Community-Based Trial of a Triple-Combination Agent for the Treatment of Facial Melasma

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Melasma is a common hyperpigmentation disorder that is frequently recalcitrant to treatment. An 8-week, multicenter, open-label, community-based study evaluated a new therapeutic approach that combines tretinoin 0.05%, hydroquinone 4.0%, and fluocinolone acetonide 0.01% (RA+HQ+FA) in a hydrophilic cream formulation. The trial enrolled 1290 patients of diverse races/ethnicities with a full range of Fitzpatrick skin types (I through VI). The mean Melasma Area and Severity Index (MASI) decreased significantly at both weeks 4 and 8 compared with baseline in the overall study population and across all Fitzpatrick skin types and races/ethnicities (P<.0001). The mean MASI darkness and homogeneity scores likewise fell significantly at weeks 4 and 8 in all facial regions involved (forehead, right and left malar regions, and chin) and in all Fitzpatrick skin types (P<.0001). By week 8, investigators' global evaluations showed that 75% of patients had "moderate or marked improvement" or were "almost clear" or "clear." The study medication was found to be safe and well tolerated. The results of this study demonstrate that RA+HQ+FA produces significant rapid improvement of melasma across the range of patients seen in daily practice, including whites, Hispanics, blacks, Asians, American Indians, Alaskan natives, and Pacific Islanders.

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Melasma is a common acquired hypermelanosis that occurs primarily on sun-exposed areas of the face, neck, and forearms.[1] The etiology of melasma has been attributed to multiple factors (eg, pregnancy, oral contraceptives, estrogen-progesterone therapy, cosmetics, sun exposure, genetic and racial predilections), though the pathogenesis remains poorly understood.[2,3] Although the condition is found primarily in women, it also occurs in men. In all patients with melasma, the condition can have a serious adverse effect on quality of life by undermining social functioning and emotional well-being.[4] Unfortunately, melasma has continued to present a treatment challenge, as it is often recalcitrant to therapy.

Current approaches to the management of melasma include hypopigmenting agents (phenolic and nonphenolic derivatives), chemical peels, and some lasers, though pharmacologic therapy is the mainstay of treatment.[2,5] Hydroquinone, topical corticosteroids, azelaic acid, and tretinoin have been used alone or in various combinations.[5-16] A shortcoming of monotherapy has been the prolonged

duration of treatment required for patients to experience meaningful results. A study by Kligman and Willis[13] showed no substantial improvement in pigmentation observed after 3 months of treatment with hydroquinone, dexamethasone, or tretinoin alone. During the same time frame, however, satisfactory results were attained when these 3 agents were combined in a hydrophilic ointment. In a recent analysis of 2 well-controlled trials, significantly ($P<.001$) more patients achieved complete clearing of melasma after 8 weeks of treatment with a hydrophilic cream formulation combining tretinoin 0.05%, hydroquinone 4.0%, and fluocinolone acetonide 0.01% (RA+HQ+FA) than with the combination of any 2 of these agents.[17] To shed more light on the efficacy and safety of this formulation in the clinical practice setting, an open-label, community-based study was undertaken at multiple centers throughout the United States.

Methods

Study Design—The Prospective Investigation Gauging Melasma Reduction with a New Treatment (PIGMENT) trial was an open-label, community-based phase 4 study conducted by 393 investigators in the United States.

Patient Population—The trial enrolled men and women older than 18 years with Fitzpatrick skin types I through VI. The patients were required to have moderate to severe melasma of the face with macular lesions that were neither depressed nor atrophic. All participants provided informed consent.

Patients were excluded from the trial if they had used any of the following topical preparations or procedures on the face within the preceding 2 weeks: corticosteroids, glycolic acid, bleaching products, UV light therapy or sunbathing, topical retinoids, or scented cosmetics (medicated or nonmedicated). Also excluded were patients who had used corticosteroids or antibiotics within the preceding 4 weeks or certain other systemic preparations within the preceding 6 months (acitretin; etretinate; isotretinoin; methotrexate; or photoallergic, phototoxic, or photosensitizing drugs). Other exclusion criteria included immunocompromising conditions or the use of immunosuppressive therapy; significant endocrinologic disorders requiring contraindicated treatment with potent corticosteroids; concomitant treatment or facial skin conditions that would interfere with the study objectives or evaluations; and known sensitivities to any ingredient in the trial medication.

Treatment—The patients were instructed to apply a thin film of the triple-combination hydrophilic cream formulation (RA+HQ+FA) once daily, at night, at least 30 minutes before bedtime. Patients were instructed to rub the product lightly and uniformly on all hyperpigmented areas of the face and on one-half inch of normal-appearing skin surrounding each lesion.

