Successful Treatment of Moderate to Severe Melasma With Triple-Combination Cream and Glycolic Acid Peels: A Pilot Study

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Triple-combination (TC) cream is a stable combination of fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%, and currently is the only US Food and Drug Administration–approved drug for the topical treatment of melasma. Furthermore, it is the only US Food and Drug Administration–approved product containing hydroquinone. Anecdotal evidence suggests that improvements in melasma can be achieved with a multifactor approach involving TC cream with a variety of procedures. A pilot study was designed to evaluate the efficacy and safety of sequential treatment with TC cream and a series of glycolic acid (GA) peels in participants with moderate to severe melasma. Participants were treated with TC cream for 2 weeks before the alternating sequential treatment cycles with TC cream and GA peels began. A total of six 2-week cycles of TC cream and 5 GA peels were used. Efficacy and safety evaluations were conducted at weeks 6 and 12. Investigator global assessment (IGA) ratings indicated that 1 of 20 participants (5%) had achieved treatment success (clear/almost clear) as early as week 6 and most participants had achieved treatment success by week 12 (65% [13/20]; P<.001 vs baseline). Objective absorption spectrometry measurements of the difference in melanin for involved versus uninvolved skin confirmed that hyperpigmentation was significantly reduced in participants at weeks 6 and 12 compared with baseline (P<.001 for both). Investigator and participant evaluations revealed that most participants (≥90%) showed improvement (excellent improvement, much improved, improved) by week 12 with alternating sequential treatment with TC cream and GA peels. Furthermore, the results of this study indicated that sequential treatment with TC cream and GA peels was well-tolerated.

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Melasma is a difficult-to-treat condition characterized by areas of hyperpigmentation on the face and neck.[1] This disease historically has been underdiagnosed and undertreated because it is considered a cosmetic nuisance rather than a skin disorder.[1,2] Melasma is most prominent in women, and it has been reported that 5 to 6 million women in the United States have this condition.[1] Some suspected etiologic factors associated with the pathogenesis of melasma include UV exposure, hormonal therapies, cosmetics, phototoxic drugs, and antiseizure medications.[3]

The frequent recurrence of hyperpigmentation following treatment of melasma makes therapy for the condition challenging.[4] Therapy with the depigmenting agent hydroquinone, either as a single agent or in combination with other agents, has been used with variable success.[4-8] A triple-combination (TC) cream containing fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05% was developed for the treatment of melasma and represents the only stable TC agent commercially available.[9,10] Triple-combination cream is the only US Food and Drug Administration–approved hydroquinone-containing product, and prior studies have demonstrated the efficacy and safety of TC cream for short-term and intermittent long-term (up to 6 months) treatment of melasma.[9,11,12] In one study, 92 participants were treated with TC cream for more than 360 days without changing the adverse-event profile in comparison with shorter treatment courses.[11] The efficacious contributions of the 3 components in TC cream have been known for more than 3 decades and were first reported by Kligman and Willis.[13] In addition, prior evaluations have suggested that improvements in melasma can be achieved by using TC cream with a variety of procedures such as chemical peels and laser treatments.[2,4,14,15] This pilot study was designed to evaluate the efficacy and safety of sequential treatment with TC cream and a series of glycolic acid (GA) peels in participants with moderate to severe melasma.

Participants and Methods

An open-label study was conducted in participants 18 years and older with moderate to severe melasma. Participants receiving concurrent medication must have been on a stable dose for at least 3 months prior to enrollment and throughout the study. Participants received sequential treatment with TC cream and GA peels. Initially, participants were treated with TC cream for 2 weeks. The participants discontinued using the TC cream 2 days before the GA peel and resumed the next 2-week cycle of TC cream 2 days after the GA peel. A total of six 2-week cycles of TC cream were administered and 5 GA peels (weeks 2, 4, 6, 8, 10) were performed.

