use of hydroquinone or tretinoin; dermal melasma or a combination of dermal or epidermal melasma; postinflammatory hyperpigmentation; vitiligo; history or presence of Ota nevus; depressed or atrophic macular lesions; requirement for hormonal treatment that might enhance pigmentation; irritation of exposed skin (eg, from UV light) or facial sunburn; anticipated need to use other medicated products on the face during the study; excessive or prolonged exposure to sunlight without protective clothing; and pregnancy, breastfeeding, or planning to become pregnant during the study.

The following washout periods were required: 1 week for medicated facial cleansers and facial hair removal procedures; 30 days for topical prescription treatments, sunbathing and UV-light therapy, topical medications, bleaching products, and photosensitizing procedures or medications on the face including corticosteroids, hydroquinone, α-hydroxy acids, β-hydroxy acids, kojic acid, retinoic acid, retinol, salicylic acid, and vitamin C and vitamin D products or derivatives; 6 weeks for facial microdermabrasion; 12 weeks for systemic steroids; and 6 months for photoallergic, phototoxic, and photosensitizing drugs or systemic retinoids, methotrexate, laser resurfacing procedures, deep skin peels, and injection of dermal fillers or botulinum toxin type A.

The study was conducted in accordance with the 2004 version of the Declaration of Helsinki and all participants signed informed consent. The study was performed between May 2010 and September 2010.

Treatment Regimen—Participants were instructed to use the 4% hydroquinone skin care system plus tretinoin cream 0.025% on their entire face for 12 weeks. The 4% hydroquinone skin care system involved applying the following proprietary products: foaming gel cleanser (Nu-Derm® Foaming Gel), toner (Nu-Derm Toner), 4% hydroquinone (1 g)(Nu-Derm Clear), exfoliation enhancer containing α-hydroxy acids (0.5 g)(Nu-Derm Exfoderm Forte), and sunscreen (Nu-Derm Healthy Skin Sun Protection SPF 35)(all Nu-Derm products from OMP, Inc). The cleanser, toner, and hydroquinone were applied twice daily, and the exfoliation enhancer and sunscreen were applied each morning. Tretinoin cream 0.025% (0.5 g) was mixed with 4% hydroquinone (0.5 g) (Nu-Derm Blender) and applied each evening.

On the instruction of the investigator, participants could use a study moisturizer (Nu-Derm Action) for dryness or 0.5% hydrocortisone (Nu-Derm Tolereen) for other tolerability issues such as itching, erythema, and irritation, as needed. This study was unblinded and the investigator and participants were aware of the treatment being given.

Outcome Measures—The investigator evaluated melasma severity, melasma pigmentation intensity, melasma area and severity index (MASI) score, melasma improvement, erythema, dryness, peeling, and burning/stinging at baseline and/or weeks 4, 8, and 12 (Tables 1 and 2). Participants completed a questionnaire[13] at each time point asking them to

Table 1.

Study Evaluations

Melasma Severity (Score)	Melasma Pigmentation Intensity (Score)	Melasma Improvement	Erythema	Dryness	Peeling	Burning/Stinging
None (0): no noticeable lesion area	None (0): no noticeable lesion area	Worse	None: no erythema present	None	None	Normal, no discomfort
Minimal/trace (1): melasma covering 1%–10% of face	Minimal (1): localized deposits of pigment	Unchanged: no detectable improvement from baseline evaluation	Trace erythema	Slight flaking	Trace, localized peeling	Trace, awareness without discomfort
Mild (2 or 3): melasma covering 11%–25% of face	Mild (2 or 3): mild diffuse deposits of pigment	Slight improvement (1%–10%)	Mild erythema	Mild flaking	Mild diffuse peeling	Mild, noticeable discomfort causing intermittent awareness
Moderate (4 or 5): melasma covering 26%–40% of face	Moderate (4 or 5): moderate diffuse deposits of pigment	Mild improvement (11%–25%)	Moderate confluent erythema	Moderate flaking/scaling	Moderate: definitely noticeable peeling	Moderate, noticeable discomfort causing continuous awareness
Marked (6 or 7): melasma covering 41%–50% of face	Marked (6 or 7): marked dense deposits of pigment	Moderate improvement (26%–50%)	Marked erythema, slight edema	Marked scaling, slight fissuring	Marked: dense extensive peeling	Marked, definite discomfort that occasionally interferes with normal daily activities
Severe (8): melasma covering >50% of face	Severe (8): severe dense deposits of pigment	Marked improvement (51%–75%)	Severe erythema, edema, flare, possible erosion	Severe scaling, fissuring	Severe: extensive peeling	Severe, marked, continuous discomfort that interferes with normal daily activities
—	—	Almost complete clearing (76%–99% improvement)	—	—	—	—
—	—	Complete clearing: no signs of hyperpigmentation (100% improvement)	—	—	—	—

