Original Contribution

The combination of 2% 4-hydroxyanisole (mequinol) and 0.01% tretinoin effectively improves the appearance of solar lentigines in ethnic groups

Zoe Diana Draelos, MD

Summary

While the efficacy and safety of topical 4-hydroxyanisole (mequinol) 2%/tretinoin 0.01% therapy has been established in Caucasian populations, those with skin types I–II, little research has focused on individuals with darker skin types. The purpose of this open-label study was to evaluate the efficacy and safety of mequinol 2%/tretinoin 0.01% solution in the treatment of solar lentigines in Asian, Latin/Hispanic, and African American ethnic groups with skin types II–V. Subjects were required to have ≥ 10 solar lentigines on the dorsal forearms/hands and ≥ 3 on the face. One lesion was designated the target lesion, however, all lesions were treated. Patients were treated with topical mequinol 2%/tretinoin 0.01% and clinically evaluated at 4, 8, 12, 16, 20, and 24 weeks as well as 4 weeks following treatment cessation. At each visit, lesions were evaluated using Target and Overall Lesion Pigmentation Index scores ranging from 0 (lightest) to 8 (darkest), where 4 indicated equal pigment with surrounding skin. Efficacy was determined based on pigmentation index scores, and safety was assessed using laboratory monitoring and adverse event (AE) reporting. Over 80% of the 259 subjects completing this study responded to mequinol 2%/tretinoin 0.01% therapy, with a majority of subjects maintaining clinical benefit at 4 weeks post-treatment. Most AEs reported were tolerable and overall mequinol 2%/tretinoin 0.01% therapy had a favorable benefit-to-risk ratio. This study therefore supports the theory that topical mequinol 2%/tretinoin 0.01% is an effective and safe treatment of solar lentigines in ethnic populations, and in those with dark skin types.

Keywords: ethnic groups, mequinol, solar lentigines, tretinoin

Introduction

Solar lentigines are a common dermatologic condition that manifest as localized, hyperpigmented, macular lesions usually found on sun-exposed areas of the skin. The benign condition is caused by an increased number of active melanocytes and increased melanin production in response to chronic, accumulated ultraviolet radiation exposure. Lesions occur most frequently in fair-skinned individuals and in middle-aged and elderly populations.[1–3]

This condition currently causes significant cosmetic concerns for more than 20 million Americans and is becoming increasingly prevalent due to the increased rate at which the US population is aging.[4] Although new and effective therapies are available, the majority of therapeutic research has focused on Caucasian populations or those with skin types I or II (Table 1). This is not surprising given the epidemiological data on the disease. However, the condition affects all skin types and requires research supporting its treatment in ethnic groups and those with darker skin.[5–7]

Correspondence: Zoe Diana Draelos, MD, 2444 North Main Street, High Point, NC 27262. E-mail: zdraelos@northstate.net

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Table 1 Demographic information.

Demographic information	*n* (%)*
No. of subjects	259
Mean age ± SD, (years)	55.8 ± 10.93
Sex	
Male	45 (17.4%)
Female	214 (82.6%)
Skin type	
I – Always burns, never tans	0 (0.0%)
II – Usually burns, tans less than average	17 (6.6%)
III – Sometimes burns (mildly), tans about average	81 (31.3%)
IV – Rarely burns, tans more than average	127 (49%)
V – Rarely burns, tans profusely	34 (13.1%)
VI – Never burns, deeply pigmented	0 (0.0%)

*except where marked.

Recent evidence supports the use of combination therapy with mequinol 2%/tretinoin 0.01% (Solagé®, Barrier Therapeutics, Princeton, NJ) as an effective and safe treatment for solar lentigines.[1–4,8,9] Widely accepted treatments, such as tretinoin and hydroquinone monotherapies, and ablative treatment strategies, such as cryo- and laser removal, often produce variable depigmentation results. Additionally, such therapies often have negative side effects and can result in significant patient discomfort.[3] Mequinol 2%/tretinoin 0.01% combines two effective depigmenting agents and has been proven more effective than either agent alone while offering a safety profile similar to tretinoin monotherapy.[2] Tretinoin (all-trans-retinoic) is a vitamin A analogue thought to inhibit melanogenesis through growth factor modulation,[3,10] The exact mechanism of action of mequinol's depigmentation effects is unknown although it is speculated that it includes oxidation by tyrosinase to cytotoxic products in melanocytes, a direct/selective toxic effect on melanocytes, or inhibition of melanin formation.[11–15]

