DOI: 10.1111/j.1468-3083.2011.04135.x JEADV

ORIGINAL ARTICLE

Preventing melasma recurrence: prescribing a maintenance regimen with an effective triple combination cream based on long-standing clinical severity

I. Arellano,[†,*] T. Cestari,[‡] J. Ocampo-Candiani,[§] L. Azulay-Abulafia,[¶] P. Bezerra Trindade Neto,[**] D. Hexsel,[††] J. Machado-Pinto,[‡‡] H. Muñoz,[§§] M.C. Rivitti-Machado,[¶¶] J.A. Sittart,[***] A.R. Trindade de Almeida,[†††] V. Rego,[‡‡‡] F. Paliargues,[§§§] K. Marques-Hassun[¶¶¶]

[†]Hospital General de México O.P.D., Mexico
[‡]Hospital de Clinicas de Porto Alegre, University of Rio Grande do Sul, Brazil
[§]Hospital Universitario José E Gonzalez, Mexico
[¶]Instituto de Dermatologia e Estética do Rio de Janeiro, Brazil
[**]Hospital Universitário Onofre Lopes, Brazil
[††]Centro Brasileiro de Estudos Em Dermatologia, Brazil
[‡‡]Hospital Santa Casa de Misericórdia, Brazil
[§§]Hospital Juárez de México, Mexico
[¶¶]Hospital das Clinícas da FMUSP, São Paulo, Brazil
[***]Hospital do Servidor Publico do Estado de São Paulo, Brazil
[†††]Hospital do Servidor Publico Municipal de São Paulo, Brazil
[‡‡‡]Universidade Federal da Bahia, Brazil
[§§§]Galderma R&D, France
[¶¶¶]Universidade Federal de São Paulo, Brazil
*Correspondence: I. Arellano. E-mail: mariare1@yahoo.com

Abstract

Background The relapsing nature of melasma emphasizes the need to maintain efficacy achieved after acute treatment.

Objective To compare clinical efficacy and safety of two 6-month Triple Combination (TC; containing fluocinolone acetonide, hydroquinone and tretinoin) maintenance regimens in subjects with moderate to severe melasma, after daily treatment up to 8 weeks.

Methods This randomized, investigator-blinded, controlled study had a maintenance phase of 6 months. Sixteen centres in Brazil and Mexico enrolled 242 subjects 18 years or older attaining no or mild melasma after 8 weeks of daily TC applications. Subjects were randomized to receive TC in a twice weekly or tapering regimen [3/week (1st month), 2/week (2nd month), 1/week (4th month)].

Efficacy and safety measurements included median time to relapse and relapse-free rate, Global Severity Score, Melasma Area and Severity Index score (MASI), subject's assessment, quality of life questionnaire (MelasQol), and adverse events.

Results The majority (78.8%) had no or mild melasma (GSS ≤ 1) at week 8 and entered maintenance phase. After 6 months, 53% of patients remained relapse-free with improved quality of life, and time to relapse was similar between groups (about 190 days). Melasma severity at study entry, not maintenance baseline, influenced relapse rate. The twice weekly regimen tended to show better effectiveness in postponing relapse in severe melasma. Both regimens were safe.

Conclusions After resolution of melasma with TC, maintenance therapy over 6 months was successful in preventing relapse in over half of the patients who entered maintenance phase. Prescribing medicines should be adapted to patients based on melasma severity.

Received: 16 November 2010; Accepted: 10 May 2011

Conflict of interest

The investigating authors received payments for this research study. One of the authors is an employee of Galderma (Paliargues).

Funding sources

This study was funded by Galderma R&D, Sophia Antipolis, France, and the Latin American Pigmentary Disorders Academy is supported by an educational grant from Galderma International.

Introduction

using percentages of darkness, homogeneity, and area of melasma for the forehead, malar regions and chin), and subject's assessment. A validated subject's quality of life questionnaire (MelasQol[19]) was also completed at the baseline of both the initial and maintenance phases, and endpoint of the maintenance phase. In addition, the MelasQol adapted to both the Spanish[20] and Brazilian Portuguese[21] languages was used as appropriate. The MelasQol score ranges from 10 to 70, with lower scores indicating a better quality of life.

