Continuous therapy followed by a maintenance therapy regimen with a triple combination cream for melasma

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Background: Melasma is often recalcitrant to treatment. Triple combination (TC) cream is an effective and approved treatment for melasma.

Objective: We sought to determine the efficacy and safety of continuous therapy followed by a maintenance treatment regimen during a period of 24 weeks with a TC cream containing hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%.

Methods: Seventy patients with melasma were treated with a TC cream daily for 12 weeks, after which, if clear or almost clear, they applied the cream twice per week for 12 more weeks. For patients who were not clear or almost clear after 12 weeks, daily treatment was continued.

Results: In all, 25 patients completing the study per protocol were treated daily for 24 weeks (cohort A); 6 patients were treated daily for 12 weeks followed by 12 weeks of maintenance therapy (cohort B); and 21 patients were treated daily for 12 weeks, relapsed during the maintenance phase, and returned to daily dosing (cohort C). Pigmentation was significantly reduced at weeks 12 and 24 and global melasma severity improved at week 24 in cohorts A and C compared with baseline. Adverse events occurred in 53% of patients and were primarily mild in severity.

Limitations: This was an open-label trial.

Conclusion: About half of patients treated with a TC cream for melasma were able to begin maintenance therapy twice per week after 12 weeks; however, relapses occurred in most of these patients, requiring resumption of daily therapy. The cream is safe in the treatment of moderate to severe melasma for up to 24 weeks when used intermittently or continuously. Significant reductions in melasma severity scores were seen at weeks 12 and 24 when compared with baseline scores in all evaluable study groups (J Am Acad Dermatol 2010;62:962-7.)

Key words: hydroquinone; melasma; pigmentation; tretinoin.

Melasma is a common, persistent disorder of hyperpigmentation that affects a significant portion of the population, particularly patients with skin of color.[1] Affected patients often have melasma for many years and a significant effect on quality of life has been documented.[2,3] Treatment

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of melasma is often difficult, despite the availability of many treatment modalities.[4] Because melasma may be present for many years and relapse after improvement is common, development of a maintenance regimen after initial improvement would help in the management of this disorder. A combination cream containing hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% has been shown to be effective in the treatment of melasma, however, maintenance of reductions in melasma severity were not addressed.[5,6] We report the results of a study to determine the efficacy and safety of a 24-week, long-term continuous and maintenance treatment regimen with a triple combination (TC) cream. We also assessed atrophy and cell markers histologically, which will be reported separately.

CAPSULE SUMMARY

- After 12 weeks of use of a triple combination cream, about half of patients with melasma improved enough to enter a maintenance phase.
- The majority of patients who entered a maintenance phase, in which treatment was given twice per week, relapsed, requiring resumption of daily therapy.
- Significant reduction in severity of melasma was observed in all groups after 12 and 24 weeks.

METHODS

Patients with moderate to severe melasma, aged 18 to 65 years, were recruited for this study, which was approved by a local institutional review board for each site. All patients were informed of the benefits and risks of the study after which they signed an informed consent form. The presence of moderate to severe melasma was based on a previously described melasma severity scale.[5] Two investigational sites in the United States participated in this study. Female patients of childbearing potential were required to have a negative urine pregnancy test result at the beginning of the study, and agreed to practice appropriate birth control to prevent pregnancy during the study. Those patients on oral contraceptives had been on a stable dose for at least 6 months before study entry, which was not expected to change during the study.