Although multiple recent studies have shown mequinol 2%/tretinoin 0.01% combination therapy to provide clinically significant improvement in up to 80% of patients, little work has been done to specifically evaluate its efficacy in ethnic populations or in those with darker skin tones.[2,3] One study has suggested that 2% hydroquinone-cyclodextrin therapy significantly reduced pigmentation in Asian patients with solar lentigines, another study explored concomitant application of all-trans-retinoic acid aqueous gel with hydroquinone-lactic acid ointment for bleaching of senile lentigines and post-inflammatory hyperpigmentations, while other work has looked at hyperpigmentation responses to topical whitening agents in women of South-east Asian descent.[5–7] With the exception of these investigations, no studies have specifically addressed solar lentigines in non-Caucasian individuals.

Given the limited exploration in these patient populations, the present study was designed to assess the efficacy and safety of mequinol 2%/tretinoin 0.01% therapy in ethnic groups.

Methods

The present study was an open-label, single-arm safety and efficacy study of mequinol 2%/tretinoin 0.01% topical solution in the depigmentation of circumscribed macular solar lentigines in males and females ≥ 30 years of Asian, Latin/Hispanic, African American ethnicity and skin types II–V. Using the wand applicator to specifically target only the solar lentigines, subjects applied the quick-drying test solution twice daily to lesions on the face, forearms, and hands for up to 24 weeks.

After giving written informed consent, 45 (17.4%) males and 214 (82.6%) females (total $n = 259$) were enrolled into 17 study centers in the United States and 3 in Canada. The mean age of the subjects was 55.8 years, with a range of 31–82 years. Sixty-three (24.3%) of the subjects were Asian, 35 (13.5%) were African American, and 161 (62.2%) were Hispanic (Table 1). Eligible subjects were demonstrably nongravid and had ≥ 10 solar lentigines on the dorsal forearms/hands and ≥ 3 on the face. A single lesion in each area was designated as a target lesion, however, all lesions were treated. At baseline the overall lesion pigmentation index score was 6 on a 9-point scale ranging from 0 (lightest) to 8 (darkest), where 4 (equal) indicated equal pigmentation with the surrounding skin (Table 2).

Subjects returned to the clinic for evaluations after 4, 8, 12, 16, 20 and 24 weeks of treatment and again 4 weeks later for follow-up assessment. In this open-label, single-arm study, all the assessments for a subject were performed by the same investigator; evaluations were

Table 2 Lesion pigmentation index.

0 – Extremely lighter than pigment of surrounding skin (depigmented)
1 – Markedly lighter than pigment of surrounding skin
2 – Moderately lighter than pigment of surrounding skin
3 – Slightly lighter than pigment of surrounding skin
4 – Equal with pigment of surrounding skin
5 – Slightly darker than pigment of surrounding skin
6 – Moderately darker than pigment of surrounding skin
7 – Markedly darker than pigment of surrounding skin
8 – Extremely darker than pigment of surrounding skin

based on the target lesions presented at baseline. Based on investigator interest, experience and training, color photographs, for illustrative purposes only, were taken at three selected study sites at baseline, week 24, or upon successful depigmentation to grade 4 (Fig. 1a,b). Figure 2a,b is representative before and after images of subjects with deeply pigmented skin who were treated with the test formulation. At each visit, a Target and an Overall Lesion Pigmentation Index Score were recorded based on clinical assessment for each of the two treatment areas, resulting in a total of four scores per visit. Pregnancy status was monitored at each visit, and laboratory tests (blood chemistry, urinalysis, and hematology) were performed at baseline, 12 weeks, and 24 weeks (or at last visit) for safety monitoring. For each treated lesion, if a score of 4 was reached, treatment was stopped for that lesion. When all treated lesions were at grade 4, treatment was stopped altogether, regardless of study duration.

