

A Comprehensive Review of the Long-Term and Short-Term Treatment of Melasma with a Triple Combination Cream

Hele M. T. K

Trillium Creek Dermatology Center, Medina, Ohio, USA

Abstract

Melasma is a common disorder of hyperpigmentation and generally involves areas of the face and neck. Hyperpigmentation is especially prevalent in darker complected patients and is often difficult to treat. Hydroquinone, tretinoin, and topical corticosteroids are well established monotherapeutic agents for treating melasma and hyperpigmentation; however, a stable, once-daily formulation triple combination cream containing 0.05% tretinoin, 4.0% hydroquinone, and 0.01% fluocinolone acetonide (Tri-Luma®) represents the only commercially available combination of all three agents. This product is approved by the US FDA for the treatment of facial melasma. A number of publications have described the safety and efficacy of triple combination cream in over 2000 patients with melasma, some of whom were treated for >12 months.

In the initial 8-week study, 29% of patients experienced complete clearing of melasma by week 8, and 77% were clear or almost clear by week 8. Similarly, good results were seen in the two long-term studies, with the clear/mild rate ranging from 78% to 84% of patients at month 6 and from 81% to 94% of patients at month 12. Adverse events were almost always mild in severity and typically occurred only at the application site. The primary concern for most physicians using corticosteroid-containing products on the face is skin atrophy. However, only two cases of skin atrophy were reported across the three published studies.

Overall, the results of these extensive studies indicate that triple combination cream is efficacious in treating melasma and exhibits a safe profile with low potential for adverse events.

Melasma is a common skin disorder that appears as an irregular brown or light-to-gray brown macular hypermelanosis.^[1] There are three distinct patterns of melasma: centrofacial, malar, and mandibular patterns.^[2] Certain etiologic factors have been identified in the pathogenesis of melasma. These factors include genetic influences, UV radiation exposure, hormonal therapies, cosmetics, phototoxic drugs, and use of antiepileptic medications.^[1] Although

melasma affects women more than men,^[3] who make up only 10% of melasma patients.^[5] It is reported that 5–6 million American women are affected by melasma annually.^[6]

Cutaneous disorders, including melasma, postinflammatory pigmentation, acne keloidalis nuchae, scalp and facial folliculitis, keloids and alopecias, occur more frequently in skin of color.^[7]

these areas of their life would improve. Successful treatment of melasma is paramount for these very reasons.

In recognition of the importance to patients and their physicians of treating the condition, several current treatments have been used to combat melasma. These treatments include hypopigmenting agents, chemical peels, dermabrasion, and lasers. The most fre-

of up to 8 weeks.^[15] Because both trials were similar in design, the results were presented together. After good safety and efficacy for the cream had been demonstrated in these trials, a 12-month extension trial was conducted to establish the safety of triple combination cream for longer treatment periods.^[16] In addition to the extension trial, a prospectively designed 12-month trial was



Table I. Percentage success (primary and secondary)^a with triple combination therapy and dual combination therapies in patients with melasma^[15]

Combination therapies	RA + HQ + FA	RA + HQ	RA + FA	HQ + FA
Primary success (%)	28.6*	10.1	1.9	3.1
Secondary success (%)	77.0*	46.8	27.3	42.2

a Primary success = complete clearing on or before day 56; secondary success = complete or near-complete clearing on or before day 56.

FA = fluocinolone acetonide; HQ = hydroquinone; RA = tretinoin. * $p < 0.001$ vs dual-combination therapies (RA + HQ; RA + FA; HQ + FA).

from baseline was assessed on an 8-point scale, ranging from 0 (completely clear) to 7 (worse). Assessments were made at baseline and at each subsequent visit.