Efficacy and safety evaluations were conducted at weeks 6 and 12. The severity of melasma was determined by the investigator global assessment (IGA) based on a 5-point scale, with success defined as a score of 0 or 1 (clear or almost clear). *P* values comparing end-of-treatment scores with baseline scores and comparing week 12 scores with week 6 scores were determined using the Wilcoxon signed rank test. The exact binomial test was used to compare success rates to zero, the sign test was used to compare the week 12 success rates with the week 6 success rates, and exact 95% confidence intervals (CIs) were constructed for the success rates. The degree of hyperpigmentation (melanin index) was objectively determined using the Skin Pigmentation Analyzer® SPA 99. This instrument provides an objective absorption spectrometry measurement of hyperpigmentation by measuring both melanin and erythema. The difference score represents the difference in the melanin index between an involved (melasma) site and an adjacent uninvolved site. *P* values comparing difference scores with baseline difference scores were determined using mixed-effects regression analysis. Additionally, investigators and participants made subjective evaluations of improvement of treatment areas at each postbaseline visit before receiving the GA peels. These evaluations were based on a 5-point scale, with excellent improvement defined as clear or almost clear with significant clearance of hyperpigmentation (≥90%); much improved was defined as 50% to 75% clearance of hyperpigmentation. All analyses were conducted using the SAS® software version 9.1.

Cutaneous tolerability assessments including evaluations of erythema, scaling, dryness, stinging/burning, edema, and telangiectasia associated with TC cream treatment were conducted prior to GA peels, and assessments of erythema, desquamation, pruritus, and burning sensation associated with GA peels were conducted after the GA peels. Reports of cutaneous irritation were scored on a 4-point scale (none, mild, moderate, severe). Adverse events were reported and evaluated for severity and relatedness to the study treatments (both TC cream applications and GA peels).

Efficacy data were evaluated in the intention-to-treat population, which consisted of the entire population enrolled (individuals assigned a participant number). Safety data were evaluated in the safety population, which consisted of any participant who received at least one dose of TC cream study medication.

This study was approved by an institutional review board and informed consent was given by all participants.

Results

Twenty participants were enrolled in this pilot study. Most participants were female (95%; 19/20) and Hispanic or Latino (65%; 13/20). There was an even distribution of participants among the various Fitzpatrick skin type categories, with 25% (5/20) of participants with skin type II, 15% (3/20) with skin type III, 20% (4/20) with skin type IV, 35% (7/20)

