Original Contribution

A comparison of triple combination cream and hydroquinone 4% cream for the treatment of moderate to severe facial melasma

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Summary

The aim of this study was to compare the efficacy and safety of a triple combination (TC) cream and monotherapy with hydroquinone (HQ) cream in the treatment of moderate to severe facial melasma. A total of 120 patients applied TC cream once daily or HQ cream twice daily for 8 weeks. Evaluations included static global severity assessment of melasma, improvement of melasma over time, local tolerability, and adverse events. TC cream was significantly more effective than HQ cream from week 4 onwards: lesions were approximately equivalent to the surrounding skin in 35% of all TC-treated patients, compared to 5% of those who used HQ cream ($P = 0.0001$). Improvement of more than 75% was achieved by 73% of TC cream patients and 49% of HQ cream patients ($P = 0.007$). The incidence of adverse events (erythema, burning sensation, and desquamation) was similar in both groups. No patient dropped out of the study because of drug-related adverse events. TC cream was more effective than the HQ cream for the treatment of moderate to severe facial melasma. Both products had similar safety profiles.

Keywords: facial melasma, fluocinolone acetonide, hydroquinone, stable fixed combination, topical therapy, tretinoin

Introduction

Cutaneous melasma is a common dermatologic disease, occurring in all races, but more commonly in Asian and Hispanic women with dark skin and of child-bearing age.[1–5]

Many factors have been implicated in the pathogenesis of melasma; however, the most important ones remain ultraviolet (UV) radiation, hereditary predisposition, and hormonal dysfunction.[2,3]

Therapy for melasma remains a challenge and topical treatments are the mainstay.[2,6,7] Current approaches to the management of melasma include hydroquinone (HQ), considered the gold standard depigmenting agent, and other molecules such as azelaic acid, tretinoin (RA), alpha and beta hydroxy acids, and topical corticosteroids used as monotherapy or in various combinations.[7–15] A shortcoming of monotherapy has been the length of treatment required to experience significant results. A classic study conducted by Kligman and Willis showed no substantial improvement in pigmentation after 3 months of treatment with HQ, dexamethasone, or RA alone. However, they did observe satisfactory results when the substances were used as combination of 0.1% RA, 5.0%

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HQ, and 0.1% dexamethasone in a hydrophilic ointment.[15] Furthermore, other experimental and clinical studies showed that the use of retinoids prevents the epidermal atrophy that may occur with topical corticosteroids.[16,17] This may be a result of the ability of retinoids to induce hyperplasia of epidermal cells as well as dermal collagen synthesis.[16,17]

Recently, a stable fixed combination therapy was developed containing HQ 4%, RA 0.05%, and fluocinolone acetonide (FA) 0.01%, a low potency (Class VI American classification) corticosteroid.[18] This formula is currently marketed under the trade name Tri-Luma® Cream (Galderma Laboratories L.P.), hereafter called triple combination (TC).

The aim of the present study was to compare the clinical efficacy and safety of TC cream with that of 4% HQ in patients with moderate to severe facial melasma.

Materials and methods

This study was a randomized, controlled, open-label clinical trial conducted in 120 patients from four hospitals in Brazil. It was conducted in accordance with the principles of the Declaration of Helsinki and its amendments, and in compliance with local regulatory requirements. Patients provided their written informed consent prior to study procedures and were at least 18 years of age, of either gender, with moderate to severe facial melasma. Pregnant women or patients with specific exclusion criteria were not allowed to participate in the study. Specific washout periods for previous treatments were to be respected.

Eligible patients were randomized to receive one of the two treatments as follows: TC cream (HQ 4%, RA 0.05%, and fluocinolone acetonide 0.01%) once daily or HQ cream (HQ 4%; Claripel™, Stiefel Laboratories Inc., Miami, FL, USA) twice daily. Both treatments were applied to the affected facial areas for 8 weeks. Study visits were held at weeks 0, 2, 4, 6, and 8. Subjects from both groups received sunscreen (SPF 30) and were instructed to apply on the face at least once a day.

The primary efficacy variable was the *investigator's static evaluation of melasma severity* at each visit using the following scale: 0 = melasma lesions very similar to the 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); and 3 = severe (markedly darker than the surrounding normal skin). "Primary success" was defined as a melasma severity score of 0 at week 8.