Significantly more patients (26.1%, $p < 0.001$) treated with triple combination cream experienced complete clearing compared with each of the dual-therapy groups at week 8 (table I). The percentages of patients with complete clearing in the tretinoin plus hydroquinone, tretinoin plus fluocinolone acetonide, and hydroquinone plus fluocinolone acetonide groups were 9.5%, 1.9%, and 2.5%, respectively. The percentages of patients who experienced complete clearing on or before day 56 were slightly higher with

triple combination cream (28.6% vs 10.1% for tretinoin plus hydroquinone, 1.9% for tretinoin plus fluocinolone acetonide, and 3.1% for hydroquinone plus fluocinolone acetonide; $p < 0.001$). A significantly greater percentage of the triple combination treatment group experienced complete or near-complete clearing by day 56 compared with each of the dual-therapy groups (77% vs 46.8% for tretinoin plus hydroquinone, 27.3% for tretinoin plus fluocinolone acetonide, and 42.2% for hydroquinone plus fluocinolone acetonide; $p < 0.001$).

The most frequently occurring adverse events in the triple combination treatment group were application site erythema, desquamation, burning, dryness, and pruritus (table II). Only one patient receiving hydroquinone plus fluocinolone acetonide experienced skin atrophy. Sixteen of a total of 102 adverse events were considered by the investigators to be probably or possibly related to the study drugs.

2. Long-Term Safety and Efficacy of Triple Combination Cream in Melasma Patients Previously Treated with Triple Combination Cream or One of its Dyads

Although no instances of skin atrophy were reported in the 8-week trials, the medical community called for longer-term evaluation of the safety of the triple combination cream, and this was

Table II. Summary of adverse events with triple combination cream in patients with melasma

Adverse events	No. of patients (%)		
	Taylor et al. ^[15] (n = 161)	Torok et al. ^[16] (n = 569)	Torok et al. ^[17] (n = 228)
Acne breakouts	NR	NR	23 (10)
Application site reaction	NR	37 (7)	NR
Atrophy	0	2 (<1)	0
Burning	29 (18)	43 (8)	NR
Desquamation	61 (38)	167 (29)	~33% ^a
Dryness	29 (18)	52 (9)	NR
Erythema	66 (41)	187 (33)	~33% ^a
Hyperpigmentation/pigmentation changes	NR	30 (5)	11 (5)
Inflammation	NR	31 (6)	NR
Perioral dermatitis	NR	NR	2 (1)
Pruritus	18 (11)	27 (5)	NR
Rash	NR	35 (6)	NR
Rosacea	NR	1 (<1)	NR
Telangiectasia	NR	23 (4)	6 (3)

a The report indicated that "approximately one-third of patients" experienced these adverse events.

NR = not reported.

the objective of the next two studies discussed here. A 12-month extension study^[16] included patients who were enrolled in the previously discussed study.^[15] Of the 641 patients that participated in the original study, 585 were enrolled in the 12-month extension study. All of these patients were treated with once-nightly triple combination cream irrespective of their treatment arm in the original study. In addition, patients used a sun protection factor (SPF)-30 sunscreen with both UVA and UVB protection and were asked to use protective clothing and avoid sun exposure.

A total of 389 patients completed the first 6 months of the study, and 327 patients completed the 12-month treatment. Thirty-one percent of patients discontinued participation in the study by request (for reasons that were not stated) and 25% were lost to follow-up. The intent-to-treat (ITT) population consisted of 569 patients: 142 (25%) from the triple combination cream group and 427 (75%) from the dyad groups in the initial 8-week randomized study.

A total of 346 patients (61%) experienced treatment-related adverse events (table II). The most frequently reported adverse events were erythema (33% of patients) and desquamation at the application site (29%), which were mild, transient, and did not require remedial therapy or result in discontinuation from the study. Typically, application site adverse events are more prevalent with longer treatments.^[16] However, the incidence of treatment-related adverse events in patients in the current study who had two treatment courses was 66% compared with 60% in patients who had only one treatment course. These adverse events had a higher incidence in non-Caucasian patients >40 years of age with skin phototypes I–III. Skin atrophy/thinning occurred in two patients and was mild. Rosacea occurred in one patient and facial telangiectasia in 23 patients, but this resulted in only two patients discontinuing the study. In the final analysis, only 14 patients (2.5%) reported treatment-related adverse events that ultimately led to discontinuation of treatment. There were no incidences of serious adverse events or clinically significant changes in measured laboratory parameters.