TC cream containing hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% was applied once daily at bedtime for 12 weeks. After 12 weeks of treatment, patients were evaluated and, if a level of clear or almost clear was achieved, they entered the maintenance phase, which consisted of applying TC cream only twice a week. If the pigmentation worsened during maintenance therapy, daily dosing was resumed. If a level of clear or almost clear was not obtained after the initial 12-week treatment, the patient continued with the once-daily regimen until clear, almost clear, or the study ended. If, during this second 12-week period, a patient achieved clear or almost clear, the twice-weekly schedule was used. Patients were evaluated for safety and efficacy at baseline and weeks 12, 16, 20, and 24. They were also seen at weeks 1, 13, and 25 for tolerability assessments and suture removal. Suture removal was required after biopsies to assess histopathologic changes that will be reported separately. Patients were contacted by telephone at week 2 to assess tolerability and subsequently seen during an unscheduled visit if intolerance was reported. All patients were provided with a gentle skin cleanser (Cetaphil, Galderma Laboratories, Fort Worth, TX), gentle moisturizing lotion (Cetaphil, Galderma Laboratories), and a broad-spectrum sunscreen (Ultra Sheer Dry-touch sun block SPF 45, Neutrogena, Los Angeles, CA). The cleanser was used twice daily and sunscreen was applied every morning. Moisturizer use was encouraged if irritation developed. Patients were asked to practice sun avoidance and protection as much as possible.

Assessments included evaluation of skin pigmentation with a narrowband reflectance spectrophotometer (Mexameter MX-16, Courage-Khazaka Electronic, Köln, Germany), melasma area and severity index,[6] static investigator global assessment of melasma severity, and investigator global assessment of improvement. A patient satisfaction survey was also undertaken at the end of 24 weeks. Photographs were obtained on all patients at baseline and weeks 12, 16, 20, and 24.

Tolerability assessments of erythema, peeling/scaling, dryness, stinging/burning, edema, and telangiectases were made at each visit using a 4-point scale. The investigators specifically noted the presence or absence of visible signs of cutaneous atrophy. Adverse events were monitored and recorded throughout the course of the study.

The per-protocol population was used for efficacy analyses. The mean of the differences in the melanin pigmentation index between involved and uninvolved skin was calculated at each time point. For pigmentation index results and melasma area and severity index, a regression analysis controlling for site was used to compare differences between the involved and uninvolved areas at weeks 12 and 24. For normally distributed data, a general linear model

Table I. Patient demographics

Per-protocol population	Total N = 52
Sex	
Male	1 (2%)
Female	51 (98%)
Race	
White	1 (2%)
Black/African American	12 (23%)
Hispanic/Latino	38 (73%)
Other	1 (2%)
Fitzpatrick skin type	
III	4 (8%)
IV	37 (71%)
V	9 (17%)
VI	2 (4%)
Mean age, y	44.1
Mean disease duration, y	10.7

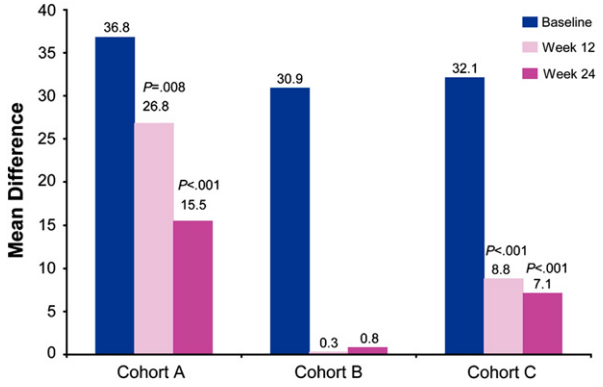

Fig 1. Difference in spectrophotometer readings between involved and uninvolved skin.

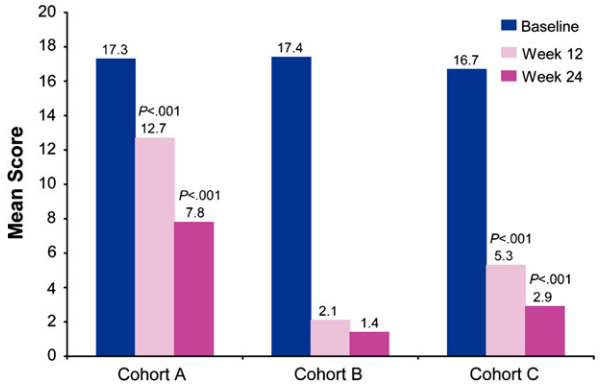

Fig 2. Improvement in melasma area and severity index score.

was used and for data that were not normally distributed, a robust regression on the median was used. A generalized estimating equation approach for ordinal data was used to analyze the data. The safety population was used for tolerability analyses. Tolerability scores were summarized descriptively.