In addition, the relapse rate was analysed according to melasma severity (GSS 2 and 3) at study entry and maintenance baseline, and per country. The MelasQol was also evaluated by severity (GSS 2 and 3) at study entry. Safety was assessed at each visit by the incidence of adverse events. Severity of adverse events was assessed by evaluators as either mild (awareness of sign or symptom, but easily tolerated), moderate (discomfort, enough to cause interference with usual activity) or severe (incapacitating with inability to work or perform usual activity).

Statistical analyses

All data analyses were done according to a pre-established analysis plan. Two study populations were analysed: the safety (all subjects randomized and treated at least once) and intent to-treat (ITT) (all randomized subjects who were dispensed study medication) populations.

Time to relapse was analysed using the log-rank statistical test by survival analysis (PROC LIFETEST from SAS) on the ITT population. The relapse-free rate was analysed on the ITT observed population, and the quality of life questionnaire on the ITT population, both using the Cochran–Mantel–Haenszel (CMH) statistic stratified by centre. All tests were two-sided at the 0.05 significance level. Other efficacy variables and adverse events were descriptively summarized.

This study was conducted in accordance with the ethical principles derived from the Declaration of Helsinki and ICH Good Clinical Practices and in compliance with local regulatory requirements, and was reviewed and approved by institutional review boards. All subjects provided their written informed consent before entering the study.

Results

Subject disposition and baseline characteristics

Out of 320 subjects who were enrolled at the study baseline, 80 were from Mexico and 240 from Brazil. The population in Mexico presented with more severe melasma than Brazil (55% with GSS 3 vs. 45.4%, respectively). In addition, Mexico had three-fourths of subjects with a skin phototype IV, while Brazil had subjects who were more evenly distributed across phototypes III to V (30.8% phototype III, 41.3% phototype IV, and 21.3% phototype V). Among these subjects who entered the initial phase with moderate or severe melasma, the majority (308, 96.3%) completed this phase (Fig. 1), and 78.8% of the subjects presented with no or mild melasma (GSS ≤ 1) at week 8. This efficacy was not impacted by the duration of melasma (78.1% when the disease was present for 5 years or less; 78.8% when the disease was present for more than 5 years). A total of 242 subjects with no or mild melasma were subsequently randomized into the maintenance phase to receive either the TC twice weekly or tapering regimen. The majority (221, 91.3%) completed the maintenance phase, and subject disposition was similar between the two groups. Most subjects who discontinued did so because they were lost to follow-up (5.9% in the twice weekly group and 2.4% in the tapering group), and very few discontinued due to adverse events (2.5% and 0.8%, respectively,) or due to lack of efficacy (0.8% only in the tapering group).

At maintenance baseline (Table 1), the demographic profile and disease characteristics were similar between the two groups.

Disease characteristics in terms of severity showed a comparable, balanced distribution between the two treatment regimens at initial phase baseline (overall 41.3% of subjects had severe melasma and a correspondingly high mean MASI score: 15.4) and at maintenance baseline (64.5% had improved to mild severity with a low mean MASI: 2.2). The chronic nature of melasma in the study population was prominent, with a mean duration of nearly

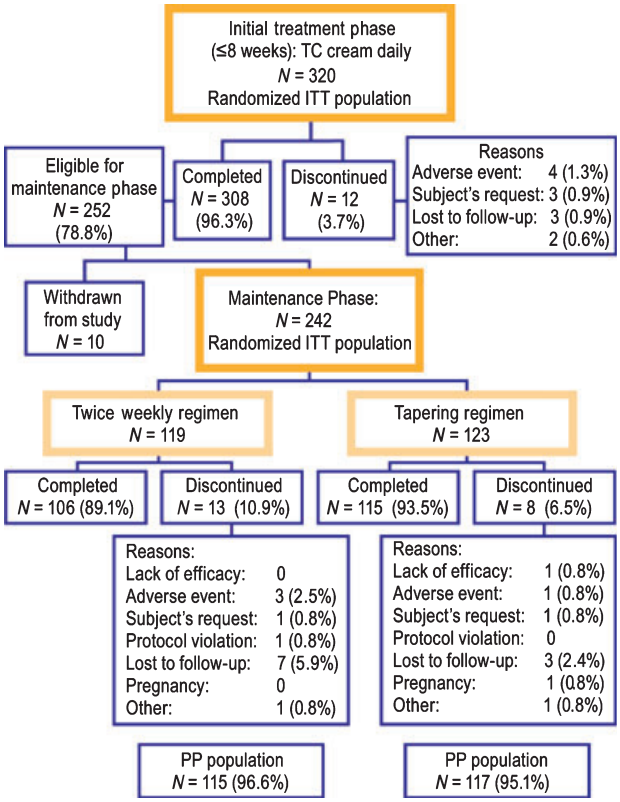

Figure 1 Subject disposition.