The physician's assessment of melasma severity at the end of this 12-month extension study showed that more patients had mild or cleared lesions than at the baseline evaluation. At baseline, 59% of patients in the previous dyad-treated groups had lesions that were moderate or severe. The incidence of former dyad-treated patients with lesions that were clear or almost clear was 70% at month 1 and 81% at month 12 with triple combination cream treatment. The Physician's Static Global Assessment at month 12 revealed that >80% of patients overall had lesions that were completely cleared or nearly cleared.

3. Long-Term Evaluation of the Safety and Efficacy of Triple Combination Cream for the Treatment of Melasma

A major concern with the long-term use of corticosteroids is the risk of skin atrophy and telangiectasia.^[19] However, it has been shown that tretinoin, in addition to providing anti-inflammatory effects, prevents corticosteroid-induced atrophy.^[20,21] The goals of this study^[17] were to confirm the safety and efficacy of triple combination therapy over a 1-year course of treatment in a disease that has a significant relapse rate.

The study enrolled both female and male patients who were ≥18 years of age and had been diagnosed with melasma of at least 3 months' duration. Patients were excluded if they had pre-existing facial skin disorders that would interfere with the study objectives, were immunocompromised or receiving immunosuppressive treatment, or were receiving corticosteroid treatment. Patients in this study were instructed to apply the triple combination cream once daily to a clean face approximately 30 minutes before bedtime. An SPF-30 sunscreen with UVA and UVB protection was provided for daily use. Protective clothing and sun avoidance was recommended. Use of cosmetics and mild moisturizers was allowed.

At monthly examinations, patients were evaluated for a satisfactory response to the triple combination cream on a 4-point scale (0 = clear, 1 = mild, 2 = moderate, 3 = severe). When the severity score reached 0 or 1, which signified complete or near-complete clearing, the treatment was halted, but the daily use of sunscreen was continued. Under the physician's supervision, if the melasma worsened, patients were retreated with the triple combination cream for an additional 8 weeks. Thus, each patient may potentially have received several courses of treatment throughout the 12-month study. Safety assessments were conducted throughout the study by reporting adverse events and laboratory test results. At each visit, all skin changes, including erythema, desquamation, burning, and stinging, were noted. Patients were also examined for the presence of telangiectasia, rosacea, dermatitis, atrophy, or worsening hyperpigmentation. In addition, a complete blood cell count, serum chemistry tests, and urinalysis were performed at selected sites at the initiation and completion of treatment.

Efficacy assessments were measured in terms of the degree of pigmentation of the target melasma lesion. Investigators assigned this score using a 4-point scale: 0 = melasma lesion 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 surround-

ing normal skin); and 3 = severe (markedly darker than the surrounding normal skin). A Physician's Static Global Assessment of melasma was performed at each treatment visit. A score of 0, 1, or 2 was assigned using the following scale: 0 = completely cleared, no evidence of hyperpigmentation; 1 = nearly cleared, only minor visual evidence of hyperpigmentation; and 2 = significant evidence of hyperpigmentation. A similar assessment of melasma was made by the patients, which included an assessment of all treated areas. This assessment was performed at each visit and rated as 1 = completely cleared; 2 = nearly cleared; or 3 = significant hyperpigmentation present. Regression analysis and longitudinal analyses were performed for the long-term safety and selected efficacy evaluations. All patients who received the triple combination cream were included in the analysis as the ITT population.

Altogether, 228 patients were enrolled, with 173 patients (76%) completing the study; the rest of the patients discontinued because of loss to follow-up or by personal request (for reasons that were not stated). Most patients had only one or two courses of treatment, which lasted between 173 and 177 days. The duration of each course and the interval between the courses decreased in those patients who required more than two courses of therapy.

