

A randomized controlled trial of the efficacy and safety of a fixed triple combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) compared with hydroquinone 4% cream in Asian patients with moderate to severe melasma

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Summary

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Conflicts of interest

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Background Melasma is an acquired, chronic hypermelanosis for which therapy remains a challenge.

Objectives To compare the efficacy and safety of a triple combination [TC: fluocinolone acetonide 0.01%, hydroquinone (HQ) 4%, tretinoin 0.05%] vs. HQ 4% after 8 weeks of treatment of moderate to severe facial melasma in Asian patients.

Methods This was a multicentre, randomized, controlled, investigator-blinded, parallel comparison study. East and South-East Asian patients aged 18 years or older, with a clinical diagnosis of moderate to severe melasma, were enrolled in this study. Patients were enrolled at baseline and treated daily for 8 weeks with TC cream (one application at bedtime) or HQ cream (twice daily). There were four study visits: at baseline and weeks 2, 4 and 8. The primary efficacy variable was the melasma global severity score (GSS). Other outcome measures included Melasma Area and Severity Index, global improvement and patient satisfaction. Safety was assessed through the reporting of adverse events.

Results TC had superior efficacy to HQ for the primary variable: 77/120 patients (64.2%) on TC had GSS 'none' or 'mild' at week 8 vs. 48/122 patients (39.4%) on HQ ($P < 0.001$). The secondary efficacy variables confirmed these results. Patient satisfaction was in favour of TC (90/127, 70.8%, vs. 64/129, 49.6%; $P = 0.005$). More patients had related adverse events on TC (63/129, 48.8%) than on HQ (18/131, 13.7%) but most were mild and none was severe.

Conclusions Efficacy in Asians and patient satisfaction were superior with the fixed TC than with HQ 4%.

Melasma is an acquired, chronic, symmetrical hypermelanosis characterized by light to dark brown patches of hyperpigmentation on sun-exposed areas, predominantly on the face.¹ It is a very frequent disease, although its true incidence is

unknown. Almost all patients affected by melasma are women (90%), with only 10% of cases in men for whom the causes are not well defined.² Many factors have been implicated in the pathogenesis of melasma; however, the most important

ones remain ultraviolet radiation, hereditary predisposition and hormonal dysfunction.^{3,4}

Therapy remains a challenge for this chronic recurring condition and topical treatments are the mainstay.^{3,5,6} Current approaches to the management of melasma include hydroquinone (HQ), a commonly used depigmenting agent, and other molecules such as azelaic acid, tretinoin, topical corticosteroids, and alpha and beta hydroxy acids; these products are used either as monotherapy or in various combinations.^{6–11} In addition, patients are recommended to use a daily sunscreen.

Recently the Pigmentary Disorders Academy (PDA) undertook an evaluation of all clinical trials in melasma performed in the last 20 years and published a consensus statement on the treatment of melasma.¹² **The PDA's expert opinion was that topical fixed triple combinations (TCs) should be used as first-line therapy for melasma.** Dual therapies and monotherapies have a slower onset of action and lower efficacy, and are therefore recommended for use only in patients who are intolerant to triple therapy or if triple therapy is not available.

A study conducted by Kligman and Willis showed no substantial improvement in pigmentation after 3 months of treatment with HQ, dexamethasone or tretinoin (retinoic acid, RA) alone, while satisfactory results were observed when the substances were used as a combination of 5.0% HQ, 0.1% RA and 0.1% dexamethasone in a hydrophilic ointment.¹¹

Recently, a stable fixed combination therapy containing fluocinolone acetonide (FA), a low potency (class VI) corticosteroid, plus HQ, a bleaching agent, plus RA, a vitamin A derivative, was developed. This formula is currently marketed under the trade name of Tri-Luma[®] cream in several countries in Asia, Latin America and the U.S.A. and was the subject of the present clinical investigation. It is hereafter referred to as TC cream.