The secondary efficacy variables were evaluations of the overall improvement by the investigator and by the subject. *Evaluation of overall improvement by the investigator* was performed at each visit using a scale from 5 (completely cleared [100%]) to −1 (worsening, hyperpigmentation darker than that of baseline melasma). "Secondary success" was defined as an improvement score between 3 and 5. *Overall evaluation by the subject* was performed at week 8 using a scale from 1 (excellent) to 4 (poor).

Tolerability was evaluated at each visit by assessing the incidence of expected adverse events (i.e., skin atrophy, telangiectasia, or erythema). All other adverse events occurring during the study were also recorded.

The statistical analysis of this non-inferiority study was performed on the per-protocol population consisting of all patients who received study medication throughout the study and who had all melasma assessments done. The following statistical tests were used: Student's *t*-test for the comparison of age between groups; one-sided analysis of variance for the comparison of treatment duration among the four centers; chi-squared test for the comparison of sex, race, phototype, and patient's overall evaluation; Fisher's exact test for the comparison of primary success, secondary success, and adverse events between groups; the Friedman's test for the comparison of melasma severity, overall improvement, and total number of symptoms within each group; and the Mann–Whitney test for the comparison of melasma severity, overall improvement, and total number of symptoms between the study groups. Two-sided tests were used and the significance level was 5%.

Results

A total of 120 patients were enrolled in the study: 60 were treated with TC cream and 60 received HQ cream. A total of 119 patients completed the 8-week study; one subject in the HQ group discontinued at week 6 due to a non-drug-related adverse event. Table 1 depicts the demographic data.

At baseline, more than 98% of all subjects in both groups had moderate (grade 2) or severe (grade 3) melasma according to the investigator's static evaluation of melasma severity. At weeks 4, 6, and 8, melasma severity scores were significantly lower in the TC cream group than in the HQ cream group ($P < 0.003$). Figure 1 shows the percentage of patients with cleared melasma at all time points. "Primary success," defined as melasma lesion approximately equivalent to the surrounding normal skin, was achieved for 35% (21/60) of patients in the TC group and for 5.1% (3/59) of subjects in the HQ cream group ($P = 0.0001$).

Table 1 Subject demographics.

		TC cream (*N* = 60)	HQ cream (*N* = 60)	*P*-values
Age (years)	Mean ± SD	47.2 ± 10.9	45.3 ± 10.8	0.336
	Range	29–70	25–73	
Sex, *N* (%)	Male	1 (2%)	6 (10%)	0.052
	Female	59 (98%)	54 (90%)	
Race, *N* (%)	Caucasian	40 (66.7%)	31 (52%)	0.173
	Black	4 (6.6%)	9 (15%)	
	Asian	–	–	
	Mixed	16 (26.7%)	20 (33%)	
Skin phototype	I	0 (0%)	0 (0%)	0.069
	II	7 (12%)	1 (2.2%)	
	III	29 (48%)	19 (42.2%)	
	IV	20 (33%)	22 (48.9%)	
	V	4 (7%)	3 (6.7%)	

HQ, hydroquinone; TC, triple combination.

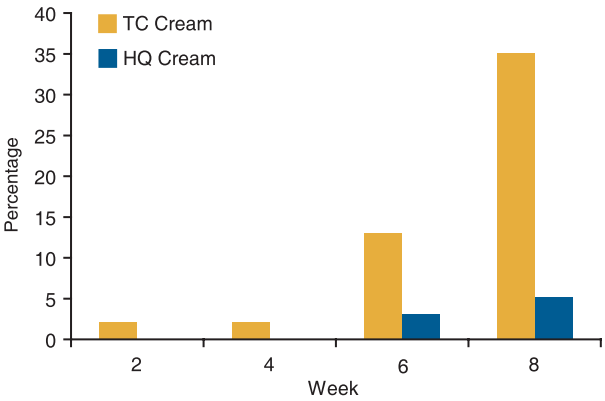

Figure 1 Percentage of subjects with cleared melasma. With a $P < 0.003$ the difference between the two treatments was significantly in favor of triple combination (TC) cream at weeks 4, 6, and 8.

The investigator's evaluation of overall improvement showed that the improvement was significantly superior with TC cream when compared to HQ cream at weeks 4, 6, and 8 ($P < 0.001$). "Secondary success," defined as > 75% improvement, was achieved for 73% (44/60) of the individuals in the TC cream group and for 49% (29/59) of patients in the HQ cream group ($P = 0.007$). Figure 2 shows the evolution of the percentage of subjects with, at least marked improvement. The proportion of subjects who considered that the treatment was "excellent" was greater for TC cream (50%) than for HQ cream (34%).