Treatment-related adverse events were experienced by 57% of patients (table III). However, most of these adverse events were mild cases of desquamation, erythema, or dryness. More importantly, no instances of skin atrophy, rosacea, or hypopigmentation

were reported throughout the study. The triple combination cream was well tolerated by patients. Only six patients (3%) had adverse events that led to discontinuation of treatment. Three of these adverse events were considered possibly related to the study drug (irregular menstrual periods, peeling of the face, and hyperpigmentation). The other three adverse events were considered unlikely to be related to the study drug (breast lump and pregnancy). No serious adverse events were reported by patients using the triple combination cream in the study.

At baseline, the physician's assessment of melasma severity was mild in 46.5% of patients, moderate in 37.3%, and severe in 16.2%. At 6 months, 84% of patients were either cleared or had mild lesions. By 12 months, the percentage of patients that were either cleared or had mild lesions had increased to 94%. The Physician's Static Global Assessment of melasma revealed that the lesions were completely or nearly cleared in 76% of patients at 6 months and in 97% at 12 months. Overall, 92.3% of patients reported having completely or nearly cleared lesions by 12 months.

These findings showed that triple combination cream, applied once daily and used with proper sun protection, is a safe and effective long-term treatment for melasma. All measures of efficacy (i.e. the physician assessment of melasma severity, and the physician's and patient's static global assessments) indicated that intermittent months of triple combination cream therapy resulted in a statistically significant improvement in melasma.

Table III. Summary of efficacy data with triple combination cream in patients with melasma

Study	Summary of efficacy by physician's assessment of melasma severity
Taylor et al. ^[15] (n = 161)	More patients (29%) experienced complete clearing with triple combination cream than with any of its dyads. 77% of patients were clear or nearly clear after 8 weeks
Torok et al. ^[16] (n = 569)	Substantially more patients were clear or mild by month 12 than at baseline (estimated from bar graph: 59% at baseline; 78% at month 6; 81% at month 12)
Torok et al. ^[17] (n = 228)	By 6 months of treatment, 84% of patients were clear or mild. By 12 months, 94% of patients were clear or mild
Grimes et al. ^[18] (n = 1042)	The percentages of patients achieving moderate to marked improvement, almost clear, or clear were 66% at week 4 and 75% at week 8. The percentage of patients achieving slight improvement to clear was 82% at week 8

4. PIGMENT (Prospective Investigation Gauging Melasma Reduction with a New Treatment) Trial

A phase IV community-based trial was initiated to elucidate the results of treating melasma with triple combination cream in a real-world clinical setting.^[18] The study was conducted by 393 investigators in the US and included men and women aged ≥ 18 years with Fitzpatrick skin types I–VI. All patients had moderate to severe facial melasma with macular lesions that were not depressed or atrophic at baseline. Patients were excluded from the study if they had used topical corticosteroids, glycolic acid, bleaching products, UV light therapy, sunbathing, topical retinoids, or scented cosmetics within 2 weeks prior to the study. Patients were also excluded if they had used systemic corticosteroids or antibacterials within the preceding 4 weeks or other systemic preparations that would interfere with the study drugs (i.e. acitretin, etretinate, isotretinoin, methotrexate, or photoallergic, phototoxic, or photosensitizing drugs) within 6 months prior to the study.