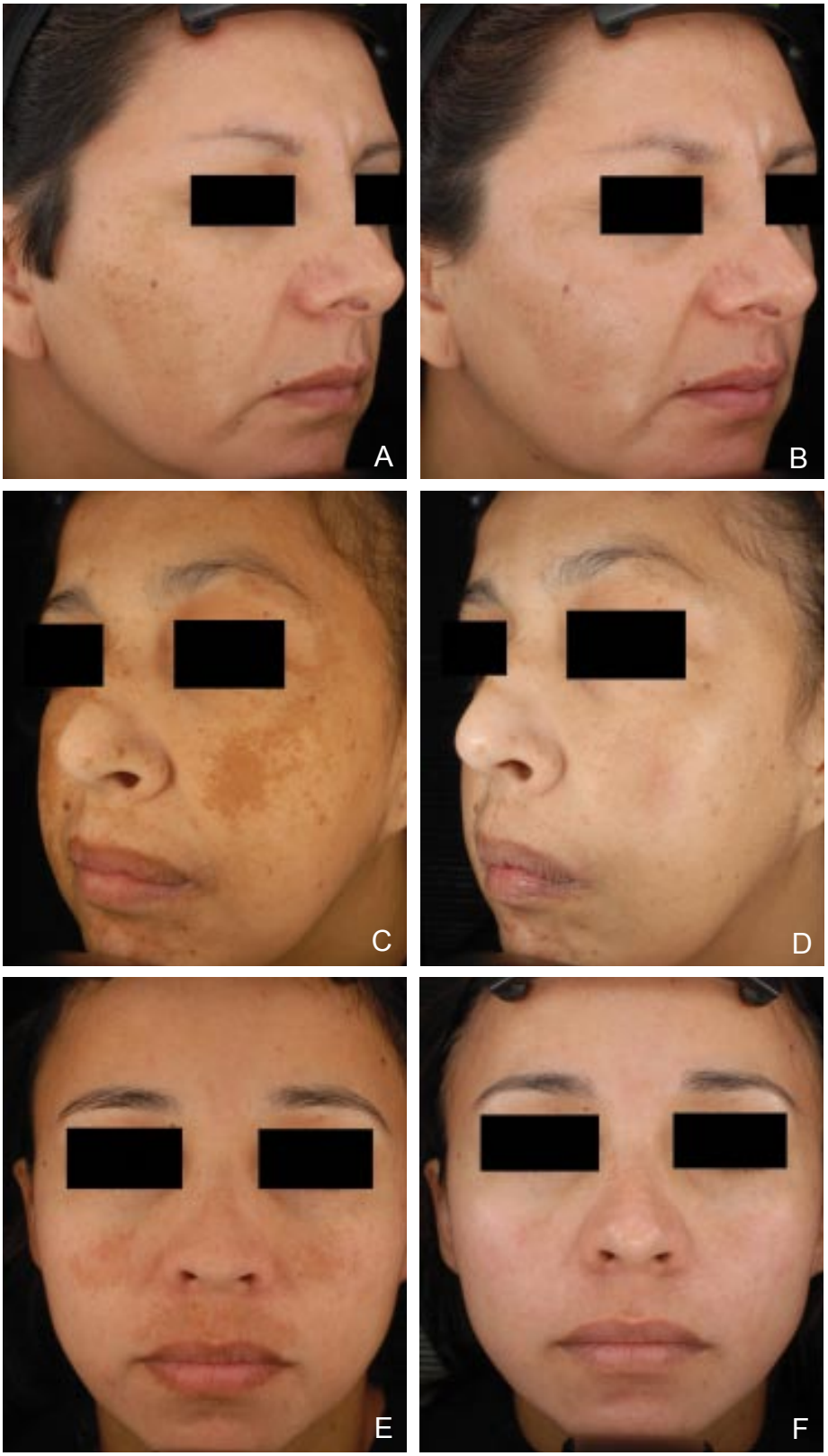

Figure 1. Participant photographs at baseline and at week 12 of treatment, demonstrating successful treatment of melasma with sequential triple-combination cream and glycolic acid peels. A 39-year-old participant with Fitzpatrick skin type V before (A) and after (B) treatment. A 42-year-old participant with Fitzpatrick skin type V before (C) and after (D) treatment. A 37-year-old participant with Fitzpatrick skin type IV before (E) and after (F) treatment.

with skin type V, and 5% (1/20) with skin type VI. The mean age (SD) of the participants in the intention-to-treat population was 43.2 (7.62) years, with a median duration of melasma of 6.5 years (range, 1–20 years). Eighty-five percent of the participants (17/20) completed the study.

Representative participant photographs illustrate the successful treatment of melasma with sequential TC cream and GA peels (Figure 1). In this pilot study, encouraging results were seen with a shift from moderate/severe IGA ratings at baseline (100%) to clear/almost clear IGA ratings at week 12, which indicated that 65% (13/20; 95% CI, 40.78%-84.61%) of participants had achieved treatment success (Figure 2). This change in distribution of the study population from the end of treatment compared with baseline was significant ($P<.001$). The week 12 success rate also was significantly different from the week 6 success rate ($P<.001$). At week 6, 1 participant (5%; 95% CI, 0.13%-24.87%) achieved almost clear results.