The most frequently reported side effects were erythema, burning sensation, and desquamation. Facial telangiectasia was reported, at the end of the study, for

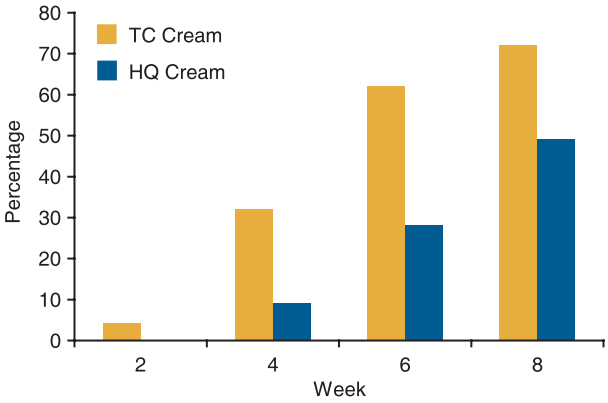

Figure 2 Percentage of subjects with at least marked improvement. Significantly ($P < 0.0005$) more subjects showed at least marked improvement with triple combination (TC) cream of their facial melasma from week 4 on.

nine patients (15%) treated with TC cream and for five patients (9%) treated with HQ cream. No case of skin atrophy was reported. There were no significant differences between the two treatment groups for the incidence of the reported adverse events. Systemic adverse events were reported for 35% of the patients in the TC cream group and 33% of the patients in the HQ cream group. The most frequently reported adverse event was headache in both groups (11 TC cream, 9 HQ cream). One patient in the HQ cream group discontinued the study due to non-treatment-related adverse event. Neither treatment was associated with any serious adverse events. No patient discontinued the study because of a drug-related adverse event.

Discussion

This was a multicenter, open-label, randomized, 8-week clinical trial comparing the once-a-day application of TC cream with the twice-a-day application of HQ cream in the treatment of moderate to severe melasma of the face.

Significantly more patients treated with TC cream had their melasma cleared at week 8 ($P < 0.0001$; 35% vs. 5.1% with HQ cream) and significantly ($P < 0.0007$) more patients treated with TC cream showed improved clearance of melasma at the same time point. Thus, the results of this study demonstrated that the treatment effect of TC cream was significantly more effective from week 4 on than HQ cream at treating moderate to severe facial melasma.

These results further confirm findings of other authors that a combination of HQ with fluocinolone acetonide and a corticosteroid is more effective than HQ alone.[15]

Furthermore, the results of the present study are in accordance with findings made in another 8-week study showing that TC cream was significantly more effective in achieving total clearing of melasma than any of its dyads (i.e., dual combinations: HQ + RA, HQ + FA, or FA + RA).[18]

Some authors have expressed concerns regarding the risk of telangiectasia and skin atrophy following long-term topical administration of corticosteroids.[7] A total of 14 cases of telangiectasia were reported at the end of treatment: nine patients (15%) treated with TC cream relative to five patients (9%) treated with HQ cream. The incidence of this adverse event is possibly related to the fact that certain patients applied the studied drugs to the whole face, hence exposing a greater surface and is not related to the treatment of melasma using the medications. However, none of these events resulted in the discontinuation of the study. Previous clinical long-term investigations confirmed that the incidence of telangiectasia with TC cream did not exceed 4% of the total study population.[19]

The absence of skin atrophy with TC cream may be related to the presence of RA, preventing corticosteroid-induced atrophy without lessening the anti-inflammatory effect, as proposed by Kligman *et al*. and McMichael *et al*.[16,17] Furthermore, the relatively low incidence of side effects commonly associated with corticosteroids may be due to the fact that fluocinolone acetonide in a concentration of 0.01% is a medium to low potency (Class VI) corticosteroid.

Local adverse events, such as erythema, burning sensation, and desquamation, were equally distributed in both groups.

In conclusion, an 8-week treatment with a once-a-day application of TC cream was shown to be significantly more effective (73% vs. 49%) than a twice-a-day application of HQ in the treatment of moderate to severe facial melasma, while showing similar and good safety profiles.

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