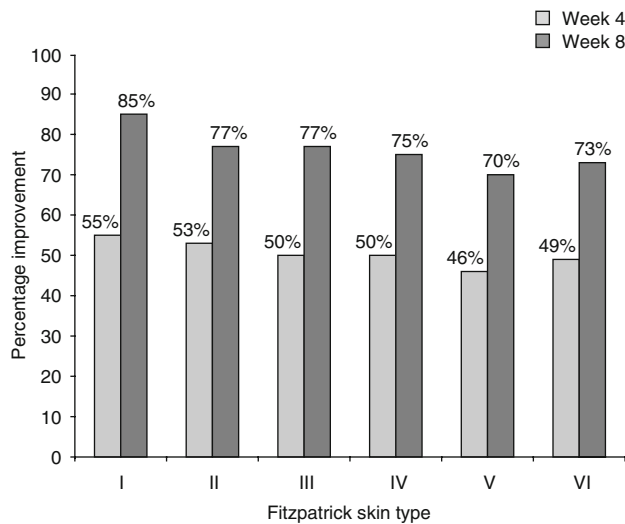


Fig. 1. Percentage improvement in mean overall Melasma Area and Severity Index (MASI) score by Fitzpatrick skin type with use of a tretinoin, hydroquinone, and fluocinolone acetonide cream formulation in the PIGMENT (Prospective Investigation Gauging Melasma Reduction with a New Treatment) study.^[18] Improvements in mean overall MASI score across the Fitzpatrick skin types were significant compared with the baseline scores ($p < 0.0001$).

Patients in the PIGMENT study were instructed to apply the hydrophilic triple combination cream formulation at night, at least 30 minutes before bedtime. To apply the cream, patients were instructed to rub a thin film on all hyperpigmented areas of the face

and on the half-inch of normal-appearing skin surrounding each lesion.

Treatment evaluations were conducted at weeks 4 and 8 using the Melasma Area and Severity Index (MASI), MASI darkness score, MASI homogeneity score, and MASI area score. An investigator's global assessment of improvement was used that was based on a 7-point scale from 1 (worse) to 7 (clear). Quality of life was also evaluated at baseline and week 8 using a patient health questionnaire. Safety assessments were performed at weeks 4 and 8.

A total of 1290 patients were enrolled in the study, and all received at least one application of triple combination cream during the 8-week duration of the trial. At weeks 4 and 8, 1131 patients (88%) and 1043 patients (81%), respectively, reported compliance.

The mean MASI score in the overall study population decreased significantly at both week 4 (7.38) and week 8 (3.64) compared with baseline (14.68) [$p < 0.0001$ for both variables at both time points] in all facial regions, which included the forehead, right and left malar regions, and chin. A similar trend was observed across the range of Fitzpatrick skin types (figure 1) and race/ethnicity (figure 2). Significant improvements ($p < 0.0001$) in the mean overall MASI score for all Fitzpatrick skin types and ethnic/racial groups were seen at weeks 4 and 8. The mean MASI darkness score and MASI homogeneity score decreased significantly from baseline to weeks 4 and 8 ($p < 0.0001$ for both time

