A LARGE 12-MONTH EXTENSION STUDY OF AN 8-WEEK TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF TRIPLE COMBINATION (TC) CREAM IN MELASMA PATIENTS PREVIOUSLY TREATED WITH TC CREAM OR ONE OF ITS DYADS

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Abstract

This was a 12-month extension of a randomized, investigator-blinded, multicenter, 8-week trial with triple combination (TC) cream in facial melasma. A total of 585 patients were enrolled in the study and 569 patients received study medication. Three hundred eighty-nine patients completed 6 months of treatment and 327 patients completed 12 months of treatment. TC cream demonstrated a favorable safety profile: only 14 patients (2.5%) discontinued the study due to treatment-related adverse events (AEs). The 2 cases of skin atrophy were mild and did not lead to withdrawal. From the 23 cases of mild telangiectasia, only 2 resulted in discontinuation. All others were transient. Results confirmed those of a previous smaller study, with both physicians and patients reporting clinically significant improvements in melasma. By month 12, 80% of patients had lesions completely cleared or nearly cleared. Once daily application of TC cream applied intermittently over a long period is a safe, tolerable, and effective treatment for moderate to severe melasma of the face.

Introduction

Cutaneous melasma is a common dermatological disease occurring in all skin types, but more commonly in darker skinned persons such as Asian and Hispanic females of child-bearing age.[1-5] Exposure to solar UV radiation is the most important environmental factor in the pathogenesis of melasma.[2,3] Therapy for melasma remains a challenge and pharmacological treatments are the mainstay.[2,6,7] Hydroquinone (HQ) has been the gold standard depigmenting agent, and has been used alone or in combination. Other treatments, such as azelaic acid, tretinoin, alpha and beta hydroxy acids, and topical corticosteroids have been used as monotherapy or in various combinations.[7,11-15]

Kligman and Willis found that monotherapy with HQ, tretinoin (RA), or the topical corticosteroid dexamethasone did not produce substantial lightening of the skin within a 3-month treatment period. However, they did observe satisfactory results with a combination of 0.1% RA, 5.0% HQ, and 0.1% dexamethasone in a hydrophilic ointment.[15] Furthermore, Kligman and Willis, as well as other researchers have noted efficacy and safety benefits with use of HQ, RA, and various topical steroids. In both

experimental and clinical studies, the use of RA and other retinoids has been found to abrogate the epidermal atrophy that can occur with topical corticosteroids. This may be potentially due to the ability of RA and other retinoids to induce hyperplasia of epidermal cells as well as dermal collagen synthesis.[16,17]

A stable fixed combination cream has been developed containing fluocinolone acetonide (FA) 0.01%, a low potency (Group VI) corticosteroid, hydroquinone 4%, and tretinoin 0.05% and is currently marketed under the trade name of Tri-Luma® Cream (Galderma Laboratories L.P., Fort Worth, TX) and hereafter called TC (triple combination). This combination was tested in two 8-week, multicenter, randomized, investigator-blind studies in a total of 641 patients with moderate to severe melasma.[18]

TC cream was shown to be significantly more effective in achieving total clearing of melasma than any of its dyads (defined as a combination of 2 of its active ingredients). In addition, TC cream demonstrated favorable safety and tolerability following 8 weeks of once daily application in the evening. As melasma is a long-term, recurring disease, it was important to test this triple-combination in patients treated intermittently for a longer duration. Hence we extended our 8-week study to confirm the local and systemic safety and efficacy results described in a recent publication by Torok et al[19] in a larger population of patients.

Material and Methods

This 12-month multicenter, open-label, non-controlled clinical study extension was conducted in accordance with the principles of the Declaration of Helsinki and all of its amendments, and in compliance with local regulatory requirements. Patients provided written informed consent prior to study procedures. All study sites received written International Review Board (IRB) approval before initiation of the study.

