Mequinol 2%/Tretinoin 0.01% Solution: An Effective and Safe Alternative to Hydroquinone 3% in the Treatment of Solar Lentigines

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A new topical solution containing 4-hydroxyanisole (mequinol) 2%/tretinoin 0.01% (Solagé®) was compared with its active components, its vehicle, and hydroquinone (HQ) 3% in the treatment of solar lentigines. In a randomized, parallel-group, double-masked study, 216 subjects applied the treatments twice daily for 16 weeks and were followed up for a further 24 weeks.

A significantly higher proportion (P≤.05) of subjects achieved clinical success with mequinol 2%/tretinoin 0.01% compared with HQ 3% as measured by both the lesional pigmentation on the forearm and the physician global assessment at the end of treatment. The proportion of subjects achieving clinical success on the face in the mequinol 2%/tretinoin 0.01% group was consistently higher than that in the HQ 3% group. Some treatment effects remained at the end of the treatment-free follow-up, with trends apparent on the face in favor of mequinol 2%/tretinoin 0.01% over HQ 3%. In all treatment groups, skin-related adverse events were mild or moderate and transient.

In conclusion, the mequinol 2%/tretinoin 0.01% solution is a highly effective and well-tolerated treatment for solar lentigines and related hyperpigmented lesions, being superior to HQ 3% for lesions on the forearm and of similar efficacy for lesions on the face.

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Solar lentigines are areas of excessive skin pigmentation resulting from increased numbers of active melanocytes and increased melanin production. Solar lentigines usually appear between 40 to 50 years of age on sun-exposed parts of the body and mainly affect white and light-skinned individuals, particularly those with high sun-exposure who do not tan easily.

Two main types of treatment exist for solar lentigines: ablative and topical. Among ablative therapies, cryotherapy, laser, and dermabrasion are the most often used; despite good clinical success rates, these procedures are invasive and commonly cause pain and discomfort for patients. In addition, ablative therapies are associated with significant side effects such as erythema and hypopigmentation; in addition, relapse or recurrence rates as high as 55% were noted 6 months after cryotherapy and dermabrasion.[1-3]

Until now, hydroquinone (HQ) was considered the gold standard of treatment for solar lentigines. It has been available for more than 30 years and is often used alone or in combination, with variously reported outcomes.[4-7] Tretinoin also has been used in the treatment of solar lentigines.

Recently, a new topical treatment containing a combination of 4-hydroxyanisole (mequinol) 2% plus tretinoin 0.01% (Solagé®) has been introduced.

Mequinol 2% has been shown to be a more effective depigmentor than HQ 3% in animal models, with a decreased propensity to cause irritation, and the combination with tretinoin showed an enhanced depigmenting activity compared with the activity of each component separately.[8,9]

The present study compared the efficacy and tolerability of the mequinol 2%/tretinoin 0.01% combination with its active components, its vehicle, and HQ 3% in the treatment of solar lentigines. The 16-week treatment phase was followed up by a 24-week treatment-free period to assess the maintenance and duration of the depigmenting effect.

MATERIALS AND METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments, and in compliance with institutional review board requirements. All subjects provided a written informed consent before entering the study.

Study Design

In this multicenter, double-masked, parallel-group study, subjects had to be at least 18 years of age and had to have clinically confirmed solar lentigines affecting the forearm and face, with a lesional pigmentation grade of at least moderately darker than the pigment of surrounding skin. Subjects with a history of skin cancer or those undergoing hypopigmentation treatments during the past 6 months were excluded from the study, as were women of childbearing potential.

Subjects were randomly allocated in an equal ratio to apply either mequinol 2%/tretinoin 0.01%, HQ 3%, mequinol 2%, tretinoin 0.01%, or vehicle. Treatments were applied twice daily for 16 weeks to each designated lesion on the forearm and on the face. Sites were evaluated at regular intervals until week 16. Early discontinuation of treatment was permitted if adequate depigmentation of treatment sites was attained before the end of treatment. Subjects were evaluated throughout the treatment-free follow-up phase until week 40.

Subjects were to avoid exposure to the sun; they could not use any topical product (including sunscreens) on the treatment sites. During the posttreatment period, only moisturizers were allowed.

Clinical Evaluations

Efficacy was evaluated during the treatment period. Lesions were graded for pigmentation and for physician global assessment of improvement or worsening of the condition and of overall cosmetic effect. Based on the lesional pigmentation score, the time from baseline to clearing at any visit during the treatment or posttreatment phases of the study was analyzed.

Tolerability was evaluated throughout the study, and adverse events (AEs) were recorded. Complete laboratory analyses were performed at defined visits.

Statistical Methods

Statistical analyses for efficacy parameters were performed at baseline and at the end of treatment. Clinical success was defined by measuring the improvement in lesional pigmentation and the physician global assessment, which was ordinally scaled to measure rank transformation and analyzed by an analysis of variance for contrasts between mequinol 2%/tretinoin 0.01% and its components.