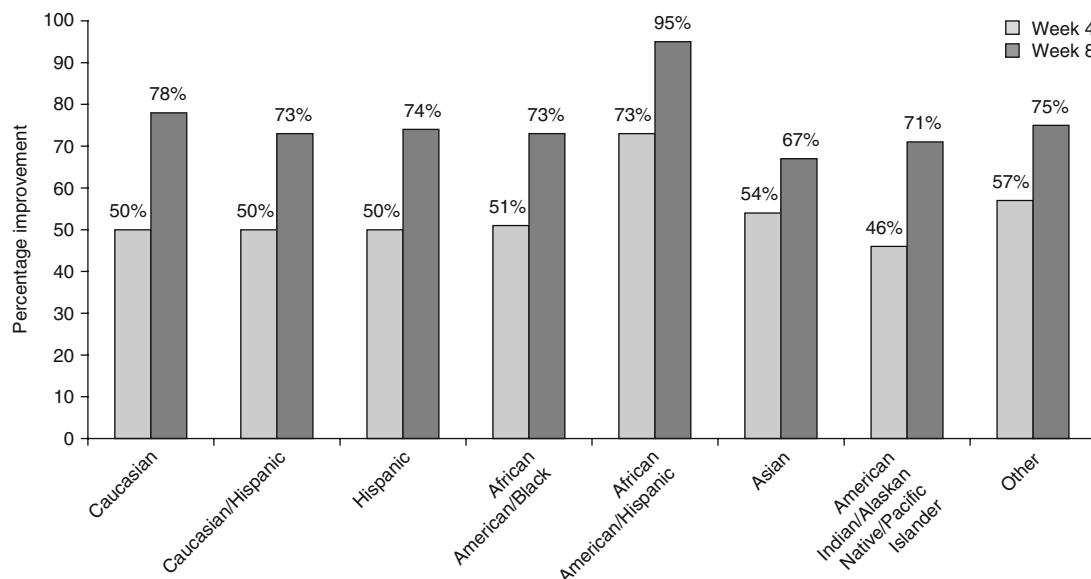


Fig. 2. Percentage improvement in mean overall Melasma Area and Severity Index (MASI) score by race/ethnicity with use of a tretinoin, hydroquinone, and fluocinolone acetonide cream formulation in the PIGMENT (Prospective Investigation Gauging Melasma Reduction with a New Treatment) study.^[18] Improvements in mean overall MASI score across all races/ethnicities were significant compared with the baseline scores ($p < 0.0001$).

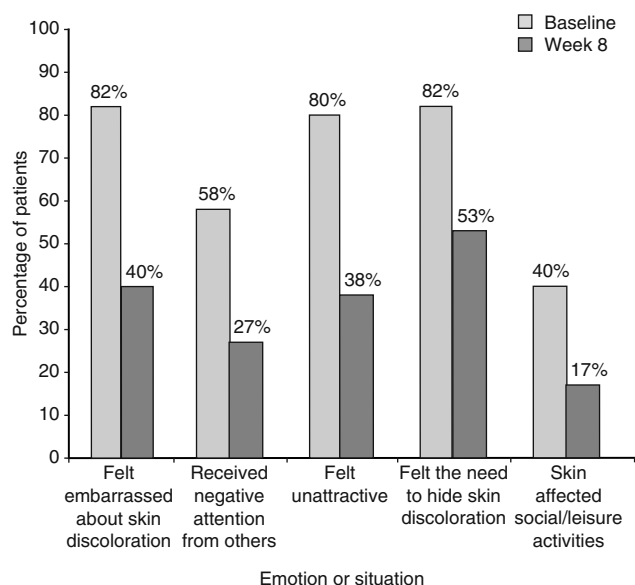


Fig. 3. Percentage of patients who experienced undesirable emotions or situations relating to their melasma at baseline and after 8 weeks of treatment with a tretinoin, hydroquinone, and fluocinolone acetone cream formulation in the PIGMENT (Prospective Investigation Gauging Melasma Reduction with a New Treatment) study.^[18]

points) in all facial regions. The MASI area score also decreased significantly across all Fitzpatrick skin types, with one exception observed on the chin of patients with skin type I.

According to the investigator's global evaluations, 66% of patients received an assessment of 'moderate to marked improvement,' 'almost clear,' or 'clear' at 4 weeks. By 8 weeks, the percentage of patients with these same ratings had increased to 75%. Furthermore, 82.1% of patients achieved some improvement by week 8.

A total of 348 patients (27%) reported at least one adverse event. The majority of these adverse events consisted of skin irritation, erythema, or dry skin. Only eight patients (1%) reported incidences of telangiectasia. No cases of atrophy or other serious adverse events were reported in the study. Forty patients (3.1%) discontinued the study because of mild or moderate skin irritation.

Because quality of life is a major concern for patients with facial melasma, patients participating in the PIGMENT study were asked to complete a health questionnaire to evaluate the impact of the disease on quality of life at baseline and following 8 weeks of treatment.^[22] The results of this questionnaire revealed that successful treatment of patients' melasma correlated with positive improvements in self consciousness about their skin, being scrutinized by others, feeling unattractive, using cosmetics to cover the hyperpigmentation, and limiting social or leisure activities be-

cause of the appearance of their skin. After 8 weeks of treatment with the triple combination cream, 60% of patients reported that they were not at all embarrassed or self conscious about their skin (baseline 18%), 73% said that others did not focus on their skin discoloration (baseline 42%), and 62% did not feel that their skin discoloration made them feel unattractive to others (baseline 20%). Only 3% of patients reported that they had to put in a lot of effort to hide their skin discoloration (baseline 18%) and only 1% of these patients said that their skin affected any social or leisure activities (baseline 5%) [figure 3].

