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

Pearl E. Grimes, MD,[a] Jag Bhawan, MD,[b] Ian L. Guevara, MD,[c] Luz E. Colón, MS,[d] Lori A. Johnson, PhD,[d] Ronald W. Gottschalk, MD, FRCPC,[d] and Amit G. Pandya, MD[c]
Los Angeles, California; Boston, Massachusetts; and Dallas and Fort Worth, Texas

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

From the Division of Dermatology, University of California, Los Angeles[a]; Department of Dermatology, Boston University School of Medicine[b]; Department of Dermatology, University of Texas Southwestern Medical Center, Dallas[c]; and Galderma Laboratories, Fort Worth.[d]

Supported by Galderma Laboratories. Clinicaltrials.gov number: NCT00469183.

Disclosure: Drs Grimes, Bhawan, and Pandya are consultants for Galderma Laboratories and have received funding to perform this study from Galderma Laboratories. Ms Colón, Dr Johnson, and Dr Gottschalk are employees of Galderma Laboratories. Dr Guevara has no conflicts of interest to declare.

Presented in poster form at the World Congress of Dermatology in Buenos Aires, Argentina, September 30 through October 5, 2007 and the Annual Meeting of the American Academy of Dermatology in San Antonio, Texas, February 1-5, 2008.

Accepted for publication June 3, 2009.

Reprints not available from the authors.

Correspondence to: Amit G. Pandya, MD, Department of Dermatology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9190. E-mail: amit.pandya@utsouthwestern.edu.

Published online April 16, 2010.

0190-9622/$36.00

doi:10.1016/j.jaad.2009.06.067

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