evaluate the following parameters over the prior week: (1) how embarrassed or self-conscious they had been because of their skin; (2) how much their skin discoloration had made them feel unattractive to others; (3) how much effort they had put into hiding their skin discoloration from others; (4) how much others had focused on their skin discoloration rather than on what they were saying or doing; and (5) how much their skin had affected any of their social and leisure activities. Each of these parameters was rated as very much, a lot, a little, or not at all.

Participants also were asked to compare the current appearance of their skin as seen in a hand mirror versus a photograph of their skin taken at the baseline visit before treatment. Next, the participants rated their satisfaction with the overall effectiveness of their

Table 2.

MASI Score

The melasma area and severity index (MASI) score is calculated by evaluating the melasma in each of 4 areas—forehead, right malar region, left malar region, and chin—in terms of percentage of total area involved, darkness compared with normal skin, and homogeneity.

The percentage area involved is classified as: 0=no involvement; 1=<10% involvement; 2=10%–29% involvement; 3=30%–49% involvement; 4=50%–69% involvement; 5=70%–89% involvement; 6=90%–100% involvement.

Darkness is classified as: 0=normal skin color without evidence of hyperpigmentation; 1=barely visible hyperpigmentation; 2=mild hyperpigmentation; 3=moderate hyperpigmentation; 4=severe hyperpigmentation.

Homogeneity is classified as: 0=normal skin color without evidence of hyperpigmentation; 1=specks of involvement; 2=small patchy areas of involvement <1.5-cm diameter; 3=patches of involvement >2-cm diameter; 4=uniform skin involvement without any clear areas.

The MASI score is calculated by multiplying the sum of the grades for darkness (D) and homogeneity (H) by the grades for percentage area involved (A) and the percentage attributed to each facial area (30% for forehead and each malar region, and 10% for chin).

Thus total MASI score = [0.3 × forehead A (forehead D + forehead H)] + [0.3 × right malar A (right malar D + right malar H)] + [0.3 × left malar A (left malar D + left malar H)] + [0.1 × chin A (chin D + chin H)].

study treatment as very satisfied, satisfied, indifferent, dissatisfied, or very dissatisfied; the effectiveness of their treatment compared with other medications as much more effective, more effective, same, less effective, or much less effective; and the ease of use of the study treatment as very easy, easy, average, difficult, or very difficult. They also were asked to rate their overall facial improvement, as well as their improvement in fine lines and wrinkles, skin texture/roughness, skin firmness, and brown spots/discoloration. These features were rated as poor or no change (0%–25%), fair (26%–50%), good (51%–75%), very good (76%–90%), or excellent (91%–100%).

Statistical Analyses—The changes from baseline in scores for erythema, dryness, peeling, and burning/stinging were evaluated using the Wilcoxon signed rank test with $P \leq .05$ considered to be statistically significant.

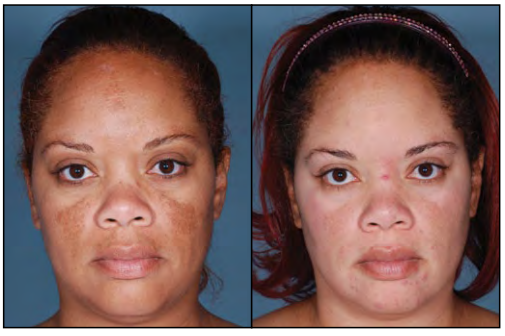
Results

Participants—A total of 20 participants enrolled in the study and 100% completed. All the participants were women, the mean age was 50 years, 65% (13/20) were black, and 35% (7/20) were white. Their Fitzpatrick skin type was IV (40% [8/20]), V (40% [8/20]), or VI (20% [4/20]). The clinical pattern of their melasma was malar in 65% (13/20) of participants and centrofacial in 35% (7/20) of participants.