5. Discussion

Historically, facial melasma has been a disease of concern for both patients and their physicians, primarily due to the devastating psychosocial effects of the condition and lack of effective treatments.^[18]

The studies presented in this review have demonstrated a favorable profile of a triple combination formulation containing 0.05% tretinoin, 4.0% hydroquinone, and 0.01% fluocinolone acetone. Two 8-week studies demonstrated the efficacy and short-term safety of the triple combination cream in the treatment of facial melasma,^[15] while two longer studies (a 12-month extension of the 8-week studies^[16] and a 12-month, open-label trial^[17]) demonstrated long-term use to be safe, effective, and tolerable for the treatment of melasma (tables II and III). In the 12-month extension study,^[16] the long-term safety evaluation of triple combination cream was conducted in >500 patients experiencing melasma. Of these 500 patients, >300 patients completed the study. Overall, triple combination cream, applied intermittently or continuously over a period of 1 year, demonstrated a safe profile in the treatment of facial melasma.^[15,17]

Two major concerns associated with prescription of long-term topical corticosteroids are the risks of skin atrophy and telangiectasia.^[23] In the large 12-month extension study,^[16] only two cases of skin atrophy were reported, and both cases were mild and did not result in discontinuation of the study drug. One of these cases had completely resolved by the end of the study and the other case remained unchanged. As demonstrated in previous studies,^[24,25] application of tretinoin can help prevent corticosteroid-induced atrophy, which accounts for the low incidence of skin atrophy seen in trials of the triple combination formulation. Furthermore, of the 23 patients (4%) who developed mild telangiectasia in the 12-month extension study, only two patients discontinued the study; 15 cases had improved or resolved by study end, leaving eight cases unchanged. The low incidence of telangiectasia, which

is commonly associated with use of corticosteroids over long periods, may be due to use of the low potency (class VI) corticosteroid fluocinolone acetonide.

The results of the PIGMENT trial^[18] demonstrated that the triple combination cream was significantly effective for the treatment of moderate to severe melasma. PIGMENT is the largest study to have enrolled a diverse ethnic population across the US, and therefore evaluated use of the triple combination cream in a sample that is representative of patients seen in clinical practice.

Overall, in the PIGMENT study, the triple combination cream formulation produced clinically significant clearing of melasma in 75% of patients within 8 weeks of treatment in all racial groups and Fitzpatrick skin types, with a low incidence of adverse events.^[18] Furthermore, positive improvements in quality of life correlated^[22] with successful treatment of melasma.

6. Conclusion

Major advances in the treatment of facial melasma have been achieved with the development of a triple combination cream consisting of 0.05% tretinoin, 4.0% hydroquinone, and 0.01% fluocinolone acetonide. Physicians and patients now have a safe and effective treatment with which to combat the condition of melasma.

Acknowledgments

The author has acted as a consultant for Galderma Laboratories LP, Intendis, Coria, and Barrier Therapeutics; as a speaker for Galderma Laboratories LP, Allergan, Novartis, Amgen, and Genentech; and as an investigator for Collagenex, Medicis, Stiefel, and Dermik. No sources of funding were used to assist in the preparation of this review.