The physician global assessment of overall cosmetic effect was dichotomized and analyzed by a weighted least squares categorical analysis using the Wald statistic for differences between mequinol 2%/tretinoin 0.01% and each of the other treatments.

Time to the pigmentation level was evaluated by a nonparametric survival analysis using the Gehan-Wilcoxon statistic.

Safety analyses were performed on all subjects included in the study. Nonparametric survival analysis using the modified Wilcoxon test was performed to test for differences among treatments in elapsed time of onset and frequency of skin-related AEs.

RESULTS

A total of 216 individuals (33 males; 183 females) were enrolled in the study: 44 subjects in each of the mequinol 2%/tretinoin 0.01%, tretinoin 0.01%, and HQ 3% groups and 42 subjects in each of the mequinol 2% and vehicle groups. Overall mean age was 63.6 years (range, 35.2–84.4 years).

At the end of the treatment phase (week 16), data from 201 subjects were available for the efficacy analysis. One hundred ninety-four subjects completed the full 40-week follow-up. Reasons for discontinuation were as follows: AEs unrelated to treatment (12), AEs considered related to treatment (mequinol 2%/tretinoin 0.01%, 2; tretinoin 0.01%, 1), voluntary withdrawal (5), and lost to follow-up (2).

Efficacy

Forearm—The proportion of subjects who achieved a significantly higher success rate ($P \leq .05$) in the physician global assessment at the end of treatment was 60% in subjects treated with mequinol 2%/tretinoin 0.01% compared with 38% in those treated with HQ 3%. Mequinol 2%/tretinoin 0.01% was significantly different ($P \leq .05$) compared with HQ 3% in lesional pigmentation (70% vs

50%, respectively). The physician global assessment of overall cosmetic effect was considered a success in 56% of subjects receiving mequinol 2%/tretinoin 0.01% compared with only 35% of those receiving HQ 3%.

All 3 measures of efficacy were significantly in favor of the mequinol 2%/tretinoin 0.01% treatment compared with either mequinol 2% or vehicle ($P \leq .05$). The differences with tretinoin 0.01% did not reach statistical significance for any efficacy measure.

Face—More than 70% of the subjects treated with mequinol 2%/tretinoin 0.01% were classified as a clinical success in the lesional pigmentation and the physician global assessment of overall cosmetic effect. For all these measures, the proportion of subjects with clinical success in the mequinol 2%/tretinoin 0.01% group was consistently higher (by as much as 17%) than that in the HQ 3% group.

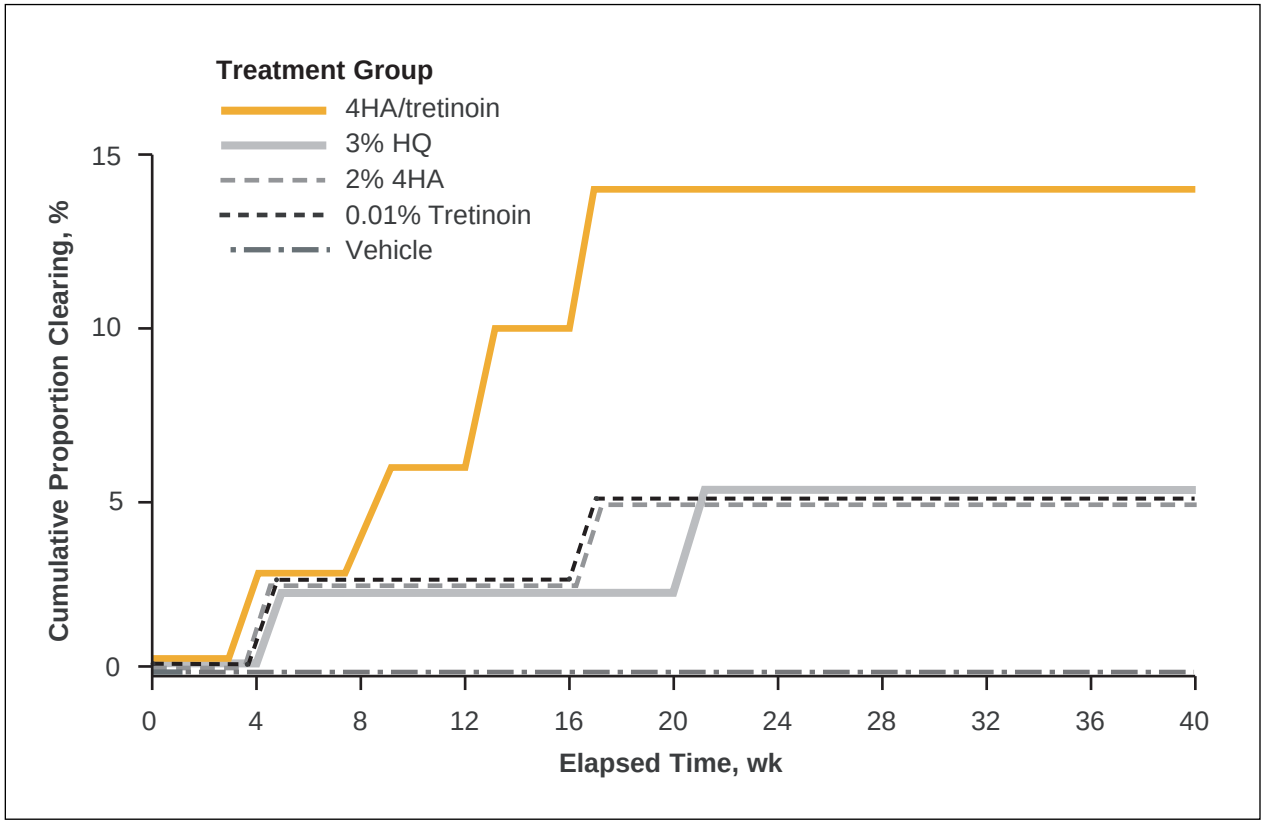
Mequinol 2%/tretinoin 0.01% was significantly more effective ($P \leq .05$) than the vehicle solution in all measures of efficacy. In addition, all comparisons with tretinoin 0.01% or mequinol 2% showed differences in favor of the mequinol 2%/tretinoin 0.01% treatment; the difference against mequinol 2% in the physician global assessment was statistically significant ($P \leq .05$).