Efficacy—Treatment was associated with significant reductions from baseline in melasma severity ($P \leq .01$ from week 4 onward), melasma pigmentation intensity ($P \leq .001$ from week 4 onward), and MASI score ($P \leq .001$ from week 4 onward)(Figures 1–4). The proportion of participants who achieved at least a 1-grade improvement from baseline in melasma severity at weeks 4, 8, and 12 was 47% (9/19), 70% (14/20), and 80% (16/20), respectively. Similarly, the proportion of participants who achieved at least a 1-grade improvement in melasma pigmentation intensity was 74% (14/19), 75% (15/20), and 85% (17/20), respectively. The proportion of participants with at least a marked (≥51%) improvement in melasma at these same time points was 16% (3/19), 40% (8/20), and 60% (12/20), respectively. Between baseline and week 12, the proportion of participants whose melasma was at least moderate in severity declined from 70% (14/20) to 35% (7/20), and the proportion of participants whose melasma pigmentation intensity was at least moderate in severity declined from 80% (16/20) to 30% (6/20).

The participant evaluations showed that their QOL also was improved after treatment (Figure 5). The proportion of participants who felt embarrassed or self-conscious about their skin very much or a lot in the prior week declined from 80% (16/20) to 20% (4/20) between baseline and week 12. Similarly, the proportion of participants who believed their skin discoloration made them feel unattractive very much or a lot declined from 80% (16/20) to 35% (7/20), the proportion who made very much or a lot of effort to hide their skin discoloration declined from 90% (18/20) to 37% (7/19), the proportion who felt that others focused very much or a lot on their skin discoloration rather than on what they said or did declined from 55% (11/20) to 15% (3/20), and

	Baseline	Week 12	Baseline	Week 12
Melasma severity score	5	4	4	1
Melasma pigmentation intensity score	5	4	4	1



	Baseline	Week 12
Melasma severity score	3	1
Melasma pigmentation intensity score	4	1

	Baseline	Week 12	Baseline	Week 12
Melasma severity score	5	4	4	2
Melasma pigmentation intensity score	5	3	6	2

Figure 1. Photographic documentation of improvements in melasma. The scores for melasma severity (0=none; 1=minimal/trace; 2 or 3=mild; 4 or 5=moderate; 6 or 7=marked; 8=severe) and melasma pigmentation intensity (0=none; 1=minimal; 2 or 3=mild; 4 or 5=moderate; 6 or 7=marked; 8=severe) declined (ie, improved) between baseline and week 12.

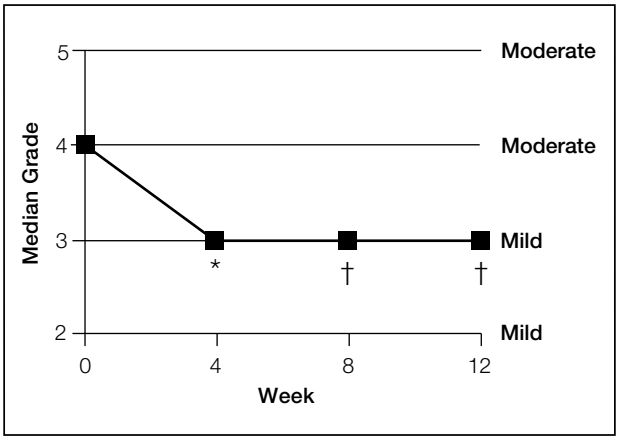


Figure 2. Median grade for melasma severity. Asterisk indicates $P \leq .01$; dagger, $P \leq .001$ vs baseline.

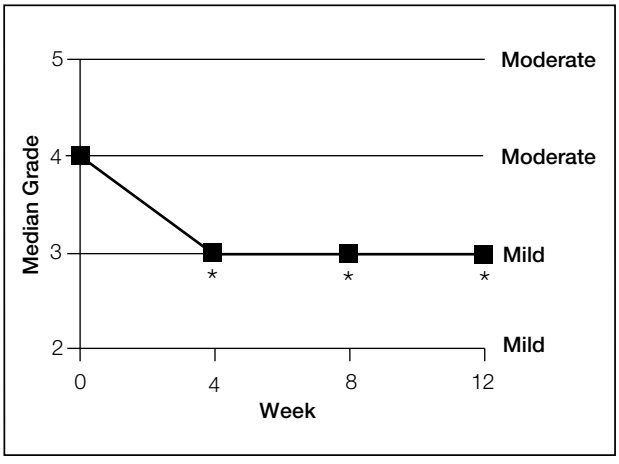


Figure 3. Median grade for melasma pigmentation intensity. Asterisk indicates $P \leq .001$ vs baseline.

