

Safety and Efficacy of Combined Use of 4-Hydroxyanisole (mequinol) 2%/Tretinoin 0.01% Solution and Sunscreen in Solar Lentigines

Jean Paul Ortonne, MD; Francisco Camacho, MD; Nicholas Wainwright, MD; Louise Bergfelt, MD; Wiete Westerhof, MD; Diane Roseeuw, MD

The objective of this open-label, noncontrolled study was to evaluate the safety of a combination solution containing 4-hydroxyanisole (mequinol) 2%/tretinoin 0.01% (Solagé®) with a sunscreen in the treatment of solar lentigines. The study included a total of 406 subjects for a treatment period up to 24 weeks. Efficacy was evaluated clinically by grading the pigmentation level of the treated areas on the face and forearms. A total of 378 subjects were included in the safety population. Of the 173 subjects with skin-related and treatment-related adverse events, severity was reported as mild in 79 subjects, moderate in 71, and severe in 23. Hypopigmentation was observed in 4 subjects and had definitively resolved in 3 of these subjects at the end of the study or after treatment had been discontinued. Halo hypopigmentation was reported in 16 subjects. No allergic reactions were observed. Efficacy evaluation was based on data for 370 subjects. A total of 325 (88%) subjects had

facial target lesions almost clear to clear, and a total of 298 (81%) subjects had forearm target lesions almost clear to clear. Our study shows that the mequinol 2%/tretinoin 0.01% solution is effective, convenient, and safe in the treatment of solar lentigines.

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Solar lentigines commonly occur on the sun-exposed parts of the body and are areas of excessive pigmentation, which manifest as localized, pigmented macular lesions. Lesions typically occur on the forearms, dorsa of hands, shoulders, neck, and face. Lesions tend to be multiple, appear in middle age, and be found predominantly in white individuals and in sun-exposed people who burn easily and who do not tan.^{1,2}

At present, treatment for solar lentigines is not completely satisfactory because it produces either inadequate depigmentation or irritation, or both, and sometimes even scars. Physical modalities of treatment include dermabrasion, cryotherapy, and laser therapy.³⁻⁵ Cryotherapy produces variable results, with occasional blistering and scarring. In addition to the high recurrence rate (55%) after 6 months, cryotherapy is also painful—as is the healing process—and therefore may not be suitable in the treatment of multiple lesions or in subjects with darker skin because of the potential for hypopigmentation.

Laser therapy has been shown to provide good results. However, it is complicated, painful, time-consuming, and expensive; may instigate posttreatment erythema; and does not exclude recurrence of lesions.^{6,7}

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Dr. Ortonne is from the Hôpital de l'Archet, Nice, France. Dr. Camacho is from the H.U. Virgen de la Macarena, Sevilla, Spain. Dr. Wainwright is from Monklands Hospital, Airdrie, Scotland. Dr. Bergfelt is from Kungsbacka, Sweden. Dr. Westerhof is from the Stichting Nederlands Instituut voor Pigmentstoornissen, Amsterdam Zuidoost, Netherlands. Dr. Roseeuw is from the AZ-VUB Jette, Bruxelles, Belgium.

This article was supported by an educational grant from Galderma Laboratories, LP. The authors report no conflict of interest. Reprints: Jean Paul Ortonne, MD, Hôpital de l'Archet, Service de Dermatologie, Rte Saint Antoine de Ginestière 151, 06002 Nice Cedex 03, France (e-mail: ortonne@unice.fr).

Tretinoin is marketed worldwide in concentrations ranging from 0.01% to 0.1% in topical preparations (alone or in combination) for use in the treatment of acne vulgaris, hyperpigmentary disorders, mitigation of mottled hyperpigmentation, and some of the other changes that result from chronic sun exposure. Its potential for producing local irritation, especially at higher concentrations, is well documented, and the therapeutic effect of topical tretinoin in hyperpigmented lesions is believed to be its ability to inhibit melanogenesis.^{3,4} In melanoma cell lines, retinoic acid has been shown to be a potent inhibitor of inducible pigmentation. In addition, retinoids have been reported to reduce the cohesiveness of corneocytes and thus to promote desquamation.^{4,8,9}

Hydroquinone, a topically applied depigmenting agent, has a long history of clinical use in the treatment of hyperpigmentation disorders in concentrations ranging from 2% to 10% and is available in several countries. 4-Hydroxyanisole (mequinol) has been marketed in several European countries at concentrations ranging from 5% to 20%. It is a substrate to the enzyme tyrosinase and acts as a competitive inhibitor of melanogenesis, but its exact mechanism of action remains unknown.¹⁰ Tretinoin and hydroquinone have been used for many years in the treatment of hyperpigmented lesions.