Patients were at least 18 years of age, of either gender, with melasma of the face and previously enrolled in a 8-week randomized clinical trial with TC cream or one of its dyads.[18] In the present extension study, all patients were treated with TC cream, irrespective of their previous treatment group. The treatment was applied once daily approximately 30 minutes before bedtime after washing the facial area with a mild cleanser. A thin layer was applied to cover the whole melasma lesion including the outside of its borders extending to the normal pigmented skin. A sunscreen with a sun protection factor 30 and both ultraviolet A and B protection was provided for daily use. Protective clothing and avoidance of sun exposure to the face was recommended and cosmetics were allowed.

Patients who entered the present study fell into 2 groups. The first group included those patients with a satisfactory resolution of melasma (melasma severity score 0: melasma lesions approximately equivalent to surrounding normal skin or with minimal residual hyperpigmentation or 1: mild, slightly darker than surrounding normal skin) after 8 weeks of treatment. These patients were followed every 2 months and re-treated as necessary once daily. The second group included those patients who did not achieve satisfactory melasma severity scores during the initial 8-week randomized study (melasma severity score > 1). This category of patients was re-treated once daily upon entry and followed-up monthly during re-treatment until satisfactory resolution or lack of response was demonstrated, at which time treatment was stopped except for use of sunscreen. They, like the previous group of patients, continued to be followed-up every 2 months when off treatment.

The determination and evaluation of long-term local and systemic safety was the primary purpose of this study. Safety was measured by the occurrence of adverse events (AEs) and laboratory test results. Expected AEs, including erythema, skin peeling, burning, stinging, telangiectasia, rosacea, dermatitis, atrophy, and grayish discoloration of skin or black dots were specifically solicited by the evaluator at each visit. Laboratory testing consisted of complete blood count, serum chemistries, and urinalysis.

To assess efficacy, the severity of the patient's melasma was scored at each visit by the investigator as follows: 0 melasma lesions approximately equivalent to surrounding normal skin or with minimal residual hyperpigmentation; 1 mild (slightly darker than the surrounding normal skin); 2 moderate (moderately darker than the surrounding normal skin); 3 severe (markedly darker than the surrounding normal skin). The physician's global assessment of melasma was scored at each treatment

visit as follows: 0 completely clear, no evidence of hyperpigmentation; 1 nearly clear, only minor visual evidence of hyperpigmentation; 2 significant evidence of hyperpigmentation.

A patient's global assessment of melasma, which included an assessment of all treated areas, was performed at each treatment visit as follows: 1 completely cleared; 2 nearly cleared; 3 significant hyperpigmentation present.

Statistical Methods

All patients who received the study drug were included in the analyses (intent-to-treat [ITT] Population). Descriptive statistics were provided for all variables for all patients in the ITT Population. For certain variables, descriptive statistics were provided broken down by treatment group in the initial 8-week study and by duration of treatment with TC cream.

Results

A total of 585 patients were enrolled in the study and 569 patients received study medication. A total of 389 patients completed the first 6 months of the study and 327 patients completed the 12 months treatment. The most common reasons for discontinuation were patient request (31%) and lost to follow-up (25%). The ITT population consisted of 569 patients: 142 (25%) from the TC cream group and 427 (75%) from the dyad groups in the initial 8-week randomized study. Details on Baseline characteristics are provided in Table 1.

Table 1. Patient Demographics.

	Number (%) of patients 569 (100.0%)
Age in years	
Mean±SD	43.2±8.9
Gender	
Male	9 (2%)
Female	560 (98%)
Race	
Caucasian	375 (66%)
Black	16 (3%)
Asian	24 (4%)
Other	154 (27%)
Skin Phototype	
I	52 (9%)
II	178 (31%)
III	221 (39%)
IV	118 (21%)
V	0 (0%)

The mean cumulative exposure to TC cream in the present study was 204 days. When data were combined with data from the initial 8-week study, the mean cumulative exposure to TC cream was 218 days (256 days in the previous TC cream group and 206 days in the previous dyads groups). A total of 330 patients applied the cream for more than 180 days and 92 patients applied TC cream for more than 360 days. There was an average of 2 treatment courses. Each one required less time to achieve the desired result. Patients were retreated as early as one month.