Table 1 Demographics and disease characteristics (ITT)

	Twice weekly regimen (*N* = 119)	Tapering regimen (*N* = 123)
Maintenance baseline – demographics		
Gender		
Male	7 (5.9%)	4 (3.3%)
Female	112 (94.1%)	119 (96.7%)
Age (in years)		
Mean ± SD	41.2 ± 8.18	41.4 ± 6.9
(Min, Max)	(19, 73)	(25, 59)
Phototype		
II	6 (5.0%)	9 (7.3%)
III	38 (31.9%)	39 (31.7%)
IV	53 (44.5%)	56 (45.5%)
V	22 (18.5%)	19 (15.4%)
Study baseline – disease characteristics		
MASI		
Mean ± SD	15.0 ± 6.1	15.8 ± 7.1
GSS (distribution across grades)		
2: Moderate	67 (56.3%)	75 (61.0%)
3: Severe	52 (43.7%)	48 (39.0%)
Subject's assessment		
0: Completely clear	–	–
1: Minor	10 (8.4%)	13 (10.6%)
2: Significant	109 (91.6%)	110 (89.4%)
Maintenance baseline – disease characteristics		
MASI		
Mean ± SD	2.3 ± 2.4	2.1 ± 2.3
GSS (distribution across grades)		
0: None	42 (35.3%)	44 (35.8%)
1: Mild	77 (64.7%)	79 (64.2%)
Subject's assessment		
0: Completely clear	41 (34.5%)	33 (26.8%)
1: Minor	77 (64.7%)	90 (73.2%)
2: Significant	1 (0.8%)	–
Duration of melasma		
Mean ± SD	10.70 ± 7.41	11.08 ± 7.55
<1 year	3 (2.5%)	2 (1.7%)
1–5 years	27 (22.7%)	28 (23.1%)
>5 years	89 (74.8%)	91 (75.2%)

*Worst score is the maximum score observed across the four face locations.

GSS, Global Severity Score.

11 years, and three-fourths of the population who had melasma for over 5 years.

Efficacy evaluation

In the overall population, both regimens were highly effective and similar in terms of the time to relapse and relapse-free rate (Fig. 2). The median time to relapse (50% of subjects with a first relapse) in both groups was comparable: 192 days for the twice weekly regimen vs. 190 days for the tapering regimen ($P = 0.74$).

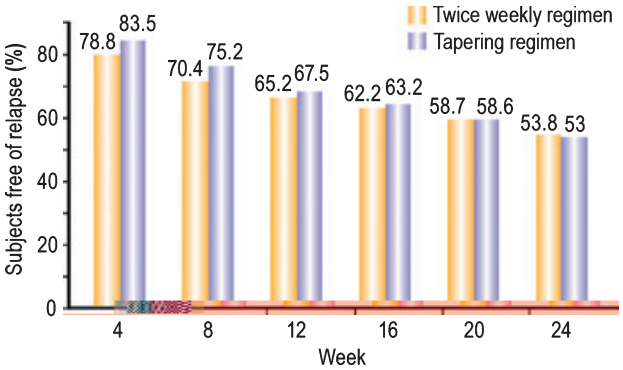

Figure 2 Maintenance phase: overall percent of subjects free of relapse* at each visit (ITT observed). *No relapse was defined as the subject having a GSS score of 0 (none) or 1 (mild).

Accordingly, the relapse rate (relapse defined as GSS ≥ 2, meaning moderate or severe melasma) during the maintenance phase was similar between groups. At 6 months, more than half of the subjects were relapse-free (53.8% in the twice weekly and 53.0% in the tapering regimen, $P = 0.901$). Subjects with lower phototypes tended to have fewer relapses (63.4% relapse-free subjects with phototype III vs. 44.7% with phototypes IV and V).