Several studies have been performed, comparing TC cream with the three corresponding dyads of its active ingredients (FA + HQ, FA + RA and HQ + RA). These studies all demonstrated better efficacy of TC cream.^{13–15} Another recent study compared TC cream (once daily) with HQ cream (twice daily) for 8 weeks in 120 Latin American patients with moderate to severe facial melasma.¹⁶ TC cream was significantly more effective than HQ cream from week 4 onwards and both products had similar safety profiles. Furthermore, it has been demonstrated that TC cream provided a sustained efficacy and showed a good tolerability profile when used for a long period.^{14,15}

Melasma occurs more commonly in women of Asian race, comprising one-third of all the women in the world. **The prevalence of melasma in Asian skin is not known but has been estimated to be as high as 40% in women and 20% in men.**¹⁷ However, care must be taken during diagnosis as several conditions mimic melasma in Asians such as Riehl's melanosis,¹⁸ pigmented actinic lichen planus¹⁹ and acquired bilateral naevus of Ota-like macules (Hori's naevus).²⁰ Despite the known high prevalence of melasma, few clinical trials have been performed in this population. TC cream has never been

tested on a significant and relevant number of Asian patients in a randomized and controlled clinical trial. The aim of the present study was to provide controlled efficacy and safety data in an Asian population.

Patients and methods

Ethical conduct and study design

The study was performed in accordance with Good Clinical Practices and in compliance with local regulatory requirements. The appropriate national authorities and local institutional review boards approved the protocol before study commencement. All patients provided written informed consent before admission to the study.

This was an investigator-blinded, controlled, two-arm, parallel-group, multicentre, randomized clinical trial performed between December 2005 and June 2006. Nine investigator centres participated in the study: four in Korea, one in the Philippines, two in Singapore, one in Hong Kong and one in Taiwan.

The objective was to compare the clinical efficacy and safety of TC vs. HQ after 8 weeks of treatment in East and South-East Asian patients (hereafter designated as Asians) with moderate to severe facial melasma. HQ 4% was chosen as comparator as it is the most commonly used treatment for melasma.

Eligible patients were male or female Asians, aged 18 years or older, with moderate to severe melasma which had been stable for at least 3 months, with neither depressed nor atrophic macular lesions. The main exclusion criteria were pregnancy, known allergies to investigational products, likely exposure to intensive radiation, and having postinflammatory hyperpigmentation, neurodermatitis, eczema, atrophy and rosacea.

Before participating, patients underwent a washout period of 2 weeks for topical interfering treatments, 1 month for systemic corticosteroids, 3 months for laser, dermabrasion or peels, and 4 months for other interfering systemic treatments.

At study entry, a fluorescence diagnosis was performed on each patient with Wood's lamp to assess the type of melasma. Wood's light is used to determine the depth of melanin pigmentation in the skin: contrast in epidermal pigmentation is increased while contrast in dermal pigmentation is decreased under Wood's lamp illumination compared with ambient visible light.²¹

At baseline patients received, in chronological order of their inclusion in the study and according to randomization, either a fixed TC cream of HQ 4% + tretinoin 0.05% + FA 0.01% (Tri-Luma[®]; Galderma, Lausanne, Switzerland) used as topical administration on affected facial areas once daily at bedtime for 8 weeks, or HQ cream 4% (Eldoquin Forte[®]; ICN Pharmaceuticals, Inc., Costa Mesa, CA, U.S.A.) as topical administration on affected facial areas twice daily for 8 weeks.

In case of skin irritation, patients were allowed to alter product application frequency, with a maximal limit of 2 weeks, to once daily on alternate days for TC or once daily

for HQ. Moisturizing cream, preferably Cetaphil® (Galderma), could be applied to the face 1 h before study medication. Anthelios® (La Roche Posay, France) sunscreen SPF 60 was provided and its use was recommended in case of exposure to sunlight.

Due to differences in appearance and dosage regimen between the study treatments, the study could not be designed as a double-blind but as an investigator-blinded study. Study medication had to be dispensed by a person other than the investigator or evaluator. Additionally, both the person in charge of drug dispensing and the patients were instructed not to discuss the study medication with the investigator or evaluator.

Efficacy and safety assessments

Patients attended four visits at the investigator centre at baseline, week 2 (safety and compliance assessments only), and weeks 4 and 8.

The primary efficacy variable was the investigator's assessment of Global Severity Score (GSS) at week 8: distribution of patients within each of the following scores: 0, none (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); and 3, severe (markedly darker than the surrounding normal skin).