Efficacy was determined by clinical assessment using Target Lesion and Overall Lesion Pigmentation Index scores and was quantified by dividing responders into three categories:

- Complete responders – subjects who reached an Overall Lesion Pigmentation Index of 4;
- Partial responders – subjects who had significant improvement in their pigmentation, defined as an improvement of at least 1 grade, compared to baseline;
- Treatment failures – subjects who did not fulfill the above criteria or subjects achieving an Overall Lesion Pigmentation Index score of less than 4.

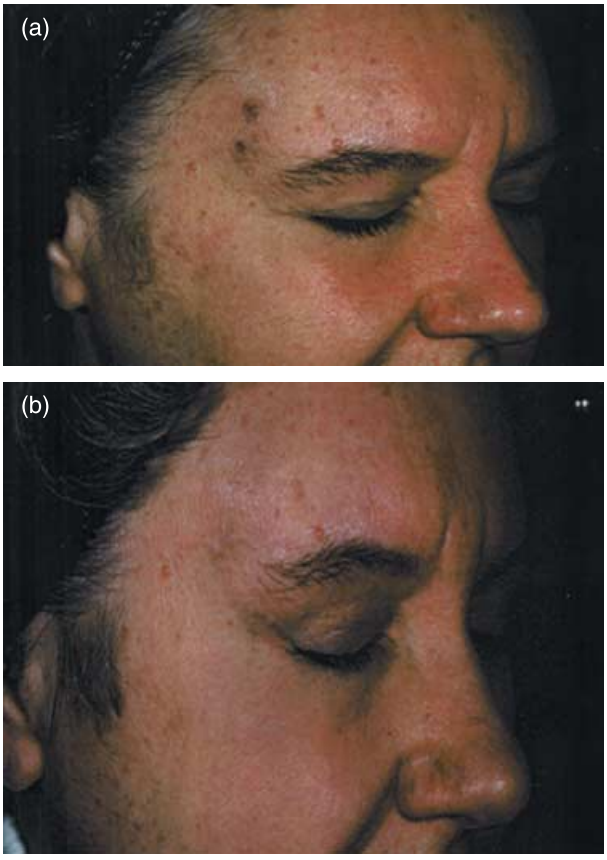

Figure 1 Facial pigmentation lightening occurred in the facial treatment sites after 24 weeks of therapy in an African American subject. (a) baseline and (b) 24 weeks.

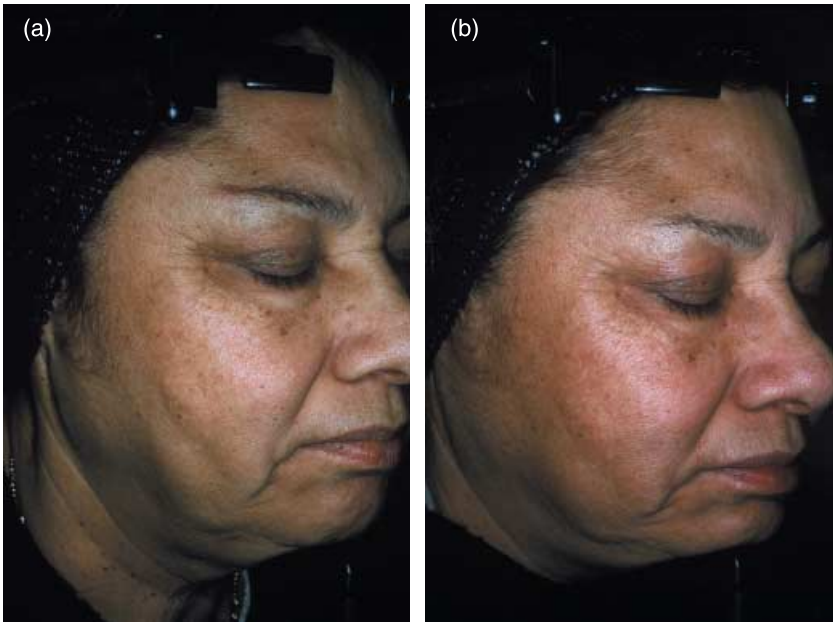

Figure 2 Representative (a) before and (b) after images of subjects with deeply pigmented skin who were treated with the test formulation.