Objective absorption spectrometry measurements of the difference in melanin for involved versus uninvolved skin (difference score is the difference in the melanin index) indicated that hyperpigmentation was significantly reduced in participants at weeks 6 and 12 compared with baseline ($P<.001$ for both)(Figure 3). At baseline, the mean difference score was 8.3 (95% CI, 5.69-10.91), which was reduced to 4.2 at week 6 (95% CI, 2.33-6.14) and further reduced to 2.8 at week 12 (95% CI, 0.62-4.91). Investigator and participant assessments indicated that 90% of participants or more showed improvement (excellent improvement, much improved, improved) at weeks 6 and 12 with sequential TC cream and GA peels (Figure 4). Investigator evaluations indicated that by week 12, 50% (10/20) of participants had excellent improvement while 30% (6/20) were much improved and 15% (3/20) were improved. Participant evaluations indicated that by week 12, 30% (6/20) of participants had excellent improvement while

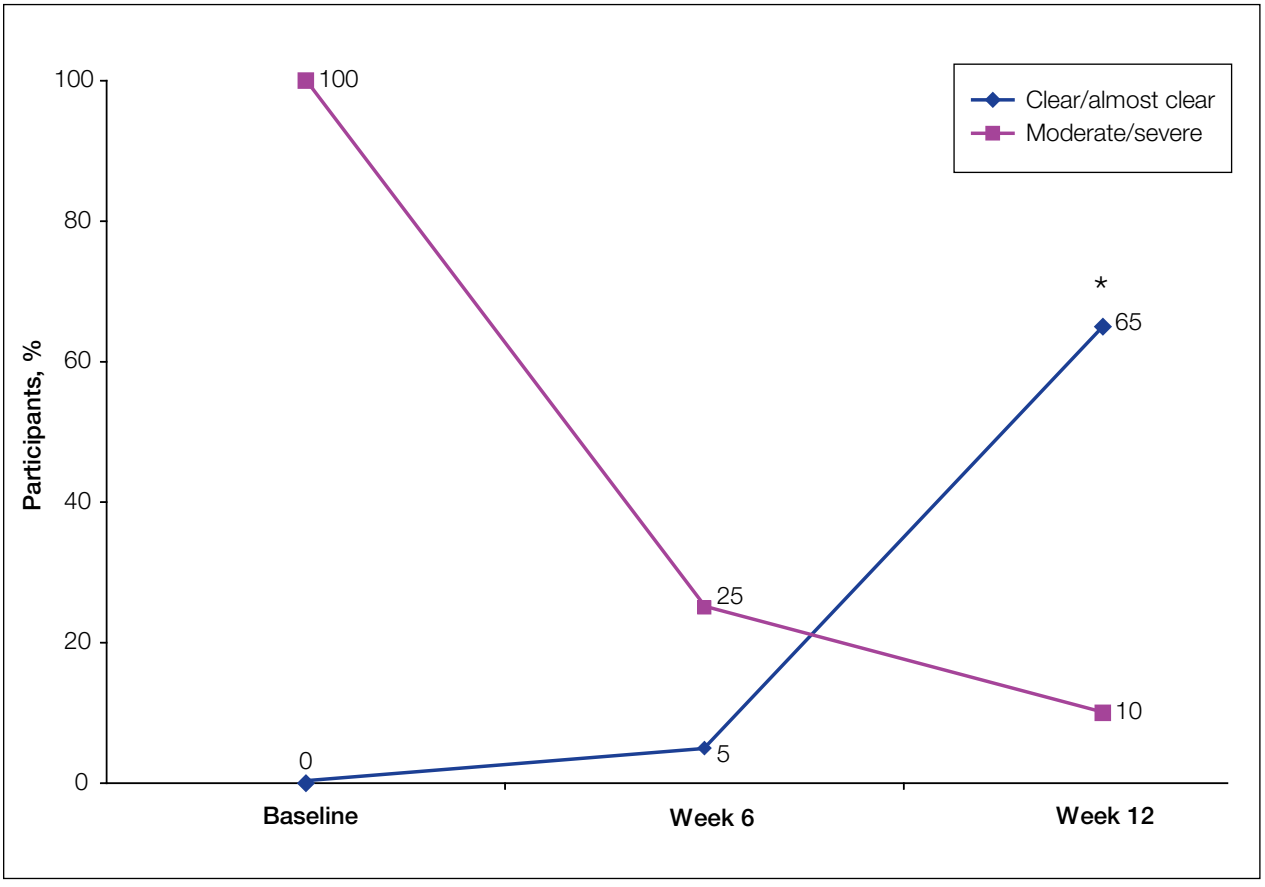

Figure 2. Shift to treatment success in the intention-to-treat population. Investigator global assessment was based on a 5-point scale, with success defined as a score of 0 or 1 (clear or almost clear). Asterisk indicates $P<.001$ (week 12 success rate vs week 6 success rate). The week 6 success rate was 5% (1/20; 95% confidence interval [CI], 0.13%-24.87%) and the week 12 success rate was 65% (13/20; 95% CI, 40.78%-84.61%).