More importantly, the relapse rate was strongly influenced by the melasma severity at study entry (Table 2). As the severity of baseline melasma worsened (higher GSS), relapse occurred more rapidly. For those with severe melasma (GSS = 3 upon study entry), the twice weekly regimen tended to be more effective in terms of relapse-free subjects (14.6% more than the tapering regimen, $P = 0.063$). Similarly, as subjects in Mexico had a more severe melasma (GSS = 3), the twice weekly regimen showed a trend towards higher success in preventing relapse (63% subjects relapse-free vs. 40.7% in the tapering regimen, $P = 0.077$).

However, the relapse rate was not impacted by melasma severity at maintenance baseline. Relapse-free rates were similar whether subjects had no melasma (56.8% in the twice weekly group; 56.1% in the tapering group) or mild melasma (52.2% in the twice weekly group; 51.4% in the tapering group).

At the end of the study (6 months) for relapse-free subjects in both groups, the prevention of melasma recurrence was clearly

Table 2 Subjects free of relapse at 6 months according to severity of melasma (ITT observed)

	Twice weekly regimen	Tapering regimen
Severity of melasma at study entry		
Moderate	37 (61.7%)	48 (68.6%)
Severe	20 (43.5%)	13 (28.9%)
Severity of melasma at maintenance baseline		
None	21 (56.8%)	23 (56.1%)
Mild	36 (52.2%)	38 (51.4%)

demonstrated in terms of disease characteristics. The GSS remained low (Fig. 3), though it still showed a trend towards a slight increase compared to maintenance baseline. Still, it was reduced by 63% compared to study entry. Both maintenance regimens had overall similar scores, rated none or mild. Following the evolution of the GSS, MASI scores essentially remained low for both regimens (Fig. 4) and a reduction of 84% was observed compared to study entry. Darkness, homogeneity and total area scores also remained low; all parameters evolved in a similar fashion, notably in that a certain characteristic did not predominate over others. The subject's assessment reflected that of the investigator, in that the subject noticed a marked improvement. Regardless of the regimen, all relapse-free subjects rated their melasma as completely clear or minor. Fig. 5 is an example of subjects from each regimen at study entry, maintenance baseline and after 6 months of successful maintenance treatment.

In the population who relapsed, there was no apparent rebound effect observed. In this case, the clinical term rebound means worsening of the severity scores compared to baseline after a relapse of melasma. The mean GSS, though worse compared to maintenance baseline as expected, decreased by 13% compared to study entry. The MASI scores had also no observed rebound effect: even though they were higher than maintenance baseline, MASI mean scores were diminished by 42% compared to those at study entry. Subject's assessment of their melasma again mirrored the investigator's assessments. The majority (about 90%) of subjects in both groups rated their melasma as significant, which seems usual with relapse and was higher than the maintenance baseline, although not any higher than at study entry.

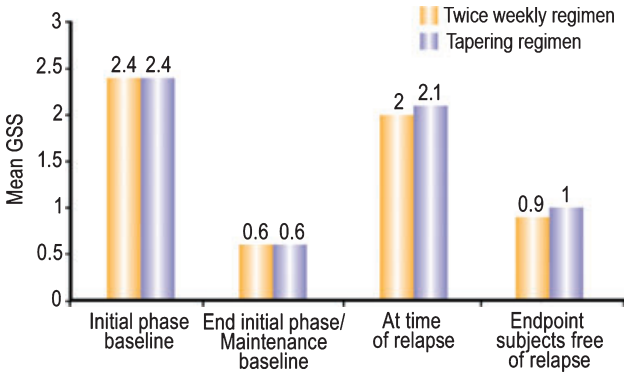

Figure 3 GSS mean scores across study for both maintenance regimens (ITT population).