A total of 346 patients (61%) experienced treatment-related adverse events (AEs) (Table 2). The most frequently-reported AEs were application site erythema and application site desquamation, both occurring in approximately one third of patients. Most of these treatment-related AEs were mild, transient, did not require remedial therapy, and did not result in discontinuation from the study. Application site AEs tended to have an increase in incidence with longer treatment duration. However, the incidence of treatment-related AEs in patients who had 2 treatment courses (66%) was not notably higher than the incidence in those patients who only had one treatment course (60%). These AEs also tended to have a higher incidence in patients over 40 years of age, in non-Caucasian patients, and in patients with skin phototypes I to III. Skin atrophy/thinning occurred in 2 patients and rosacea occurred in one patient (both less than 1%), facial telangiectasia occurred in 23 patients (4%). The 2 cases of skin atrophy/thinning described were mild and did not result in study discontinuation; one case had resolved by the end of the study and one case was unchanged. All 23 cases of telangiectasia were mild and only 2 resulted in study discontinuation; 15 cases had resolved or improved by the end of the study while 8 cases were unchanged.

Overall, TC cream was well tolerated by patients and only 14 patients (2.5%) had treatment-related AEs leading to discontinuation of the treatment. TC cream was not associated with any serious adverse events or clinically meaningful laboratory changes.

Table 2. Treatment-Related Adverse Events Occurring in 5% or More of Patients.*

	All patients N=569 N (%)	≥ 180 days on TC Cream† N=330 N (%)	≥ 360 days in study†† N=399 N (%)
At least one treatment-related AE	346 (61%)	227 (69%)	258 (65%)
Application site AEs	345 (61%)	226 (69%)	257 (64%)
Application site burning	43 (8%)	29 (9%)	32 (8%)
Application site desquamation	167 (29%)	109 (33%)	126 (32%)
Application site dryness	52 (9%)	33 (10%)	38 (10%)
Application site erythema	187 (33%)	126 (38%)	142 (36%)
Application site inflammation	31 (6%)	24 (7%)	24 (6%)
Application site pigmentation changes	30 (5%)	21 (6%)	24 (6%)
Application site pruritus	27 (5%)	22 (7%)	23 (6%)
Application site rash	35 (6%)	20 (6%)	27 (7%)
Application site reaction	37 (7%)	24 (7%)	29 (7%)

*Treatment-related AE = an AE considered by the investigator to be possibly or probably related to study drug.
† Patients with ≥ 180 cumulative days of treatment with TC cream (includes the initial 8-week randomized study).
†† Patients with ≥ 360 days (12 months) in the study (includes the initial 8-week randomized study).

While evaluation of efficacy was not the primary purpose of the study, selected efficacy parameters were collected and examined. The physician's assessment of melasma severity showed that at Month 12 substantially more patients had mild or cleared lesions compared with Baseline (Figure 1). This was particularly evident in those patients who received dyads in the initial 8-week study.

At Baseline, 59% of patients in the previous dyads groups had lesions that were scored as moderate and severe. For patients in the previous dyads groups, the incidence of patients with lesions that were clear or almost clear was 70% at Month 1 and 81% at Month 12.

The Physician's Static Global Assessment also demonstrated that by Month 12 more than 80% of patients who remained in the study had lesions that were either completely cleared or nearly cleared (Figure 2).

The Patient's Static Global Assessment paralleled the findings of the other efficacy variables (Figure 3). Again, the effect was particularly remarkable for the prior dyads group.

Discussion and Conclusion

The present 12-month extension study, which is the only long-term safety evaluation of TC cream conducted in more than 500 patients with melasma where more than 300 patients completed the study, demonstrated that TC cream applied intermittently or continuously over one year demonstrated a favorable safety profile in the treatment of melasma of the face. Only 14 patients (2.5%) discontinued the study due to treatment-related AEs. This is a low incidence for a long-term study, suggesting that patients were not unduly bothered by the side effects of the treatment. Even if more that 60% of the patients experienced AEs during this study, most of them were considered local mild reactions. These reactions were not unexpected with the

Figure 1. Physician's Assessment of Melasma Severity Over Time.