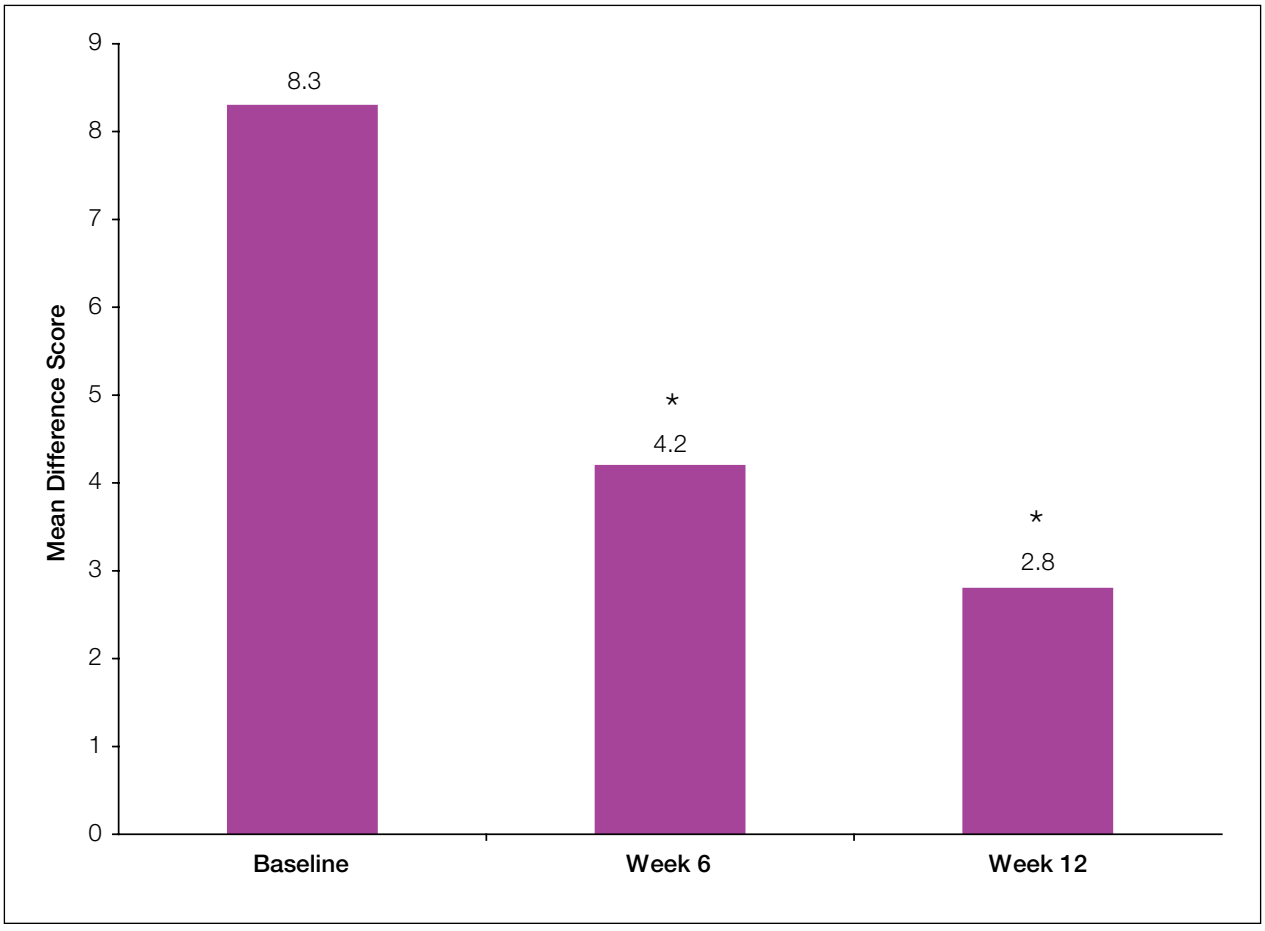

Figure 3. Difference in melanin for involved versus uninvolved skin in the intention-to-treat population. The melanin index measured the degree of hyperpigmentation using the Skin Pigmentation Analyzer® SPA 99. The difference score represents the difference in the melanin index between an involved (melasma) site and an adjacent uninvolved site. Asterisk indicates $P<.001$ (difference score vs baseline difference score). Comparison of difference score at week 12 with difference score at week 6 was not statistically significant ($P\geq.05$). The baseline mean difference score was 8.3 (95% confidence interval [CI], 5.69-10.91), the week 6 mean difference score was 4.2 (95% CI, 2.33-6.14), and the week 12 mean difference score was 2.8 (95% CI, 0.62-4.91).

45% (9/20) were much improved and 20% (4/20) were improved.

The tolerability assessments of cutaneous irritation for TC cream were reported to be between none and mild in severity. None of the cutaneous irritation was reported as severe. Tolerability assessments for GA peels were mild to moderate with some being assessed as severe by the investigator. A total of 11 adverse events were reported by 8 participants. All of these events were mild (100%) in severity, with 91% (10/11) of the events possibly, probably, or definitely related to at least one of the study treatments (TC cream or GA peels).

Comment

There are few US Food and Drug Administration–approved modalities available for the treatment of melasma.[5,7] Although there are no widely accepted combination regimens for the treatment of melasma, some therapies reported in the literature include drug treatment in conjunction with procedures such as chemical peels, microdermabrasion, and/or laser treatments.[16] Prior studies have suggested that an approach involving TC cream with other treatments may result in clinically significant improvements in melasma.[2,4,14,15] Furthermore, Kligman and Willis[13] reported that there were benefits from the effects of all 3 components of their formulated cream containing hydroquinone, tretinoin, and a topical corticosteroid. They asserted that tretinoin induced changes in the skin barrier and facilitated the penetration of the hydroquinone component.[13] It also was reported that the corticosteroid component reduced the retinoid-induced irritation, and the retinoid normalized the skin thinning seen with the corticosteroid component.[13,17] In addition, it has been