Efficacy and Safety Assessments—The Melasma Area and Severity Index (MASI) was used to evaluate the efficacy of treatment at weeks 4 and 8. The severity of melasma was assessed on the basis of the MASI darkness score (measuring the shade of melasma lesions compared with the shade of the surrounding skin), the MASI homogeneity score (evaluating the uniformity of composition of the patient's hyperpigmentation), and the MASI area score (reflecting the size of the affected area). In addition, the investigators performed a Global Assessment of Improvement (using a 7-point scale, where 1=worse and 7=clear) at weeks 4 and 8. The change in quality of life was measured at week 8 using a patient health questionnaire.[18]

Safety variables, assessed at weeks 4 and 8, included local tolerance of treatment (occurrence of skin irritation, skin atrophy, or telangiectasia), serious adverse events, and nonserious adverse events.

Statistical Methods—Data tabulation and averages were used in lieu of statistical analyses. Analysis of variance was performed on the MASI score results.

Results

Patients—A total of 1290 patients were enrolled in the PIGMENT trial and were included in the safety analysis. Of this group, 1042 patients (80.8%) completed the study and were included in the efficacy analysis. Among the 248 patients (19.2%) who discontinued the study, the reasons for discontinuation were as follows: lost to follow-up (11.4%), adverse events (3.1%), clearing of melasma (1.3%), patient request (1.5%), pregnancy (0.3%), and treatment failure (0.5%). The reason for discontinuation was not reported in 1.2% of the group.

The patients enrolled in the study ranged from 15 to 84 years of age and were predominantly female (96.2%). Demographic characteristics are summarized in Table 1. All Fitzpatrick skin types were represented (Table 2).

Efficacy—All 1290 patients had at least one application of RA+HQ+FA cream during the 8-week duration of the trial. When questioned at week 4, 1131 patients (88%) indicated that they had complied with the treatment regimen. A total of 1043 patients (81%) reported compliance at week 8.

As shown in Figure 1, the mean overall MASI score in the study population decreased significantly at both weeks 4 and 8 compared with baseline (7.38 and 3.64 vs 14.68, respectively; $P<.0001$ for both

Table 1.

Patient Demographics

Variable	Patients (N=1290)
Age, y	(n=1289)
Mean±SD	43.50±10.28
Range	15–84
Gender, n (%)	(n=1287)
Male	46 (3.6)
Female	1241 (96.4)
Race, n (%)	(n=1290)
White	800 (62.0)
Hispanic	204 (15.8)
Black	130 (10.1)
Asian	94 (7.3)
American Indian/ Alaskan native/ Pacific Islander	14 (1.1)
Other	43 (3.3)
Not reported	5 (0.4)

time points). Significant decreases were apparent at both time points across all Fitzpatrick skin types and all races or ethnicities ($P<.0001$ for all subgroups; Table 3).

The mean MASI darkness score and mean MASI homogeneity score (Figure 2) likewise decreased significantly at weeks 4 and 8 compared with baseline ($P<.0001$ for both variables at both time points) in all facial regions of interest (forehead, right and left malar regions, and chin). The mean MASI area score also decreased significantly from baseline to weeks 4 and 8 ($P<.0001$ for both time points) in all regions of interest. The decrease was significant across all Fitzpatrick skin types (with the exception of the chin in patients with skin type I).

The investigators' global evaluations found that 66% of patients achieved an assessment of "moderate to marked improvement," "almost clear," or "clear" at week 4. By week 8, 75% of patients had attained these ratings. The proportion of patients achieving some type of improvement ("slight improvement" to "clear") at week 8 was 82%.

Safety—Treatment with RA+HQ+FA was well tolerated. A total of 348 patients (27%) reported at least one adverse event. The majority of adverse events were related to the skin, most commonly consisting of skin irritation, erythema, or dry skin. Telangiectasia occurred in only 8 patients (<1%). No atrophy, serious adverse events, or deaths were reported.

Table 2.

Distribution of Fitzpatrick Skin Types*

Fitzpatrick Skin Type	Definition	Patients, n (%) (n=1260)
I	Always burns easily; never tans	21 (1.7)
II	Always burns easily; tans minimally and with difficulty	213 (16.9)
III	Burns minimally; tans gradually and uniformly (light brown)	415 (32.9)
IV	Burns minimally; always tans well (moderate brown)	346 (27.5)
V	Rarely burns; tans profusely (dark brown)	191 (15.2)
VI	Rarely burns; tans deeply (black); tans profusely	72 (5.7)
Not reported		2 (0.2)

*Interestingly, melasma was equally common in skin types I to III (lighter complexions) and skin types IV to VI (darker complexions).