The time to reach a response in partial and complete responders was defined as the time from first treatment application to the first measurable response.

In addition to the aforementioned laboratory tests, safety was assessed by evaluating reported adverse events (AEs). Assessment of AEs, including abnormal pigmentation changes, was performed at each visit, and any events were recorded throughout the duration of the study. Subjects were instructed to avoid sun exposure as well as exposure to other sources of ultraviolet radiation (i.e., tanning beds) whenever possible for the duration of the study. They were also instructed to keep treatment areas covered with clothing or shielded from the sun.

Results

Over 80% of subjects responded to treatment as assessed by Overall Lesion Pigmentation Index scores. One hundred and seventy-six (68.0%) and 198 (76.4%) subjects had partial responses for the arm and face, respectively, while 35 (13.5%) and 21 (8.1%) subjects experienced complete responses for the same respective areas. Forty-eight (18.5%) and 40 (15.4%) subjects had treatment failures for the arm and face, respectively.

Over 85% of subjects responded to treatment based on Target Lesion Pigmentation Index scores. Once again the majority of subjects had a partial response to treatment with 176 (68.0%) and 185 (71.4%) showing a lesion improvement by at least 1 grade for the arm and face regions, respectively. Forty-nine (18.9%) and 45 (17.4%) subjects experienced complete responses, while 34 (13.1%) and 29 (11.2%) subjects had treatment failures for the arm and face, respectively.

The median time to response (partial and complete) for the Overall Lesion Pigmentation Index was 56 days (range 21–173 days) for both the arm and face. Median response times were 51 and 35 days for the Target Lesion Pigmentation Index for the same respective regions. At 4-week follow-up, the majority of subjects maintained the same pigmentation index scores as observed at the last treatment visit.

Exposure to the study medication ranged from 1 to 232 days (mean of 151.2 days) with most subjects (> 70% per area) receiving treatment for over 141 days. Mequinol 2%/tretinoin 0.01% treatment showed an overall favorable safety profile consistent with previous clinical studies.[1–3] Of 259 subjects, 160 (61.8%) reported 1 or more AEs; 125 (48.3%) subjects reported 1 or more dermatological AEs. Thirty-two (12.4%) subjects reported hypopigmentation or halo-hypopigmentation (12 [4.6%] and 20 [7.7%], respectively) (Table 3). The majority of these events (84%) resolved during the study. Drug-related AEs were reported by 121 (46.7%) subjects, all of whom had dermatological AEs. Thirteen (5%) subjects discontinued treatment due to an AE, nine (3.5%) of which were dermatological in nature. Additionally, 15 (5.8%) subjects stopped treatment due to dermatological AEs in one area (either the face or arm) but remained in the study and continued undergoing treatment in the nonaffected area. Serious AEs were reported by six (2.3%) subjects; all were nondermatological, including one subject who died of a myocardial infarction considered unrelated to study treatment by the investigators. Laboratory AEs were infrequent; hematuria occurred in nine (3.5%) subjects (seven of which were female). No laboratory AE resulted in treatment discontinuation and none were considered related to treatment by the investigators.

Table 3 Summary of adverse events.

	Number of subjects *n* (%)
Total number of subjects	259
Skin and appendages	125 (48.3%)
Erythema	64 (24.7%)
Skin discomfort	52 (20.1%)
Halo-hypopigmentation	20 (7.7%)
Irritant dermatitis*	17 (6.6%)
Desquamation	16 (6.2%)
Pruritus	13 (5.0%)
Hypopigmentation	12 (4.6%)
Dry skin	8 (3.1%)
Body as a whole	35 (13.5%)
Flu syndrome	17 (6.6%)
Headache	9 (3.5%)
Accidental injury	8 (3.1%)
Respiratory system	22 (8.5%)
Pharyngitis	13 (5.0%)
Urogenital system	21 (8.1%)
Hematuria	9 (3.5%)
Total subjects reporting AEs	160 (61.8%)

A subject was counted only once per AE regardless of the number of occurrences.
*Defined as erythema plus at least two additional, prespecified signs/symptoms (scaling, dryness, stinging/burning) starting at the same time.