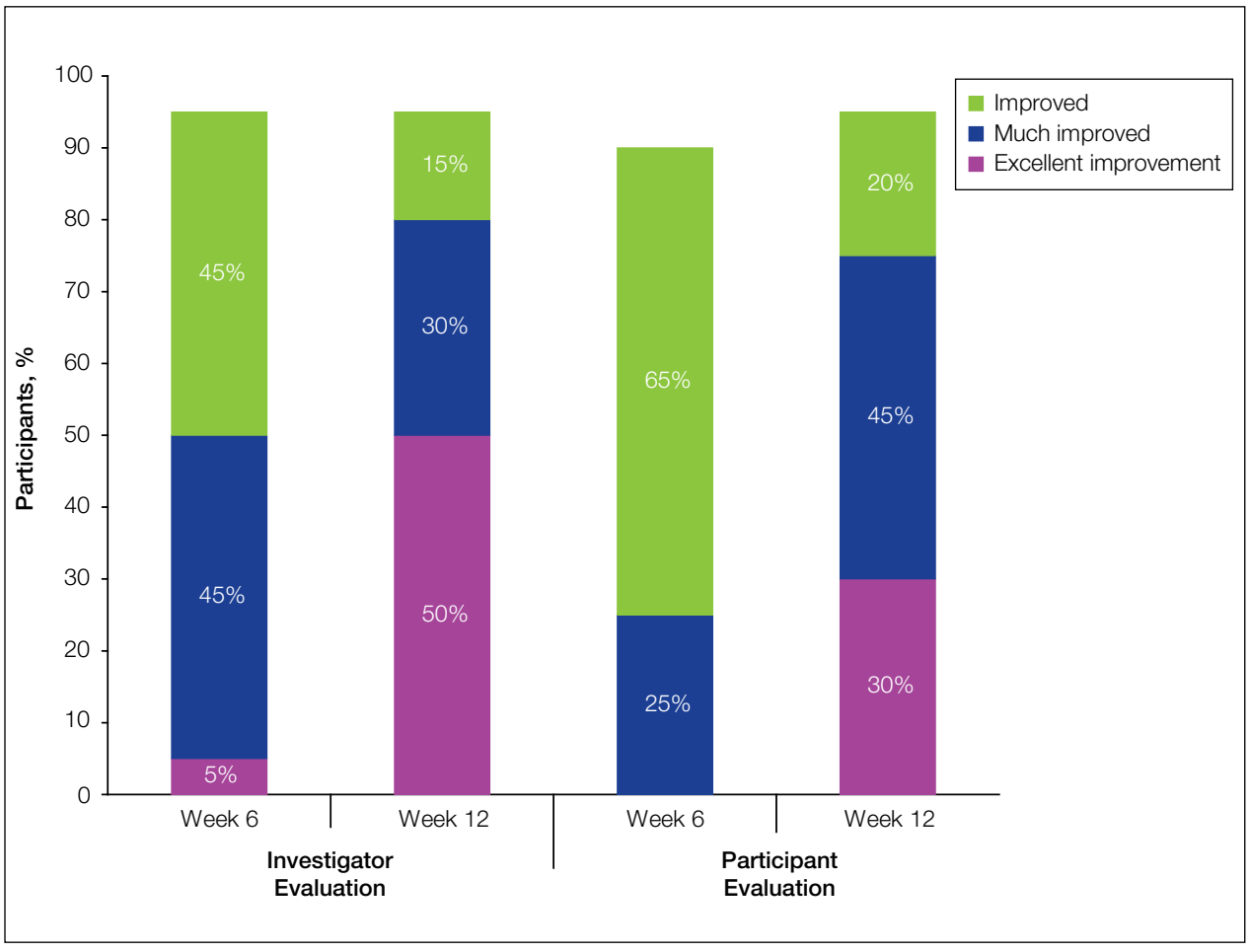

Figure 4. Subjective evaluations of improvement made by both investigators and participants. Improvement was shown in 90% of participants or more at weeks 6 and 12 by both investigator and participant assessments (N=20).

reported in murine models that were inflicted with 2 full-thickness wounds on the skin of their backs that tretinoin rapidly increased the reepithelialization of wounded skin to speed up healing.[18] The benefits of using TC cream as pretreatment and posttreatment therapies in conjunction with other dermatologic procedures such as chemical peels, microdermabrasion, and/or laser treatments for melasma also have been reported in prior studies.[2,14-16,19]

The results of this pilot study of 20 participants showed encouraging results that sequential treatment with TC cream and GA peels for melasma therapy were efficacious and well-tolerated. Investigator global assessment ratings indicated that 65% (13/20) of participants had achieved treatment success (clear/almost clear) at week 12, which was significantly different from baseline and week 6 rates ($P<.001$ for both). Objective absorption spectrometry measurements (melanin index) for involved versus uninvolved skin demonstrated that the degree of hyperpigmentation was significantly reduced in participants at weeks 6 and 12 compared with baseline ($P<.001$ for both). In addition, 90% of participants or more showed improvement at weeks 6 and 12 by both investigator and participant assessments. These results suggest that using TC cream in sequence with GA peels may enhance the results typically seen with either of these approaches alone. Larger studies and/or greater experience with this approach are needed to confirm the results seen in this small study.

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