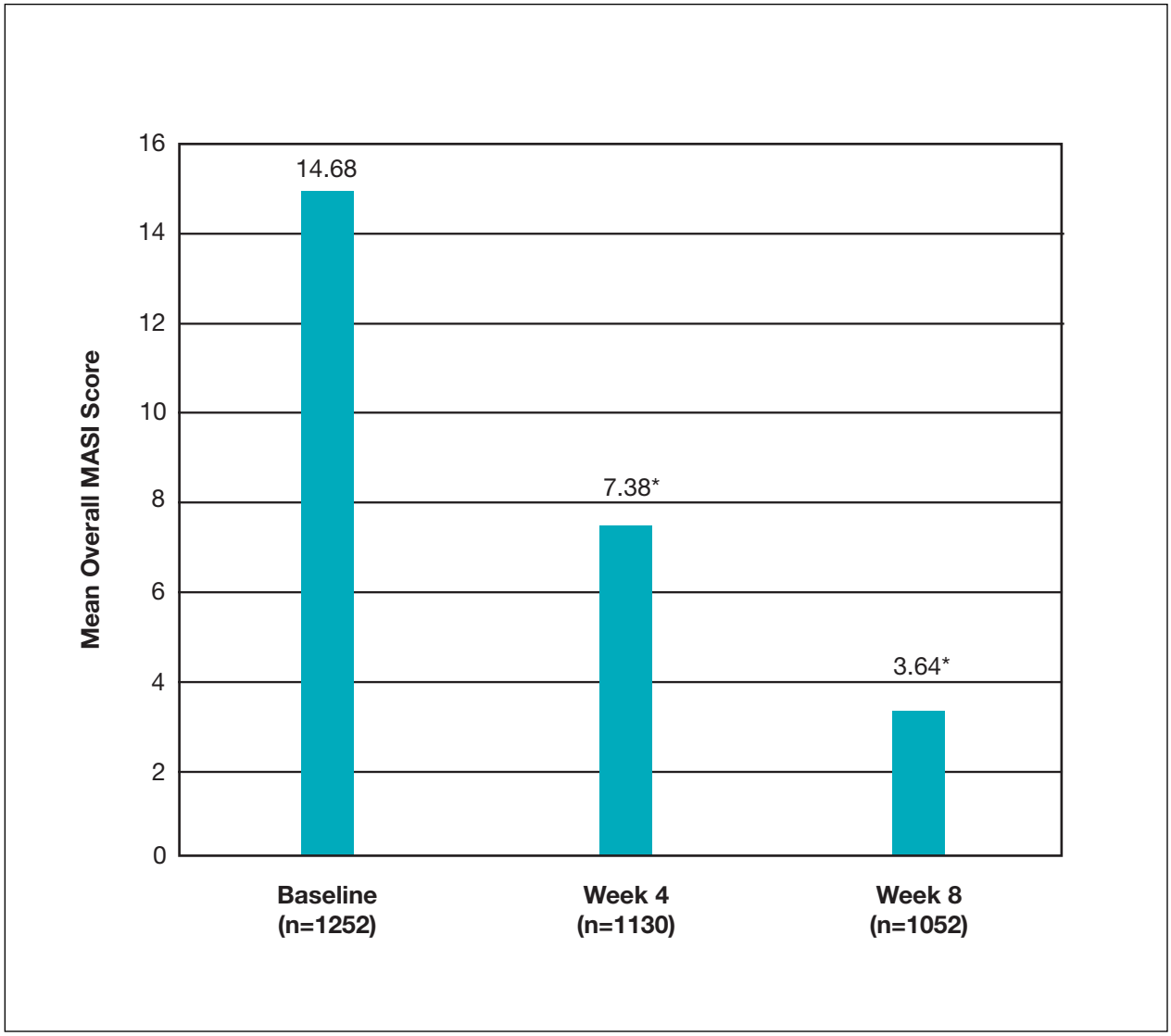

Figure 1. Change in mean overall Melasma Area and Severity Index (MASI) score. Asterisk indicates *P*<.0001 vs baseline.

Only 40 patients (3%) discontinued the study because of adverse events. These events were generally mild or moderate and most often involved skin irritation. The relationship to study medication was deemed probable or highly probable in most cases.