Conclusions

Overall, mequinol 2%/tretinoin 0.01% combination therapy demonstrated a favorable risk-to-benefit ratio in

the treatment of solar lentigines in Asian, Latin/Hispanic, and African American subjects with skin types II–V.

This study has demonstrated that over 80% of treated subjects achieved a significant response to the therapy for both arm and facial lesions, the majority of which maintained clinical benefit 4 weeks post-treatment. These results mirror efficacy findings previously reported for light-skinned individuals and provide new evidence supporting the use of mequinol 2%/tretinoin 0.01% specifically in ethnic and dark-skinned populations.[2] It is important to note that mequinol 2%/tretinoin 0.01% was found to have favorable treatment response times (both partial and complete) comparable, if not better, than those seen with other therapies.[16,17] The median response time for the Overall Lesion Pigmentation Index was 56 days (range 21–173 days) for both the arm and face; median response times were 51 and 35 days for the Target Lesion Pigmentation Index for the same respective regions. Noting the realistic amount of time it may take for a noticeable difference when treating solar lentigines may help in the management of patient expectations for therapy and ultimately support compliance.

There are no racial differences in the number of melanocytes,[18,19] but the actual number of melanocytes differ from one person to another or from one area of the body to another,[20] which may account for the differences in treatment response of the test drug. All treatment modalities have nonresponders. The small proportion of subjects in this trial with no improvement is not surprising and was probably due to the individual's unique biologic makeup. The approximately 3% difference in response with treated facial and arm lesions is consistent with the results found in studies of light-skinned subjects and most likely not linked to racial differences[2,3] but rather to the difference in size and distribution of melanosomes in the two areas.

Although AEs were reported by a significant number of patients, the treatment was overall tolerable, especially when considering the overwhelming treatment response rate. The most commonly reported AEs were erythema, skin discomfort, and halo-hypopigmentation, occurring in 24.7%, 20.1%, and 7.7% of subjects, respectively. These results are significantly more favorable than AE results previously reported in light skin populations further supporting the use of mequinol 2%/tretinoin 0.01% in dark-skinned individuals.[2]

Because of the inherent ethnic differences in skin biology, it was important to target a specific population of subjects with darker skin. Although the efficacy and safety results of this trial were similar to those of earlier studies[1–3] that comprised a majority of light-skinned subjects, two differences in ethnic skin biology were of concern—absorption and irritation response—as they may have affected efficacy and safety of the test drug.

The barrier properties of skin can produce variations in skin permeability and thus absorption. When skin types V and VI was compared to types II and III, researchers concluded that darker skin was more compact than lighter skin probably due to more cornified cell layers, and that darker skin showed greater epidermal barrier.[21] These results support the findings of an earlier study that found that lighter skin was more permeable to certain chemicals than darker skin.[22]

In the 1980s and early 1990s, researchers studied racial and ethnic differences in irritant reaction to topically applied chemicals by using biologic parameters. Based on findings from several studies, Berardesca *et al.*[23–27] concluded that:

- black subjects' skin displays a stronger skin irritant reaction than white subjects';
- the skin of black subjects is more sensitive to irritants than the skin of white subjects;
- black subjects display less erythema, less blood vessel reactivity, and less cutaneous blood flow to irritants than white or Hispanic subjects;
- Hispanic subjects show a stronger irritant reaction compared with white subjects; their irritant reaction is similar to that of black subjects;
- Hispanic subjects have stronger irritant reactions when injured with concentrated chemical;
- Hispanic and white subjects have similar erythematous reactions.

Many current treatment strategies for solar lentigines are associated with either inadequate depigmentation responses or unfavorable side effects resulting in severe patient discomfort.[3] It has been widely reported that formulations containing hydroquinone and/or glucocorticoids are associated with an increased risk of ochronosis, a paradoxical hyperpigmentation response.[28] Such adverse reactions can be alarming to patients who initially sought treatment in order to resolve hyperpigmentation abnormalities. Through avoidance of undesirable side effects such as ochronosis, mequinol 2%/tretinoin 0.01% offers patients an attractive alternative to other therapies being used to treat solar lentigo. Therefore, the present study supports the use of mequinol 2%/tretinoin 0.01% combination therapy as an effective, tolerable treatment option for ethnic and dark-skinned subjects.

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