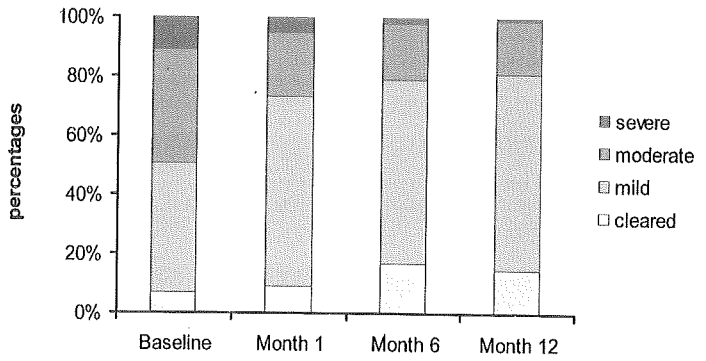


Figure 2. Physician's Static Global Assessment of Melasma.

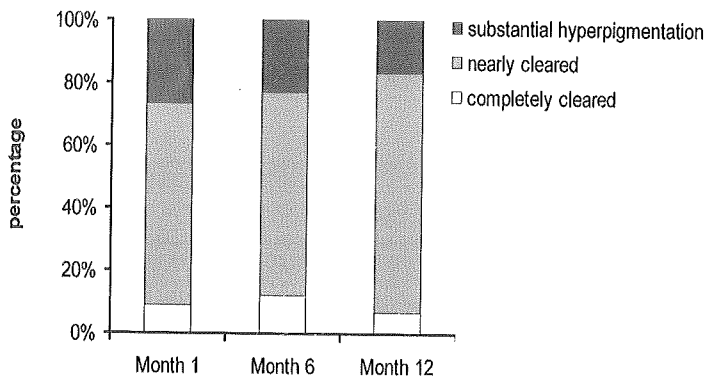
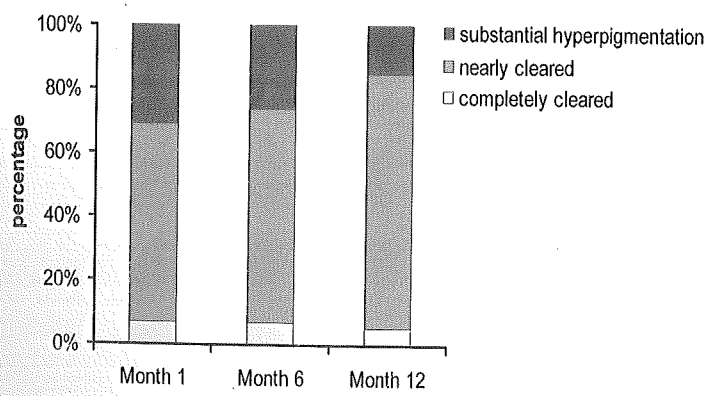


Figure 3. Patient's Static Global Assessment of Melasma.



TC cream as both hydroquinone and tretinoin are known to cause a certain amount of irritation of the application site.[1,2]

In the past, concerns have been expressed regarding the risk of skin atrophy and telangiectasia following long-term topical administration of corticosteroids.[7] However, only 2 cases of skin atrophy/skin thinning in the present study were reported and both were mild and did not result in study discontinuation. This low incidence may be due to the presence of the tretinoin, which has been demonstrated to prevent corticosteroid-induced atrophy without lessening the anti-inflammatory effect.[16,17] Only 4% of the patients developed mild telangiectasia from which 2 resulted in study discontinuation. The relatively low incidence of these side effects after such a long treatment period and the fact that they are commonly associated with corticosteroids may be due to the fact that fluocinolone acetonide in a concentration of 0.01% is a relatively low potency (Class VI) corticosteroid. Both physicians and patients reported clinically significant improvements in melasma lesions during the 12-month extension of treatment.

In conclusion, the present 12-month extension study confirmed recent research work demonstrating that TC cream applied once daily over a long-term period is a safe, tolerable, and effective treatment for melasma of the face.[19]

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