EFFICACY AND SAFETY OF A NEW FORMULATION FOR THE TREATMENT OF CUTANEOUS MELASMA


BACKGROUND

Cutaneous melasma is a relatively common dermatological disease, occurring in an estimated 5 to 6 million women in the U.S. Approximately 10% of cases occur in men who experience the same clinical and histological characteristics seen in females.

Therapy for melasma remains a challenge. Current approaches involve the use of pharmacological agents, chemical peeling, and laser treatment. Pharmacological treatments are the mainstay. However, monotherapy is often associated with suboptimal results.

The combination of tretinoin, hydroquinone, and fluocinolone acetonide steroids demonstrates synergistic actions for treating cutaneous melasma. A formulation, RA + HQ + FA, contains tretinoin 0.05%, hydroquinone 4.0%, and fluocinolone acetonide 0.01% in a hydrophilic cream base. This new formulation was designed to minimize adverse reactions seen with past formulations, to simplify usage, and to give a predictable response.

OBJECTIVE

The primary objective of the double-blind, randomized studies was to compare the efficacy and safety of the once-daily administration of the triple combination agent, RA + HQ + FA, to the following three dual combinations, all in the same vehicle: tretinoin 0.05% plus fluocinolone acetonide 0.01% (RA + FA); hydroquinone 4.0% plus fluocinolone acetonide 0.01% (HQ + FA); tretinoin 0.05% plus hydroquinone 4.0% (RA + HQ). The primary objective of the 12-month open-label extension trial was to assess long-term local and systemic safety of this formulation.

METHODS

The clinical evaluation of RA + HQ + FA was based on two multicenter, randomized, double-blind, parallel-group studies involving 641 predominantly female, adult patients with moderate to severe melasma and skin phototypes I through IV. The primary efficacy endpoint involved the proportion of intent-to-treat patients in each treatment group who achieved complete clearing at week 8. The secondary endpoints involved the proportion of intent-to-treat patients in each treatment group who achieved complete or near-complete clearing (ie, mild residual hyperpigmentation) at week 8, as well as the proportion of patients who achieved improvement from baseline severity. The integrated results of the 2 studies are presented here.

In addition, a 12-month multicenter, open-label extension trial of these previous two studies was also initiated. The main objective of this extension trial was to provide long-term safety data, though efficacy data was also obtained. Five hundred eighty-five patients were enrolled in this trial to ensure an adequate number of evaluable patients at the end of the 12-month period. This extension trial involved two groups of patients: those who had experienced satisfactory resolution of melasma (eg, a melasma severity score of 0 to 1) in the previous double-blind, randomized trials and those who did not achieve satisfactory results in the previous trials. The first group of patients was followed every 2 months and retreated as necessary. When the investigator and patient judged that further treatment was necessary, the patient could begin a RA + HQ + FA QO treatment regimen and continue treatment until satisfactory resolution (a melasma severity score of 0 to 1) or lack of response (melasma severity score >1) was observed. Treatment could occur at any time during the 12-month trial. The second group of patients was treated according to the RA + HQ + FA treatment regimen when they entered the continuation trial; these patients followed the same protocol as the first group. The interim efficacy and safety results of this continuation trial are also presented here.

EFFICACY RESULTS

Double-blind, randomized trials

Significantly more of the RA + HQ + FA treated patients experienced complete clearing compared to each of the dual-therapy groups at week 8 (29% vs 10% for RA + HQ, 2% for RA + FA, and 3% for HQ + FA, P<0.001). Significantly more of the RA + HQ + FA treated patients experienced complete or near-complete clearing compared to each of the dual-therapy groups (71% vs 43% for HQ + FA, 27% for RA + FA, and 43% for RA + HQ, P<0.001).

Improvement from baseline severity occurred in all treatment groups. However, the greatest improvement occurred in the RA + HQ + FA group. Among the 124 patients in the triple therapy group who had melasma of moderate severity at baseline, 35 (22%) experienced clearing at 8 weeks, while an additional 63 patients (39%) who started with moderate melasma had only mild melasma. Eighteen patients (11%) in the triple combination group who had severe melasma did not show any change from baseline at 8 weeks. Of the 37 patients in the RA + HQ + FA group with severe melasma at baseline, 6 (17%) demonstrated clearing at 8 weeks while an additional 11 patients (30%) had melasma of mild severity at 8 weeks. Nineteen of the 37 patients with severe disease at baseline (51%) had moderate disease at the end of the study, while two of the patients with severe disease at baseline (12%) evidenced the same level of severity at the end of the study.

According to investigators’ assessment, patients treated with RA + HQ + FA demonstrated gradual improvement throughout the 8-week study with the greatest improvement occurring after at least 4 weeks of treatment. After 4 weeks of treatment, approximately 50% of patients demonstrated a 50% to 15% improvement compared to baseline, after 8 weeks, more than 95% of patients showed such improvement. This same improvement was significantly greater than any of the dual-therapy groups (P<0.001).

Open-label extension trial: interim data

By 10 months, the percentage of patients who evidenced improvement in melasma symptoms was 48.5% (153/315). The number of patients whose melasma had cleared increased from 38 patients (20%) at the start of the open-label extension to 86 (20%) by the end of 10 months. According to physician’s global assessment, only 17% of patients (41 patients) experienced significant hyperpigmentation at month 10 compared to 27% (125 patients) at month one. In the event of a patient relapse, the length of treatment time was reduced when RA + HQ + FA cream was re-introduced.
TRIPLE COMBINATION AGENT OF FACIAL MELASMA

Comparison at 8 Weeks.

SAFETY

Double-blind, randomized trials
Application site erythema, desquamation, burning, dryness, and pruritus were the most frequently occurring adverse events in the RA + HQ + FA treatment group. None incidence of dermal atrophy was reported with RA + HQ + FA. The majority of adverse events in all treatment groups were mild in severity. Only application site adverse events were considered by the investigators to be treatment-related.

No patients in the RA + HQ + FA group discontinued treatment due to adverse events.

Open-label extension trial: interim data
The majority of treatment-related adverse events were of mild severity at the end of 12 months (Table). No increase in severity of adverse events was observed with long-term use. Only 28 out of 569 patients discontinued the study due to adverse events at the end of 12 months; only 16 of these adverse events were considered by the investigator to be probably or possibly drug-related. No clinically important changes in laboratory parameters were noted. Overall, RA + HQ + FA demonstrated a favorable safety profile in 569 patients, including 314 patients treated for 5 months or more and 172 patients treated for 12 months.

REFERENCES


CONCLUSION

RA + HQ + FA is a formulation using 3 well-established agents for the safe treatment of melasma. The combined results of two well-controlled clinical trials demonstrate that this triple formulation was significantly more effective in achieving complete or near complete clearing of melasma than any of the dual combination products tested. The interim results of the extension trial demonstrate that RA + HQ + FA is practical and well-tolerated. Thus, RA + HQ + FA is a safe and effective agent for melasma of the face. This triple combination product poses no additional risks compared to its individual drug components.

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