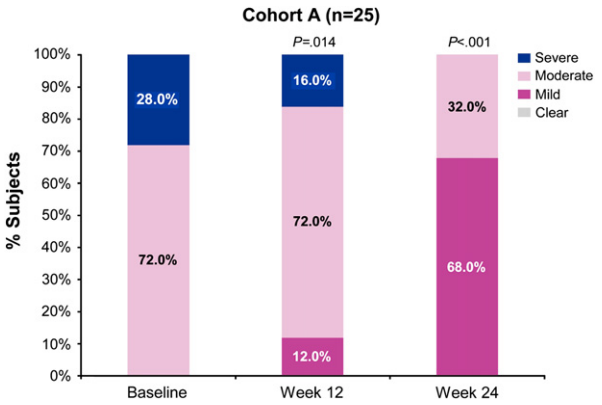

Fig 3. Investigator global assessment of melasma severity, cohort A.

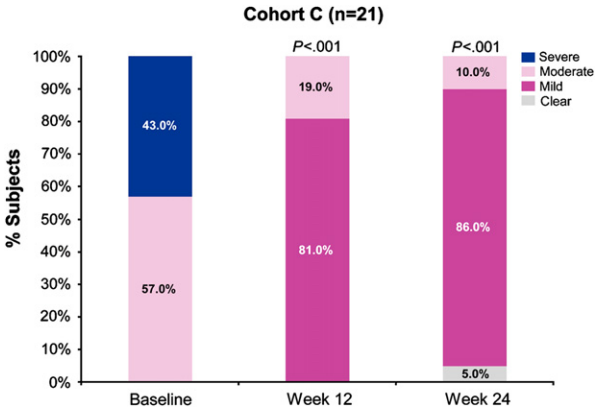

Fig 4. Investigator global assessment of melasma severity, cohort C.

RESULTS

Seventy patients were enrolled in the study and 60 completed all 24 weeks of therapy. Because of protocol violations, 8 additional patients were excluded, therefore, 52 patients were evaluated as the per-protocol population. Table I presents patient demographic information. The majority of the per-protocol population was female (98%) and Hispanic (73%) with Fitzpatrick skin type IV (71%). Mean age was 44.1 years and the average duration of melasma at the time of enrollment was 10.7 years. In all, 25 patients completed the 24-week study with daily dosing of TC cream (cohort A), 6 patients completed the study with 12 weeks of daily dosing followed by 12 weeks of maintenance (cohort B), and 21 patients completed the study with 12 weeks of daily dosing and a combination of daily dosing and twice-weekly maintenance dosing because of recurrence of melasma for an additional 12 weeks (cohort C). Efficacy data are presented with the per-protocol population whereas the safety data are presented with the safety population (n = 64).

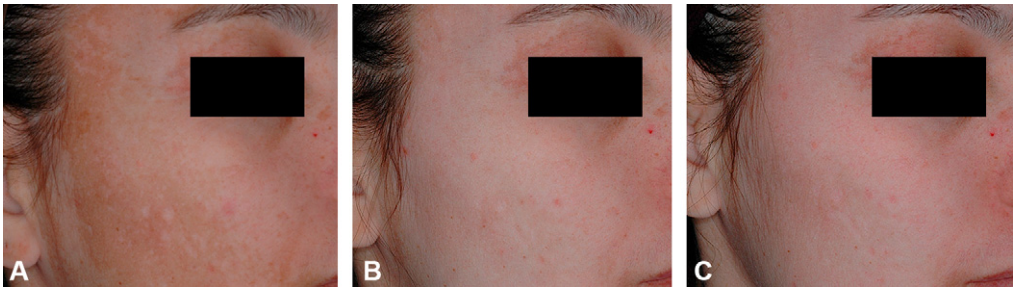

Fig 5. **A**, Patient from cohort C at baseline. **B**, After 12 weeks of daily treatment with triple combination cream. **C**, At 24 weeks. Patient received twice weekly maintenance therapy from weeks 12 to 16, relapsed, and required daily therapy until week 20, followed by maintenance therapy again until week 24.