The therapies mentioned have some limitations, and, thus, a product with an enhanced benefit:risk ratio was thought to provide tangible advantages in the management of solar lentigines. Recently, a solution containing mequinol 2%/tretinoin 0.01% (Solagé®) has been launched in the United States and Canada. The aim of the study was to evaluate the safety and efficacy of topical mequinol 2%/tretinoin 0.01% solution when used concomitantly with a sunscreen.

The design of this study was similar to a previously published clinical trial,¹¹ but with the main difference of having a 1-week treatment duration observational period preceding the 24-week duration period.

Methods

The present study was an open-label, noncontrolled, multicenter study and was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with independent ethics committee requirements. All subjects provided a written informed consent before entering the study.

Subjects and Materials—Subjects had to be 30 years or older with a skin type of I to V. They

could be of either sex and had to have clinically diagnosed solar lentigines with an Overall Lesion Pigmentation Index of at least grade 6 (moderately darker than surrounding skin) on both the dorsal forearms (including dorsal hands) and the face. Each forearm had to have at least 5 solar lentigines. The facial treatment area, excluding the ocular area, had to have at least 3 solar lentigines. Target lesions on the forearm and face had to be at least 5 mm in length. To adequately assess the change in the pigment of the lesions, solar lentigines had to be surrounded by normally pigmented skin.

Subjects were told to avoid exposure to the sun or to other UV radiation sources (eg, artificial sun bed) as much as possible and also to avoid recreational or occupational exposure to potentially bleaching products containing hydroquinone or hydroquinone derivatives (eg, photographic developer, industrial cleaning solution). Subjects also were instructed to always protect treatment areas from the sun.

Pregnant or nursing women and subjects who had a history of sensitivity to any of the ingredients in the formulations, had a history of skin cancer, or had used any topical treatments on their forearms or face up to 6 months before enrollment were excluded from the study.

During the treatment period, mequinol 2%/tretinoin 0.01% was to be applied twice daily on individual lesions for up to 24 weeks. Subjects were told not to shower or bathe the treatment areas for at least 6 hours after application.

Sunscreen was to be applied every morning, 30 minutes after applying the study medication. Subjects who planned to be exposed to the sun for more than 6 hours were advised to reapply the sunscreen. The use of a moisturizer was permitted for the duration of the study. Only a routine cleansing regimen and only the use of minimal amounts of cosmetics without sun protection properties were allowed during the study.

Subjects who reached a pigmentation level equal to the normal surrounding skin on all treatment areas at the end of the treatment phase or earlier entered a 4-week follow-up period.

Safety assessments were based on reported adverse events and on standard clinical laboratory tests.

Clinical efficacy was assessed by grading the pigmentation level of the 2 treatment areas (face and forearm) and the target lesions, respectively, using a bipolar ordinal grade scale of 0 through 8: 0=extremely lighter, 1=markedly lighter, 2=moderately lighter, 3=slightly lighter, 4=equal pigment to surrounding skin, 5=slightly darker, 6=moderately darker, 7=markedly darker, and 8=extremely darker. Complete response (clear or

Subject Demographics

Characteristics	N=406
Mean age, y (SD)	62.3 (9.3)
Sex, n (%)	
Male	57 (14%)
Female	349 (86%)
Skin type, n (%)	
I—Always burns, never tans	6 (1%)
II—Usually burns, tans less than average	110 (27%)
III—Sometimes burns (mild), tans about average	241 (59%)
IV—Rarely burns, tans more than average	48 (12%)
V—Brown skin: rarely burns, tans profusely	1 (<1%)

almost clear) was defined as reaching grades 4 or 5. Partial response was defined as at least one grade of improvement when compared with baseline values.

A subject was considered to have completed the study when a complete response was reached in both areas (face and forearm) or after completion of the 4-week follow-up period that proceeded the 24 weeks of treatment.

Statistics—The study was designed to evaluate primarily the safety of mequinol 2%/tretinoin 0.01%. The per protocol sample size was 500 subjects to be enrolled over a period of 8 months. With a 20% dropout rate, this sample size was sufficiently large to ensure that any adverse event with a true incidence rate of at least 0.75% over the 24-week treatment period had a 95% chance to be observed in at least one subject.

With the 406 subjects enrolled in the study, using the same dropout rate, this sample size was sufficiently large to ensure that any adverse event with a true incidence of at least 0.92% over the 24-week treatment period had a 95% chance to be observed in at least one subject.