The secondary efficacy variables were as follows: (i) investigator's assessment of GSS: percentage of patients with each score at week 4; (ii) Melasma Area and Severity Index (MASI) (described by Kimbrough-Green *et al.*⁷): percentage change from baseline at weeks 4 and 8; (iii) investigator's assessment of global improvement from baseline (on a seven-point scale ranging from completely clear to worse) at week 8; and (iv) patient's static global assessment (0, completely clear, no evidence of hyperpigmentation; 1, only minor visual evidence of hyperpigmentation; 2, significant evidence of hyperpigmentation) at week 8.

Patient satisfaction was assessed by questionnaire at week 8. Adverse events were recorded throughout the study.

Statistical methods

Initially, the primary efficacy variable was planned to be the success/failure variable on GSS [percentage of patients with 'success' (score = 0) and 'failure' (score > 0) at week 8]. However, following the review of blinded patient listings, it was found that less than 10% of patients in the total population had a score of 0 in the GSS. Therefore, it was judged more appropriate to consider the GSS full scale at week 8 as the primary variable.

The sample size (thus the power) was determined on the GSS success/failure variable and not on the GSS full scale. However, as the analysis of the GSS full scale showed significant results ($P < 0.05$), it was agreed that the power (thus, the sample size) was sufficient.

Based on published data,^{13,16} it was assumed that a 28% success rate would be obtained with the TC and 10% with HQ. To detect a difference of 18% between the two treatment groups, a sample of 98 evaluable patients per active group was needed, with a binomial distribution, a 90% power and an α risk set at 5% two sided. Assuming 20% of enrolled patients would be nonevaluable for the week 8 per protocol (PP) analysis, it was necessary to enrol a total of 244 patients (122 per group).

The RANUNI routine of the SAS system (SAS Institute, Cary, NC, U.S.A.) was used to assign patients randomly (ratio 1 : 1), in balanced consecutive blocks, to one of the treatment groups.

All efficacy variables were analysed in the intent-to-treat (ITT) population, consisting of all enrolled patients, with last observation carried forward (LOCF) in case of missing values. The primary efficacy variable was also analysed in the PP population, consisting of all patients who completed the study without major protocol deviation. For the patient satisfaction questionnaire, only observed cases were taken into account.

All variables (except MASI) were analysed by two-sided Cochran–Mantel–Haenszel test stratified by centre and using the rdit transformation and row mean score option with significance at the 0.05 threshold. The percentage change from baseline of MASI was submitted to an analysis of variance by including treatment group and centre as factors.

Results

Patient disposition and baseline characteristics

Two hundred and sixty patients were enrolled (ITT population): 129 in the TC group and 131 in the HQ group. All patients were Asian, 95.4% (248/260) were women, and the mean age was 45 years. Most patients had skin phototype IV (168/260, 64.6%) or III (71/260, 27.3%) (Table 1).

Overall, 247/260 patients (95.0%) completed the study: 121 (93.8%) on TC and 126 (96.2%) on HQ (Fig. 1). The PP population comprised 242 patients.

The melasma characteristics of the two treatment groups were similar at baseline (Table 1). All patients had facial melasma; only 11/260 patients (4.2%) had extrafacial involvement. The most affected location was malar. Based on Wood's light diagnosis,²¹ the most frequent types of melasma were epidermal (152/260, 58.5%) and mixed (98/260, 37.7%); only 10/260 patients (3.8%) had dermal melasma.

The melasma severity was similar in the two groups at baseline. The GSS was moderate (score 2) for 196/260 patients (75.4%) and severe (score 3) for 64/260 patients (24.6%).