The difference between involved (melasma) and uninvolved (normal) skin pigmentation as determined by spectrophotometer readings was significantly reduced at week 12 ($P \leq .008$) and week 24 ($P < .001$) in both of the primary treatment cohorts A and C when compared with baseline (Fig 1). Cohort B was not evaluated statistically because of the small number of patients in that group. Melasma area and severity index scores were significantly reduced in cohorts A and C at weeks 12 and 24 ($P < .001$ for both) compared with baseline (Fig 2). Static investigator global assessments showed that the distribution of global lesion severity significantly shifted from moderate/severe to mild/moderate or mild in cohorts A and C by week 12 ($P = .014$ for cohort A and $P < .001$ for cohort C) and at week 24 ($P < .001$ for both cohorts) (Figs 3 and 4). In addition, investigator global assessments of improvement indicated that significant improvement in melasma severity was seen in cohorts A and C ($P < .001$ for both) by week 24. Fig 5 shows an example of a patient with severe melasma who improved during the course of the study. Results of patient satisfaction surveys (Fig 6) showed that the majority of patients were satisfied with the treatment, liked using the TC cream, wanted to continue to use it, and thought the application was convenient, with mean scores around 9 (scale of 1-10 with 1 being the worst and 10 being the best).

Tolerability assessments were between 0 (none) and 1 (mild) for all parameters for all patients (Table II). No patient in any cohort at any point throughout the study was rated as having clinical atrophy by the investigator. Telangiectases were significantly increased only in cohort C at 24 weeks, when compared with baseline, and severity was mild. About half of the patients (53%) reported one or more adverse events. These events were generally mild (79%) in severity and only one serious adverse event was reported (cholelithiasis, not related to the study medication).

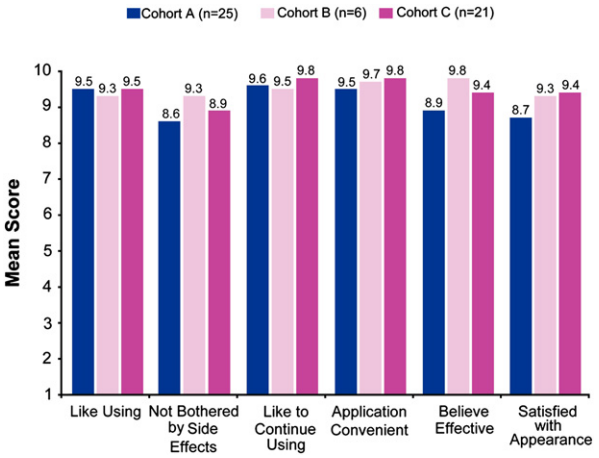

Fig 6. Results of patient satisfaction surveys.

DISCUSSION

This study confirms the efficacy and safety of TC cream in the treatment of moderate to severe melasma. The recurrent nature of melasma demonstrates the need for longer-term treatments and maintenance regimens in managing this disease. To our knowledge, this study is the first to attempt to establish a maintenance regimen for melasma. Patients showed significant improvement using several outcome measures. After 12 weeks, about half improved to the point where they were able to begin a maintenance regimen, however, most of these patients relapsed and required resumption of daily therapy. Furthermore, some patients took longer than 12 weeks to attain a status of clear or almost clear, but were able to begin the maintenance regimen before the end of the study. The majority of patients had clear or mild disease at the end of 24 weeks (67.7%). The patient in Fig 5 is a representative example of a patient who was able to use a combination of daily and maintenance therapy during the 24-week treatment period to produce excellent results. As in previous studies, significant increases in