Comment

The PIGMENT trial demonstrated that RA+HQ+FA is significantly effective for the treatment of moderate to severe melasma (*P*<.0001). These results are particularly noteworthy in view of the fact that PIGMENT was the largest study of melasma conducted to date. Moreover, the trial enrolled a diverse population from across the United States that represented the range of patients seen in clinical practice, including whites, Hispanics, blacks, Asians, American Indians, Alaskan natives, and Pacific Islanders.

The therapeutic effect was significant with regard to all objective measures of efficacy (overall MASI score, MASI darkness score, MASI homogeneity score, and MASI area score) in all facial regions involved, Fitzpatrick skin types, and races/ethnicities. Notable improvement was also apparent on investigators' global assessments, which revealed that 75% of patients had moderate improvement to total clearing of the condition after 8 weeks of treatment.

A previous analysis of data from two 8-week, multicenter, randomized, investigator-blinded trials

Table 3.

Change in Mean Overall Melasma Area and Severity Index Score by Fitzpatrick Skin Type and Race/Ethnicity

Variable	n	Improvement, %*	
		Week 4	Week 8
Fitzpatrick skin type	1260†		
I	21	55	85
II	213	53	77
III	415	50	77
IV	346	50	75
V	191	46	70
VI	72	49	73
Race/ethnicity	1260		
White	708	50	78
White/Hispanic	75	50	73
Hispanic	204	50	74
Black	123	51	73
Black/Hispanic	3	73	95
Asian	89	54	67
American Indian/ Alaskan native/ Pacific Islander	14	46	71
Other	44	57	75

*$P<.0001$ for all changes from baseline.
†Data not reported for 2 patients.

likewise found that the RA+HQ+FA formulation was significantly ($P<.001$) effective for the treatment of moderate-to-severe melasma across the range of Fitzpatrick skin types I through IV.[17] The 641 patients in these studies were randomized to receive RA+HQ+FA or the dual combinations of RA+HQ, RA+FA, or HQ+FA in the same drug concentrations. Complete clearing (the primary endpoint) occurred in significantly more patients treated with the triple combination than with the 3 other treatments (28.6% vs 10.1%, 1.9%, and 3.1%, respectively; $P<.0001$ for all comparisons). A 75% reduction in melasma/pigmentation was observed in more than 70% of patients receiving RA+HQ+FA as opposed to 30% of those receiving dual-combination treatments.[17] The results of the present study not only are consistent with these findings but also extend the observation of benefits with RA+HQ+FA to the community setting.

The high degree of efficacy observed with RA+HQ+FA may reflect the ability of each of the 3 components to address different factors involved in the pathophysiology of melasma.[13,19,20] This combination also provides for rapid clinical improvement, unlike single-agent therapy. In the present study, the majority of patients exhibited marked