Clearing of Pigmentation—The Figure depicts the cumulative percentages of early clearing of pigmentation on the forearm. On the face, early clearing was detected after 12 weeks in 4.7% of subjects; by the end of treatment, clearing with mequinol 2%/tretinoin 0.01% was apparent in 16.3% of the subjects on the face, which was higher than in comparator groups including HQ 3%, where the cumulative percentages were 2.5% and 5%, respectively.

Safety

No serious AEs were considered related to study medication, and no treatment-related abnormalities in laboratory data were reported during this study.

One hundred forty-two treatment-related AEs were reported; most were either mild (94; 66%) or moderate (46; 32%), with only 2 events (1%) classified as severe, one each in the tretinoin 0.01% group and the HQ 3% group. The most frequent treatment-related AE, burning/stinging/tingling, was noted as follows: mequinol 2%/tretinoin 0.01%, 13; HQ 3%, 7; tretinoin 0.01%, 17; mequinol 2%, 5;



Elapsed time to clearing (pigmentation equal to normal, untreated surrounding skin) of lesions on the forearm. 4HA indicates 4-hydroxyanisole; HQ, hydroquinone.

and vehicle, 4. In the mequinol 2%/tretinoin 0.01% and tretinoin 0.01% treatment groups, there were 3 and 5 reports of pruritus, respectively, and 3 and 7 reports of rash, respectively. Among the subjects with treatment-related AEs, 3 discontinued treatment: 1 each in the tretinoin 0.01% group and the mequinol 2%/tretinoin 0.01% group because of erythema and 1 in the mequinol 2%/tretinoin 0.01% group because of pruritic rash.

COMMENT

In this study, mequinol 2%/tretinoin 0.01% was an effective and well-tolerated treatment for solar lentigines. Clinical success was achieved on the forearm in most of the subjects treated with this combination, proving to be significantly superior to HQ 3%. Other measures of efficacy supported this superiority of clinical success on the forearm in the lesional pigmentation and the physician global assessment of overall cosmetic effect. With clinical success rates of 70% or more, all 3 measures of efficacy showed that the combination mequinol 2%/tretinoin 0.01% provides a highly effective treatment for solar lentigines on the face.

The combination mequinol 2%/tretinoin 0.01% was associated with maintenance of depigmenting effect over 24 weeks of treatment-free follow-up in initial responders; similar results were observed in responders from the HQ 3% group. The benefit of treatment with mequinol 2%/tretinoin 0.01% was more apparent for lesions on the face than on the forearm, a pattern also noted by Fleischer et al.[9]

Physical therapies for solar lentigines have the advantage of a relatively short treatment period and effective depigmentation.[1,2,10] However, recurrence rates (hyperpigmentation) are high, and such therapies have been associated with important side effects, such as hypopigmentation, and substantial discomfort for the subject.[2,3]

Tolerability is always a key to success with any treatment modality, particularly in older subjects with solar lentigines. In this study, the most frequent treatment-related AE (stinging/burning/tingling) in all treatment groups was transient and did not result in discontinuation of treatment.

CONCLUSION

This study has shown that combination mequinol 2%/tretinoin 0.01% solution is a highly effective and well-tolerated treatment for solar lentigines. It is superior to the gold standard HQ on the forearms and of similar efficacy on the face.

The combination of mequinol 2% plus tretinoin 0.01% represents a real advance in the treatment of solar lentigines, combining overall excellent efficacy with a good tolerability profile.

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