Data sets of all subjects enrolled were used for analyses of pretreatment characteristics. Data sets of all subjects enrolled who had applied mequinol 2%/tretinoin 0.01% at least once to any area were evaluable for safety. All subjects who had applied mequinol 2%/tretinoin 0.01% at least once on the forearm and face and who had at least one index measurement for the forearm and face after the start of treatment were evaluable for efficacy.

Results

Of the 406 subjects enrolled in the study, 4 (1%) were discharged from the study because of a major

protocol deviation of at least one eligibility criterion (2 for known history of skin cancer; 1, use of prohibited medication; and 1, being of childbearing potential without contraception). Twenty-eight (7%) of the enrolled subjects never started treatment.

Subject demographics are presented in the Table. Information on baseline pigmentation indices showed that 223 subjects (55%) had a pigmentation index of grade 6 for the forearm, with 37% for target lesions. A pigmentation index grade 6 was described in 64% of subjects' facial area, and an index grade 7 was described in 44% of subjects'

facial target lesions.

Of the initial 406 subjects, 286 (70%) finished the study: 239 (59%) completed the 24-week treatment period, and 47 (12%) had complete response in both target lesions and areas before week 24. More subjects with facial target lesions discontinued the treatment because of reaching a pigmentation index of grade 4 than did those subjects with forearm target lesions. Inversely, the proportion of subjects experiencing adverse events leading to treatment discontinuation was lower on the facial target lesions than on the forearm target lesions.

Three hundred seventy-eight (93%) subjects were included in the safety analysis. Of the 173 subjects with skin-related and treatment-related adverse events, severity was reported as mild in 79 subjects, moderate in 71, and severe in 23. The 5 most frequently reported skin-related and appendages-related adverse events were erythema (127 events, 34%); burning, stinging, tingling (45 events, 12%); skin irritation (45 events, 12%); desquamation (35 events, 9%); and pruritus (30 events, 8%).

Treatment with local steroids was required in 9 subjects for 10 adverse events: erythema (4), eczema (3), dermatitis (2), and skin irritation (1). Hypopigmentation was observed in 4 subjects and had definitively resolved in 3 of these subjects at the end of the study or after treatment had been discontinued. Halo hypopigmentation was reported in 16 subjects, with 1 subject still showing this event at the end of the study. No allergic reactions were observed. No serious drug-related adverse events and no deaths occurred; treatment with mequinol 2%/tretinoin 0.01% was not associated with any changes in laboratory results.

Twenty-eight subjects dropped out of the study because of adverse events: 2 subjects withdrew before the start of dosing because of medical events related to concomitantly provided products, and 26 subjects withdrew during the treatment period. Twenty-two subjects experienced adverse events that were evaluable by the investigators as being related to the mequinol 2%/tretinoin 0.01% solution (erythema [16], pruritus [4], desquamation [3], crusting [2], and dermatitis [2]). Some subjects were discharged from the study on request, at least partly because of occurrence or lasting of adverse events.

Of the 370 subjects evaluable for efficacy, almost clear to clear was achieved in 278 (75%) subjects on the forearm, 298 (81%) on the forearm target lesion, 316 (85%) on the face, and 325 (88%) on the facial target lesion.

At the end of treatment, 68% of subjects presented facial target lesions ranging from slightly darker to equal pigment to surrounding skin. A total of 52% of subjects presented forearm target lesions ranging from almost clear to clear. Improvement of solar lentigines increased slightly during the 4-week follow-up period in 68% of the facial target lesions and in 54% of the forearm target lesions, respectively. Median time needed to reach a diminution of at least one degree was 13.9 weeks for the forearm and 12.1 weeks for the face.

Conclusion

In this safety study, it was shown that subjects with solar lentigines treated with mequinol 2%/tretinoin 0.01% solution reported mostly mild or moderate drug-related adverse events that disappeared once the treatment was interrupted.

More than 75% of subjects achieved almost clear to clear responses on the forearm and forearm target lesions. More than 80% of subjects achieved almost clear or clear lesions on the face and facial target lesions. In addition, subjects who completed the study showed that the quality of solar lentigines even improved during the follow-up phase.

Currently used therapies often are associated with substantial discomfort for the patient, significant side effects and hypopigmentation or hyperpigmentation reactions; the present study showed that mequinol 2%/tretinoin 0.01% solution used in combination with a sunscreen is effective and convenient in the treatment of solar lentigines and offers a good safety profile.

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