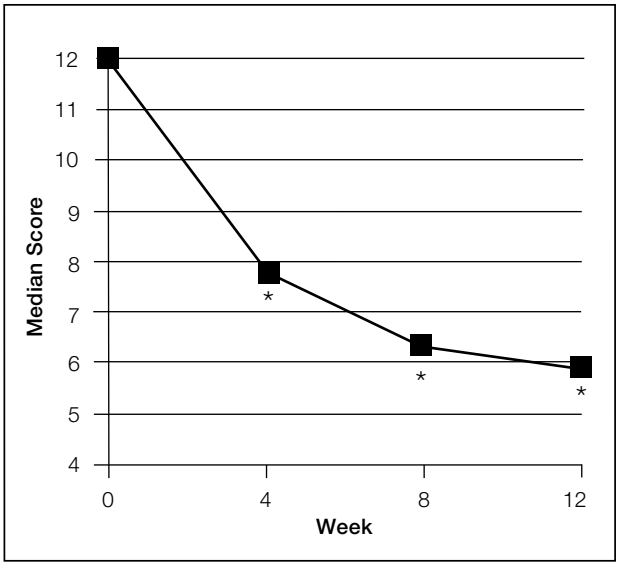


Figure 4. Median score for melasma area and severity index. Asterisk indicates $P \leq .001$ vs baseline.

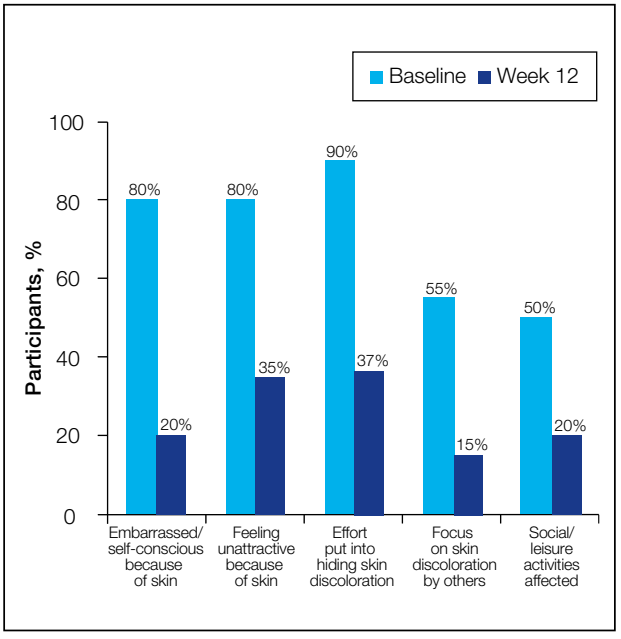


Figure 5. Very much or a lot of improvement in quality of life parameters after treatment of melasma as rated by participants.

the proportion who had any social or leisure activity affected by their skin condition very much or a lot declined from 50% (10/20) to 20% (4/20).

At week 12, 90% (18/20) of participants considered the study treatment to be very easy or easy to apply, 85% (17/20) were very satisfied or satisfied with the overall effectiveness of their treatment, and 90% (18/20) considered their study treatment to be much more effective or more effective than other medications.

The majority of participants also reported improvements in photodamage-related parameters. At week 12, good, very good, or excellent improvement (reduction) was reported in 85% (17/20) of participants for skin texture/roughness, 70% (14/20) of participants for fine lines and wrinkles, 70% (14/20) of participants for skin firmness, and 68% (13/19) of participants for brown spots/discoloration. In addition, 80% (16/20) of participants had good, very good, or excellent overall facial improvement.

Tolerability—Overall, 80% (16/20) of participants used the study moisturizer as a preventive measure against dryness and 15% (3/20) used the hydrocortisone (2 as a preventive measure, and 1 for erythema and stinging sensation). With regard to erythema, dryness, peeling, and burning/stinging, the mean grades were between none/normal and trace/slight at all time points, and the median grades were none/normal at all time points. The only significant change from baseline

for these parameters was an increase in erythema at week 12 ($P \leq .05$). Three participants had adverse events probably related to treatment (dryness and erythema; dryness and peeling; and dryness, erythema, and stinging sensation), which were all mild, except 1 case of erythema that was moderate.

Comment

The results of this study show that the 4% hydroquinone skin care system used in conjunction with tretinoin cream 0.025% is associated with significant reductions from baseline in the severity of epidermal melasma and the intensity of the melasma pigmentation from week 4 onward ($P \leq .01$ and $P \leq .001$, respectively). The median MASI score also is significantly reduced from week 4 onward ($P \leq .001$), with further reductions occurring with continued treatment for at least an additional 8 weeks.