Table II. Tolerability assessments

	Baseline				Week 12				*P* value comparing wk 12 with baseline*	Week 24				*P* value comparing wk 24 with baseline*	*P* value comparing wk 24 with wk 12†
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total		Mild	Moderate	Severe	Total		
Cohort A, N = 30															
Erythema	2 (7%)	1 (3%)		3 (10%)	11 (37%)	2 (7%)		13 (43%)	.013	13 (43%)	2 (7%)	1 (3%)	16 (53%)	.004	.698
Peeling/scaling	1 (3%)			1 (3%)	5 (17%)			5 (17%)	.088	12 (40%)			12 (40%)	<.001	.047
Stinging/burning				0 (0%)	6 (20%)	1 (3%)		7 (23%)	.02	2 (7%)			2 (7%)	.154	.18
Telangiectases	9 (30%)	1 (3%)		10 (33%)	9 (30%)	1 (3%)		10 (33%)	1	11 (37%)	4 (13%)		15 (50%)	.263	.263
Cohort B, N = 8															
Erythema	3 (38%)			3 (38%)	5 (63%)	2 (25%)		7 (88%)	n/a	5 (63%)	2 (25%)		7 (88%)	n/a	n/a
Peeling/scaling				0 (0%)	4 (50%)			4 (50%)	n/a	5 (63%)	1 (13%)		6 (75%)	n/a	n/a
Stinging/burning				0 (0%)	2 (25%)			2 (25%)	n/a	1 (13%)			1 (13%)	n/a	n/a
Telangiectases	2 (25%)			2 (25%)	5 (63%)	1 (13%)		6 (75%)	n/a	6 (75%)	1 (13%)		7 (88%)	n/a	n/a
Cohort C, N = 24															
Erythema	3 (13%)			3 (13%)	13 (54%)	4 (17%)	1 (4%)	18 (75%)	<.001	14 (58%)	3 (13%)		17 (71%)	<.001	.769
Peeling/scaling				0 (0%)	11 (46%)			11 (46%)	<.001	15 (63%)			15 (63%)	<.001	.186
Stinging/burning				0 (0%)	3 (13%)			3 (13%)	.077	1 (4%)			1 (4%)	.307	.322
Telangiectases	3 (13%)	1 (4%)		4 (17%)	9 (38%)			9 (38%)	.099	14 (58%)			14 (58%)	.002	.113

P values were not calculated for cohort B because of sample size.

n/a, Not applicable.

*Cochran-Mantel Haenszel test used to compare wks 12 and 24 with baseline.

†Cochran-Mantel Haenszel test used to compare wk 24 with wk 12.

erythema, peeling, and scaling occurred in the majority of patients, however, severity of these events was mostly mild. A significant increase in telangiectases was found only in cohort C at 24 weeks when compared with baseline but the severity was never more than mild, supporting the safe use of this cream.

TC cream has been found to be efficacious in treating melasma in a large multicenter study (n = 641), with 77% of patients with moderate to severe disease achieving complete or near-complete clearing after 8 weeks of treatment, and 26% achieving complete clearing of melasma.[5] In this study, erythema and desquamation occurred in about half of treated patients and none had clinical atrophy. Another large trial (n = 228) with TC cream in the treatment of melasma for 12 months reported similar rates of erythema and desquamation.[6] In the second large trial, telangiectases developed in 3% of treated patients, mostly mild in severity.

Depigmenting agents for the treatment of melasma are used to clear all abnormal pigmentation, after which they are often discontinued. However, because of frequent recurrences, the concept of maintenance therapy to maintain remission may be an appropriate approach for patients with chronic disease. Previous studies and the current study have noted a long duration of disease, citing average disease duration at the time of enrollment of 9 to 12 years.[7-12] Instead of treating these patients with short courses of treatment interspersed with periods off treatment, perhaps a lower concentration or lower frequency of depigmenting agent use would prevent or minimize recurrences. In the current study, twice-weekly maintenance therapy was not sufficient to prevent a relapse in the majority of the patients who achieved a status of clear or almost clear at 12 weeks of treatment. A thrice-weekly regimen may have been more successful. Alternatively, an agent containing a lower concentration of hydroquinone or a different depigmenting agent might have been successful as daily maintenance therapy. Of course, sunscreens are essential to reduce recurrences and should be part of any maintenance regimen. As we learn more about the natural history of melasma in different populations worldwide, it will be important to develop and test protocols not only to treat patients with melasma, but also to prolong their remission.

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