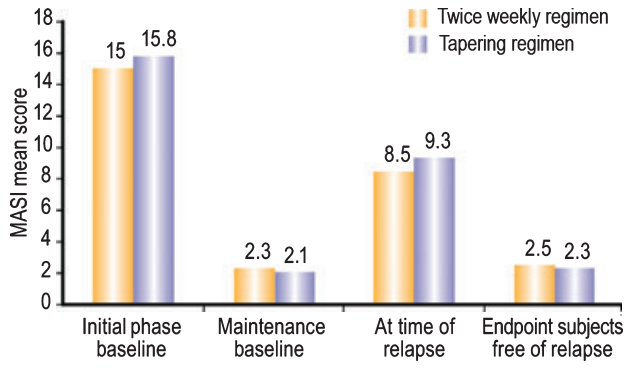

Figure 4 MASI mean scores during maintenance phase (ITT population).

Quality of life questionnaire (MelasQol)

The results of the MelasQol confirmed the efficacy and safety observed by investigators (Table 3).

Safety evaluation

Overall and during the entire study, subjects in the twice weekly group were exposed to TC for a similar period as the subjects in the tapering group (average of 168.4 days vs. 170 days, respectively). Logically, they had slightly more TC applications during the entire study (80.7 days vs. 74.0 days). The mean duration of topical use of sunscreen SPF 60 during the entire study period was similar between treatment regimens.

In the maintenance phase, treatment-related adverse events were reported by 11.6% of subjects, and erythema and skin irritation were the most frequently noted. Most of the adverse events were mild, with fewer of moderate intensity; there were no severe adverse events related to the use of TC.

The incidence of TC-related adverse events that led to discontinuation was very low, with two subjects (0.83%) reporting dermatological disorders.

Reporting of skin atrophy was nearly absent, as only one subject in the twice weekly group (0.4%) had mild skin atrophy that led to discontinuation of the study. Likewise, reporting of telangiectasia was nearly absent: six subjects (1.88%) had mild telangiectasia (during the initial phase), which already existed at baseline for two of the subjects. TC was not only shown to be safe throughout the study, but also its maintenance regimens were similar in terms of the proportion of subjects with related adverse events (10.92% vs. 12.2% in the twice weekly and tapering regimens, respectively). Related adverse events during the maintenance phase are summarized in Table 4.

Discussion

A paucity of published data exists about melasma, especially concerning the natural course of the disease, relapse rate after treatments and specific recommendations for maintenance regimens. A recent study analysed the efficacy and safety of a twice weekly maintenance regimen over 12 weeks. As data on six patients who completed this maintenance regimen (and 21 patients who did not complete it due to melasma recurrence) were available, we think that our results from a sample of 242 patients who entered the maintenance phase (and 221, 91.3%, with normal study