Table 1 Patient demography and melasma characteristics at baseline

	Triple combination (n = 129)	Hydroquinone (n = 131)	Total (n = 260)
Gender, n (%)			
Male	5 (3.9)	7 (5.3)	12 (4.6)
Female	124 (96.1)	124 (94.7)	248 (95.4)
Age (years)			
Mean $\pm$ SD	44.4 $\pm$ 7	45 $\pm$ 7.71	44.7 $\pm$ 7.36
Median	45	45	45
Range	29–62	30–70	29–70
Phototype, n (%)			
II	–	2 (1.5)	2 (0.8)
III	40 (31.0)	31 (23.7)	71 (27.3)
IV	83 (64.3)	85 (64.9)	168 (64.6)
V	6 (4.7)	13 (9.9)	19 (7.3)
Race, n (%)			
Asian	129 (100)	131 (100)	260 (100)
Type of melasma, n (%)			
Epidermal	79 (61.2)	73 (55.7)	152 (58.5)
Dermal	4 (3.1)	6 (4.6)	10 (3.8)
Mixed	46 (35.7)	52 (39.7)	98 (37.7)
GSS			
Mild (1)	–	–	–
Moderate (2), n (%)	98 (76.0)	98 (74.8)	196 (75.4)
Severe (3), n (%)	31 (24.0)	33 (25.2)	64 (24.6)
Mean $\pm$ SD	2.2 $\pm$ 0.4	2.3 $\pm$ 0.4	2.2 $\pm$ 0.4
MASI			
Mean $\pm$ SD	13.1 $\pm$ 5.9	14.0 $\pm$ 6.1	13.5 $\pm$ 6.0

GSS, global severity score; MASI, Melasma Area and Severity Index.

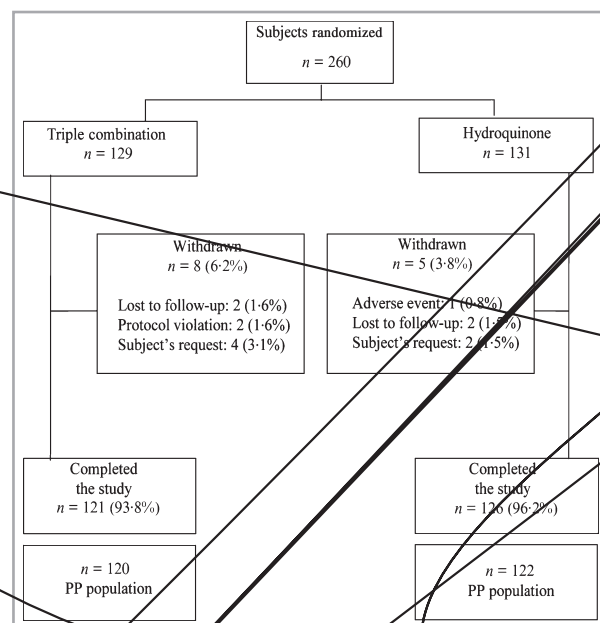
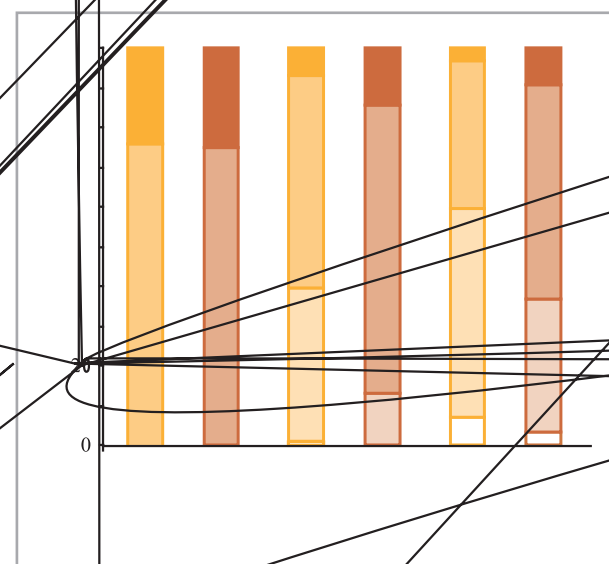


Fig 1. Flow chart of patient disposition. PP, per protocol.

Efficacy results

The analysis of the primary efficacy variable demonstrated that 77/120 patients (64.2%) in the TC group had a GSS of 'none' or 'mild' at week 8 compared with 48/122 patients (39.4%)



in the HQ group in the PP population ($P < 0.001$) and 77/129 patients (59.7%) vs. 48/131 (36.7%), respectively, in the ITT-LOCF population ($P \leq 0.001$, Fig. 2).

The difference between the efficacy of TC and that of HQ increased with higher skin phototypes (Fig. 3a) and also

increased when the melasma had a dermal component (Fig. 3b).