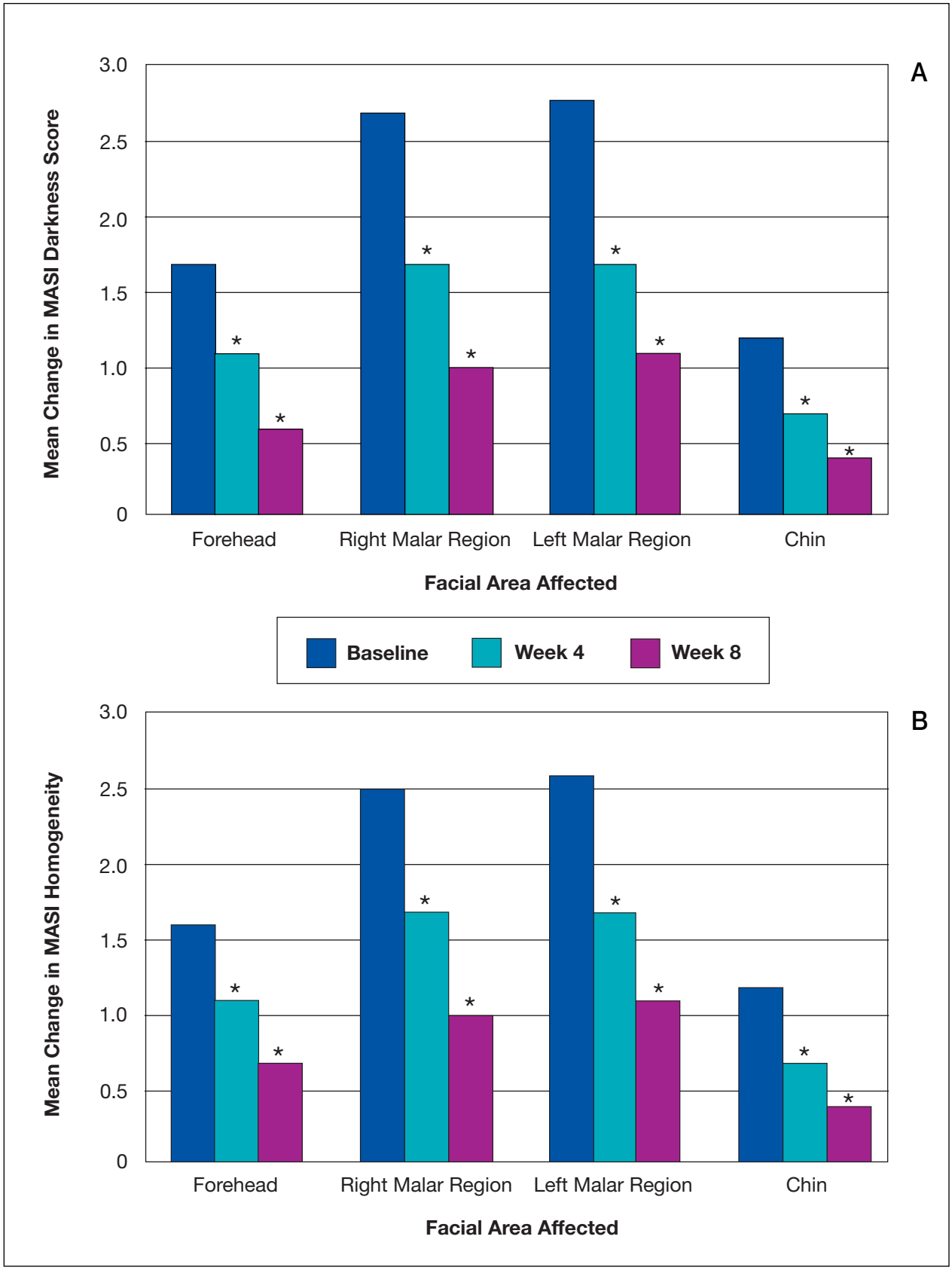

Figure 2. Mean change in Melasma Area and Severity Index (MASI) darkness score (A)(n=1260) and MASI homogeneity score (B)(n=1260) from baseline to week 4 and week 8. Asterisk indicates $P<.0001$ vs baseline.

improvement as early as 4 weeks after starting treatment and showed further improvement at 8 weeks.

This study found that RA+HQ+FA was safe and well tolerated, with nearly all adverse effects being mild or moderate in severity. Of the 1290 patients enrolled, 27% reported at least one adverse event, and 3.1% discontinued because of an adverse event. The most common adverse events reported were skin related (29.9%), for example, skin irritation (6%), erythema (5.7%), and dry skin (3.6%). No serious adverse events occurred, and few patients withdrew from the study because of untoward effects.

A favorable safety profile also was confirmed in the 2 randomized trials of RA+HQ+FA, which reported that treatment-related adverse events were typically mild and primarily consisted of erythema, desquamation, burning, dryness, or pruritus.[17] In addition, the long-term safety and tolerability of RA+HQ+FA has been demonstrated in a 12-month, open-label extension trial in which 569 patients with facial melasma were treated.[21] Overall, the adverse events were application-site reactions and were mild and transient in nature, not requiring any therapy. RA+HQ+FA was well tolerated, and only 14 patients (2.5%) discontinued the study because of treatment-related adverse events.[21]

Some observers have expressed concern about treating melasma with corticosteroids because of an increased risk of skin atrophy and telangiectasia.[5] Importantly, however, work in both animals and humans has demonstrated that the addition of a retinoid (as in the RA+HQ+FA formulation) can lessen this risk, while preserving the anti-inflammatory effects of corticosteroids.[22-25] Some investigators have suggested that this benefit of topical retinoids may be related to the retinoid's ability to partially prevent corticosteroid-induced reductions in collagen synthesis, to induce collagen synthesis, or to induce hyperplasia of the epidermal cells.[17,22,25] No skin atrophy was reported in the present study, and telangiectasia occurred in only 1% of patients. In the 2 randomized trials of RA+HQ+FA, no skin atrophy was observed[17] and the rate of telangiectasia was only 3%.[21] Most cases of telangiectasia were mild and occurred in patients who had this condition before enrollment in the trial.

Conclusion

In conclusion, the RA+HQ+FA cream formulation produces clinically significant clearing of melasma in many patients by week 4, with benefits also apparent at week 8 ($P<.0001$). Significant efficacy is achieved across all racial groups and Fitzpatrick skin types, with a minimal risk of adverse effects ($P<.0001$). The RA+HQ+FA formulation represents an important new therapeutic option for the difficult-to-treat condition of melasma.

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