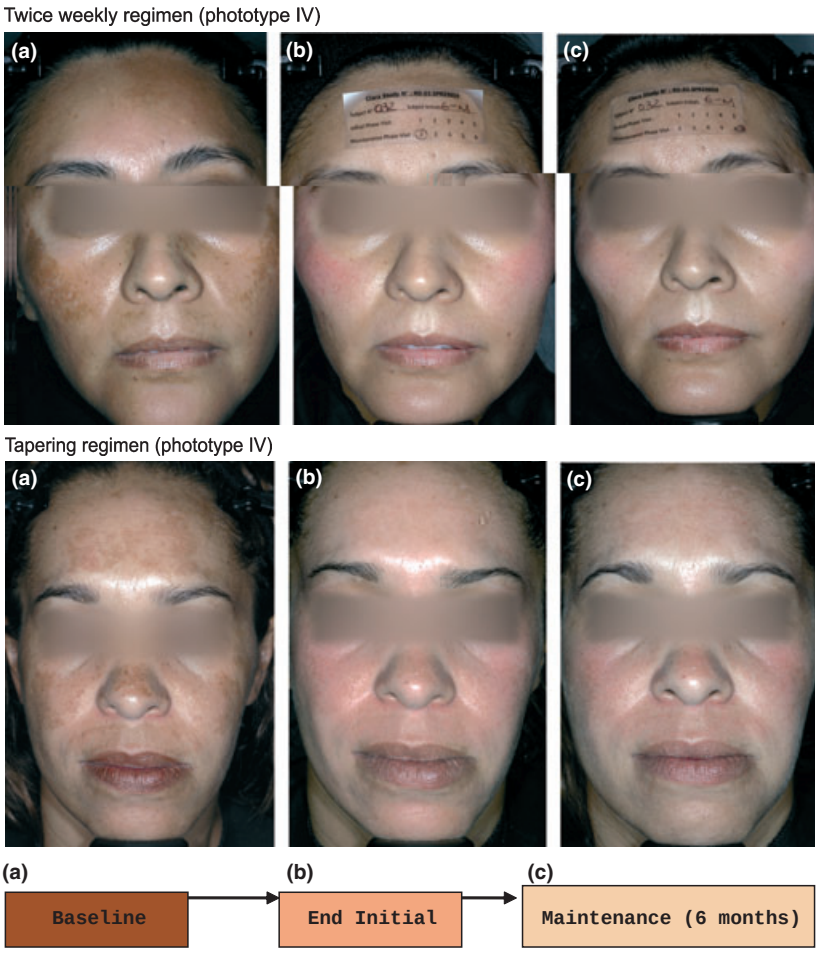

Figure 5 Effect of 6 months of TC maintenance therapy (for subjects with phototype IV in the twice weekly and tapering regimens, respectively) following 8 weeks of daily TC therapy: at (a) baseline, (b) end of daily treatment phase and (c) end of maintenance phase.

Table 3 Total score of MelasQoL at baseline and last visit (ITT)

	Baseline initial phase		Baseline maintenance phase		Endpoint maintenance phase (6 months)		
	Twice weekly regimen	Tapering regimen	Twice weekly regimen	Tapering regimen	Twice weekly regimen	Tapering regimen	*P*-value(1)
Total score							
N	118	121	118	123	110	115	0.980
Mean ± SD	42.7 ± 15.3	41.1 ± 14.7	22.6 ± 15.3	20.7 ± 13.0	29.0 ± 18.4	27.7 ± 16.2	
Median	43.5	43.0	15.5	15.0	24.5	26.0	
(Min, Max)	(10, 70)	(10, 70)	(8, 70)	(9, 60)	(5, 70)	(10, 70)	
Total score for relapsed subjects							
N	49	53	49	54	48	52	0.620
Mean ± SD	45.3 ± 13.9	42.3 ± 15.2	24.9 ± 15.5	22.6 ± 14.0	38.6 ± 18.0	36.1 ± 15.9	
Median	44.0	43.0	22.0	17.5	35.5	34.0	
(Min, Max)	(10, 70)	(10, 70)	(10, 70)	(10, 55)	(5, 70)	(10, 70)	
Total score for non-relapsed subjects							
N	56	60	56	61	57	60	0.831
Mean ± SD	41.2 ± 16.0	40.2 ± 14.8	21.7 ± 16.0	19.3 ± 12.5	21.8 ± 15.1	20.8 ± 13.0	
Median	43.0	43.0	14.5	13.0	16.0	15.0	
(Min, Max)	(10, 70)	(11, 70)	(8, 68)	(9, 60)	(10, 70)	(10, 61)	

Table 4 Summary of treatment-related adverse events during maintenance phase

Number of subjects with adverse event (%)	Twice weekly regimen (*N* = 119)	Tapering regimen (*N* = 123)
Acne	1 (0.8)	1 (0.8)
Blepharitis	1 (0.8)	–
Erythema	4 (3.4)	2 (1.6)
Pruritus	1 (0.8)	–
Papular rash	1 (0.8)	1 (0.8)
Skin atrophy	1 (0.8)	–
Skin burning sensation	1 (0.8)	–
Skin irritation	2 (1.7)	2 (1.6)
Urticaria	1 (0.8)	–
Dermatitis	–	2 (1.6)
Dermatitis (contact)	–	3 (2.4)
Eyelid oedema	–	1 (0.8)
Skin exfoliation	–	1 (0.8)

completion) clearly illustrate the fact that such long-term regimens are to be considered in treating this chronic and recurrent disease.[22] In addition, the higher clearance rates we observed could be due to the fact that subjects applied sunscreen twice daily compared to once daily in the other study. The present study is not only one of the few available regarding maintenance regimens, but it is also one of the largest controlled trials in melasma therapy accomplished in a Latin American population. Despite the fact that patients in the present study had darker phototypes (skin phototypes IV to V most represented) and more severe disease (nearly half the population presenting with severe melasma at study baseline), efficacy results are extremely close to those found in previous North American studies (77% of subjects vs. 78.8% in our study with a level of clear or almost clear after 8 weeks of TC treatment).[15]