The secondary efficacy variables confirmed the results of the primary efficacy variable. At week 4, the reduction in GSS



(7/129 patients, 5.4%, vs. 1/131 patients, 0.8%) and skin discomfort (8/129 patients, 6.2%, vs. 2/131 patients, 1.5%). Most events were mild in intensity; none was severe or serious. No patient felt the need to reduce the treatment regimen. Only one patient, on HQ, discontinued the study prematurely due to a related adverse event (skin irritation). There were no cases of telangiectasia or skin atrophy reported after the 8-week treatment.

Discussion

HQ 4% cream is commonly used for the treatment of melasma and only one previous study has compared HQ with TC cream.¹⁶ Furthermore, this is the first time that TC cream has been specifically tested in an East and South-East Asian population, in which melasma is more frequently observed than in Caucasians, and whose skin, due to differences in barrier function, is likely to react differently than in Caucasians.^{22,23}

The superior efficacy of a TC over one of its ingredients used as monotherapy might seem obvious initially. However, not only was the dosage regimen different (once daily for TC cream vs. twice daily for HQ) and this could have reduced the difference in efficacy, but also the cumulative side-effects due to the addition of a retinoid could have had an impact on patient satisfaction.

In our study, once daily application of TC had significantly greater efficacy than HQ applied twice daily with 77/120 patients (64.2%) on TC having a GSS of 'none' or 'mild' at week 8 compared with only 48/122 patients (39.4%) on HQ. This difference in efficacy was observed from week 4, demonstrating an early onset of action for TC cream (51/129 patients, 39.6%, on TC with GSS 'none' or 'mild' vs. 17/131 patients, 13.0%, on HQ). The consistency between the different efficacy evaluations should be noted. This was the first study where both GSS and MASI were used and these two parameters provided similar results in terms of difference between the two study treatments.

In our study, despite the fact that TC cream was definitely more efficacious than HQ, the percentage of patients with 'none' or 'mild' melasma (as per GSS) was slightly lower than that reported in other TC cream pivotal studies,¹³ suggesting that melasma in Asian skin may be more difficult to treat than in other populations. Indeed, Kang *et al.*²⁴ reported an increased number of melanocytes in melasma skin (compared with noninvolved skin) in a histology study in 56 Korean patients. Such an increase was not found by Grimes *et al.*²⁵ in a non-Asian population.

In our Asian population, only 58.5% of the patients had an epidermal melasma compared with 70% previously reported in the Caucasian population.¹⁰ Interestingly, the difference between the efficacy of TC and that of HQ increased when the melasma had a dermal component, although overall efficacy was slightly lower in this melasma type.

Unsurprisingly, the safety results were in favour of HQ; there were more related adverse events and more patients with

related adverse events in the TC group than in the HQ group, but none was severe and none led to permanent discontinuation of the study medication. In the HQ group, one patient discontinued from the study because of an adverse event. The most common related adverse events were erythema, skin irritation, exfoliation and discomfort. These were expected as they are known side-effects of the active ingredients of the study medications.

The study protocol planned to alter the dosage regimen (once every other day for TC cream and once daily for HQ) for up to 2 weeks if irritation occurred. No such alteration was made despite irritation in some patients. Handling TC application more carefully (once every other day) might have helped to reduce the frequency of such adverse events.

The results of the patient satisfaction questionnaire perfectly mirrored the clinical results. Even though patients were less bothered by HQ treatment side-effects than by TC side-effects, their overall satisfaction was significantly in favour of TC cream.

Before launching the study, potential irritation induced by TC cream was a concern because it is commonly accepted that Asian skin is more prone than Caucasian skin to develop irritation linked to retinoids. However, when comparing related dermatological adverse event profiles obtained in TC cream pivotal studies¹³ and in the present study, the tolerability of TC cream in Asian skin was no worse than in non-Asian skin.

Our results are in accordance with what was reported by Kang *et al.*⁹ In this paper, Korean patients treated their melasma with a TC (0.1% tretinoin, 5% HQ, 1% hydrocortisone), twice weekly for 4 months (vs. once daily for 2 months in our study). The authors stated that such a combination induces good efficacy in Asians, although slightly lower than in other populations. They also reported retinoid reactions of mild intensity, occurring slightly less frequently than in non-Asians.

In conclusion, knowing that pigmentary disorders are more visible on Asian skin and are of great cosmetic concern to Asian patients,²⁶ the fixed TC studied here could be seen as a good alternative to HQ in treatment of melasma.

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