Importantly, the 4% hydroquinone skin care system plus tretinoin cream 0.025% also achieves considerable improvements in the participants' QOL. For example, participants feel less self-conscious and less unattractive as a result of their skin and are able to reduce the amount of effort they put into hiding their skin discoloration. In addition, their social and leisure activities are less affected and they feel that other individuals focus less on their skin condition, which is important as it has been reported that one of the strongest independent predictors of a reduction in health-related QOL in women with melasma is an increased fear of negative evaluation by others.[14]

The vast majority of participants (90% [18/20]) reported that the study treatment was more effective than other medications and was easy to apply. These factors together with the good tolerability profile likely contributed to the high levels of participant satisfaction. Treatment systems such as the 4% hydroquinone skin care system used in this study tend to be popular with dermatology patients and may even enhance compliance,[15] perhaps because the system provides a carefully defined regimen that caters not only to the patient's melasma but also to the patient's everyday skin care needs, thereby avoiding the need for patients to struggle with coordinating their own skin care routine within the regimen prescribed by the physician.

Because melasma is associated with exposure to the sun, patients often have signs of photodamage in addition to their melasma. These signs may include other dyspigmentation problems, wrinkling, tactile roughness, and laxity. In addition to showing efficacy against melasma, the study treatment also was associated with improvements in various photodamage-related parameters (ie, fine lines and wrinkles, skin texture/roughness, skin firmness, brown spots/discoloration). It is likely that these improvements are at least partly attributable to tretinoin, which has previously been shown to be effective in achieving improvements in similar parameters.[16,17] Hydroquinone also likely helped improve hyperpigmentation and the exfoliation enhancer in the 4% hydroquinone skin care system, which contains glycolic and lactic acids, also may have helped improve skin texture.[18,19]

Tretinoin is associated with a risk for tolerability issues, such as erythema and peeling,[7,8] especially at higher concentrations and in patients with sensitive skin.[20] In the literature, tretinoin generally is used at concentrations of 0.05% or 0.1% for the treatment of melasma. There are 2 reports using a lower (0.025%) concentration of tretinoin in patients with melasma but only as a priming agent to reduce the risk for hyperpigmentation after chemical peels.[21,22] With the need to avoid postinflammatory hyperpigmentation being paramount in patients with darker skin, optimizing tolerability was a key objective in our study, and as a result, a 0.025% concentration of tretinoin was chosen. The 4% hydroquinone skin care system also is carefully designed to optimize tolerability. For example, the foaming gel cleanser and toner together contain *Aloe barbadensis* leaf juice and witch hazel, both having anti-inflammatory properties.[23,24] In addition, the exfoliation enhancer is designed to enhance efficacy but also may help to indirectly enhance tolerability. By helping the penetration of other components of the system into the skin, it may help efficacy to be achieved with a lower concentration of tretinoin than generally is used in the treatment of melasma, and using a lower concentration of tretinoin likely helps to minimize the potential for tolerability issues.

Triple therapy with a combination of hydroquinone, tretinoin, and steroid is commonly used in the treatment of melasma. However, the repeated and prolonged application of a steroid, especially on facial skin, may not be desirable because of the potential for causing atrophy, telangiectasia, acne, and rosacea. Triple therapy has been indicated only for short-term use (up to 8 weeks) because of this concern.[25] In our study, participants were allowed to apply topical hydrocortisone as needed if facial irritation was an issue, but only 1 participant (5%) actually used it to lessen irritation, with 2 other participants using it as a preventive measure. Participants not using the hydrocortisone were not exposed to a steroid and therefore were not at risk for steroid-induced adverse events. Given the low need for steroid use in our study, it therefore appears that the study treatment is more suitable than triple therapy for maintenance or long-term use. It also may be a more appropriate

choice than triple therapy if maximizing safety is a concern.

Conclusion

Using the 4% hydroquinone skin care system plus tretinoin cream 0.025% to treat epidermal melasma can achieve significant reductions in melasma severity, melasma pigmentation intensity, and MASI score ($P \leq .01$, $P \leq .001$, and $P \leq .001$, respectively). Importantly, treatment also is associated with considerable improvements in QOL as well as in signs of photodamage such as fine lines and wrinkles and skin texture/roughness. The treatment is well-tolerated and is associated with a high level of patient satisfaction.

Acknowledgment—Action, Blender, Exfoderm, and Obagi Nu-Derm are registered trademarks of OMP, Inc, and/or its affiliates in the United States and certain other countries.

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