In our study, two 6-month maintenance regimens with TC demonstrated efficacy and safety in patients with moderate to severe melasma, previously improved by a 8-week daily treatment [78.8% of the subjects presented with no or mild melasma (GSS $\leq$ 1) at week 8 and were able to enter the maintenance phase]. The efficacy of TC maintenance regimens was shown by investigator's assessments of continued severity reduction (GSS and MASI), and was confirmed by the subject's assessment and MelasQoL scores. Furthermore, the similar evolution of these evaluation tools suggests that further research is merited, especially in regard to the correlation between GSS (though it is not yet validated) and the validated MASI[18] evaluations. Indeed, we observed that the evolution of the GSS mirrored that of the MASI. Furthermore, in terms of methodology, limitations include that the level of pigmentation was not obtained by a chromameter, and that a vehicle group (or one with only a sunscreen) was not used as a comparison. These methods would be interesting to employ in future melasma studies.

The median time to melasma relapse was 190 days (superior to 58 days per previous data[17] with an abrupt cessation of TC after acute, daily treatment), regardless of the maintenance regimen. Kligman and Willis, the founders of a similar composition of TC therapy, observed that melasma relapse started as early as 1–2 weeks after cessation of treatment.[13] These findings emphasize that maintenance regimens could postpone melasma relapse by almost 5 months compared to the conventional cessation of daily, short-term TC therapy. The use of high SPF sunscreen was mandatory during the study, and is also strongly recommended by the Latin American Pigmentary Disorders Academy as part of fundamental melasma therapy.[14] Sunscreen use could have helped maintain the previously obtained improvement in melasma severity.

It should be noted that efficacy of the TC maintenance treatment was influenced by severity of melasma at study baseline. For patients with severe melasma upon study entry, the twice weekly regimen was clearly more effective while the tapering regimen was more appropriate for those with moderate melasma. In this study, the lack of significant difference between maintenance regimens was possibly due to the small sample size, yet a consistent trend could be observed across the different evaluations. The great diversity in phototypes represented in this study suggests that the relation between severity and melasma relapse is also applicable to the general population. Also, it is interesting to note that after 6 months of treatment, subjects using the maintenance regimen that was more effective regarding relapse prevention (according to melasma severity) understandably indicated a more positive impact on their quality of life.

In case of relapse, after the 6-month maintenance phase, re-treatment with TC is not only reasonable in terms of efficacy, but also appears to be safe over the long-term. A 12-month extension trial with intermittent daily TC application required an average of two treatment courses, and was found to be safe, tolerable and effective.[17] Furthermore, a study of histological examinations showed no epidermal/dermal atrophy in 30 patients treated up to 24 weeks with daily TC.[16] During our study, both TC regimens were safe with very few dermatological-related adverse events, likely due to the intermittent use of TC as opposed to daily use in other studies.[15,17] Though TC contains the corticosteroid fluocinolone acetonide, its low dose (0.01%) may account for the correspondingly low incidence of commonly described corticosteroid side-effects such as skin atrophy and telangiectasia.

Recent recommendations of the Latin American Pigmentary Disorders Academy define daily treatment according to the severity of melasma.[14] In the same way, our approach bases the choice of a maintenance regimen on the presenting clinical severity of melasma. In choosing a TC maintenance regimen, it is essential that the dermatologist considers the usual presentation of melasma for the patient, which can be assessed as early as the first visit. In addition, the application schedule of the regimen can be difficult to understand for the patient and thus requires further patient

education. The benefit of this lies not only in the prevention of melasma relapse, but also in the improvement in the patient's quality of life.

Conclusions

As melasma is a chronic, recurrent disease, this study's findings are important in that these alternative maintenance regimens are possible and effective for long-term maintenance treatment of moderate to severe melasma. These treatment regimens should always incorporate mandatory sunscreen use and sun avoidance.

Acknowledgements

The authors would like to thank Galadriel Bonnel, MSN, Galderma R&D, Sophia Antipolis, France, for editorial assistance.