References

- Grimes PE. Melasma: etiologic and therapeutic considerations. *Arch Dermatol* 1995; 131 (12): 1453-7
- Sanchez NP, Pathak MA, Sato S, et al. Melasma: a clinical, light microscopic, ultrastructural, and immunofluorescence study. *J Am Acad Dermatol* 1981; 4 (6): 698-710
- Kauh YC, Zachian TF. Melasma. *Adv Exp Med Biol* 1999; 455: 491-9
- Pathak MA, Fitzpatrick TB, Kraus EW. Usefulness of retinoic acid in the treatment of melasma. *J Am Acad Dermatol* 1986; 15 (4 Pt 2): 894-9
- Menter A. Rationale for the use of topical corticosteroids in melasma. *J Drugs Dermatol* 2004; 3 (2): 169-74
- American Academy of Dermatology. Dermatologists dis-'patch' dark side of melasma [online]. Available from URL: http://www.aad.org/public/News/News_Releases/Press+Release+Archives/Skin+Conditions/Melasma.htm [Accessed 2005 Dec 22]
- Taylor SC. Epidemiology of skin diseases in people of color. *Cutis* 2003; 71 (4): 271-5
- Balkrishnan R, McMichael AJ, Camacho FT, et al. Development and validation of a health-related quality of life instrument for women with melasma. *Br J Dermatol* 2003; 149 (3): 572-7
- Katsambas A, Antoniou C. Melasma: classification and treatment. *J Eur Acad Dermatol Venereol* 1995; 4: 217-23
- Engasser PG, Maibach HI. Cosmetic and dermatology: bleaching creams. *J Am Acad Dermatol* 1981; 5 (2): 143-7
- Kimbrough-Green CK, Griffiths CE, Finkel LJ, et al. Topical retinoic acid (tretinoin) for melasma in black patients: a vehicle-controlled clinical trial. *Arch Dermatol* 1994; 130 (6): 727-33
- Sanchez JL, Vazquez M. A hydroquinone solution in the treatment of melasma. *Int J Dermatol* 1982; 21 (1): 55-8
- Haddad AL, Matos LF, Brunstein F, et al. A clinical, prospective, randomized, double-blind trial comparing skin whitening complex with hydroquinone vs. placebo in the treatment of melasma. *Int J Dermatol* 2003; 42 (2): 153-6
- Griffiths CE, Finkel LJ, Ditre CM, et al. Topical tretinoin (retinoic acid) improves melasma: a vehicle-controlled, clinical trial. *Br J Dermatol* 1993; 129 (4): 415-21
- Taylor SC, Torok H, Jones T, et al. Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. *Cutis* 2003; 72 (1): 67-72
- 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 (5): 592-7
- Torok HM, Jones T, Rich P, et al. Hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%: a safe and efficacious 12-month treatment for melasma. *Cutis* 2005; 75 (1): 57-62
- Grimes P, Kelly AP, Torok H, et al. Community-based trial of a triple-combination agent for the treatment of facial melasma. *Cutis* 2006; 77 (3): 177-84
- Gano SE, Garcia RL. Topical tretinoin, hydroquinone, and betamethasone valerate in the therapy of melasma. *Cutis* 1979; 23 (2): 239-41
- Kang WH, Chun 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 (9): 587-96
- Berardesca E, Maibach H. Ethnic skin: overview of structure and function. *J Am Acad Dermatol* 2003; 48 (6 Suppl.): S139-42
- Balkrishnan R, Kelly AP, McMichael A, et al. Improved quality of life with effective treatment of facial melasma. *J Drugs Dermatol* 2004; 3 (4): 247-51
- Giannotti B, Melli MC. Current approaches to the treatment of melasma. *Clin Drug Invest* 1995; 10 Suppl. 2: 57-64
- Kligman LH, Schwartz E, Lesnik RH, et al. Topical tretinoin prevents corticosteroid-induced atrophy without lessening the anti-inflammatory effect. *Curr Probl Dermatol* 1993; 21: 79-88
- McMichael AJ, Griffiths CE, Talwar HS, et al. Concurrent application of tretinoin (retinoic acid) partially protects against corticosteroid-induced epidermal atrophy. *Br J Dermatol* 1996; 135 (1): 60-4

Correspondence and reprint requests to: Dr Helen M. Torok, Trillium Creek Dermatology Center, 5783 Outer Lake Road, Medina, OH 44526, USA.
E-mail: helenmtorok@aol.com