References

1 Javaheri SM, Handa S, Kaur I *et al.* Safety and efficacy of glycolic acid facial peel in Indian women with melasma. *Int J Dermatol* 2001; **40**: 354–357.
2 Mosher DB, Fitzpatrick TB, Ortonne J-P, Hori Y. Hypomelanoses and hypermelanoses. In Freedberg IM, Eisen AZ, Wolff K *et al.*, eds. *Fitzpatrick's Dermatology in General Medicine*, Vol. 1, McGraw-Hill, New York, NY, 1999: 945–1017.
3 Barankin B, Silver SG, Carruthera A. The skin in pregnancy. *J Cut Med Surg* 2002; **6**: 236–240.
4 Ortonne JP, Arellano I, Berneburg M *et al.* A global survey of the role of ultraviolet radiation and hormonal influences in the development of melasma. *J Eur Acad Dermatol Venereol* 2009; **23**: 1254–1262.
5 Pandya AG, Guevara IL. Disorders of hyperpigmentation. *Dermatol Clin* 2000; **18**: 91–98.
6 Vasquez M, Sanchez JL. The efficacy of a broad spectrum in the treatment of melasma. *Cutis* 1983; **32**: 92 95–96.
7 Pathak MA, Fitzpatrick TB, Kraus EW. Usefulness of retinoic acid in the treatment of melasma. *J Am Acad Dermatol* 1986; **15**: 894–899.
8 Giannotti B, Melli MC. Current approaches to the treatment of melasma. *Clin Drug Invest* 1995; **10**(Suppl. 2): 57–64.
9 Kimbrough-Green CK, Griffiths CEM, Finkel LJ *et al.* Topical retinoic acid (tretinoin) for melasma in black patients. *Arch Dermatol* 1994; **130**: 727–733.
10 Gano SE, Garcia RL. Topical tretinoin, hydroquinone, and bethamethasone valerate in the therapy of melasma. *Cutis* 1979; **23**: 239–241.
11 Kang WH, Hcun SC, Lee S. Intermittent therapy for melasma in Asian patients with combined topical agents (retinoic acid, hydroquinone and hydrocortisone): clinical and histological studies. *J Dermatol* 1998; **25**: 87–596.
12 Katsambas A, Antoniou CH. Melasma: classification and treatment. *J Eur Acad Dermatol Venereol* 1995; **4**: 217–223.
13 Kligman AM, Willis I. A new formula for depigmenting human skin. *Arch Dermatol* 1975; **111**: 40–48.
14 Cestari T, Arellano I, Hexsel D, Ortonne JP, Latin American Pigmentary Disorders Academy. Melasma in Latin America: options for therapy and treatment algorithm. *J Eur Acad Dermatol Venereol* 2009; **23**: 760–772.
15 Taylor S, Torok H, Jones T *et al.* Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. *Cutis* 2003; **72**: 67–72.
16 Bhawan J, Grimes PE, Pandya AG *et al.* A histological examination for skin atrophy following six months of treatment with Fluocinolone acetonide 0.01%, Hydroquinone 4%, Tretinoin 0.05% cream. *Am J Dermatopathol* 2009; **31**: 794–798.
17 Torok H, Taylor S, Baumann L *et al.* 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. *J Drugs Dermatol* 2005; **4**: 592–597.
18 Pandya AG, Hynan LS, Bhore R *et al.* Reliability assessment and validation of the Melasma Area and Severity Index (MASI) and a new modified MASI scoring method. *J Am Acad Dermatol* 2011; **64**: 78–83.
19 Balkrishnan R, McMichael AJ, Camacho FT *et al.* Development and validation of a health-related quality of life instrument for women in melasma. *Br J Dermatol* 2003; **149**: 572–577.
20 Dominguez AR, Balkrishnan R, Elizey AR, Pandya AG. Melasma in Latina patients: cross-cultural adaptation and validation of a quality-of-life questionnaire in Spanish language. *J Am Acad Dermatol* 2006; **55**: 59–66.
21 Cestari TF, Hexsel D, Viegas ML *et al.* Validation of a melasma quality of life questionnaire for Brazilian Portuguese language: the MelasQoL-BP study and improvement of QoL of melasma patients after triple combination therapy. *Br J Dermatol* 2006; **156**(Suppl. 1): 13–20.
22 Grimes PE, Bhawan J, Guevara IL *et al.* Continuous therapy followed by a maintenance therapy regimen with a Triple Combination cream for melasma. *J Am Acad Dermatol* 2010; **62**: 962–967.