STUDY

Photodynamic Therapy With Aminolevulinic Acid Topical Solution and Visible Blue Light in the Treatment of Multiple Actinic Keratoses of the Face and Scalp

Investigator-Blinded, Phase 3, Multicenter Trials

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Objective: To determine the safety and efficacy of photodynamic therapy (PDT) using 20% wt/vol aminolevulinic acid hydrochloride (hereinafter "ALA") and visible blue light for the treatment of multiple actinic keratoses of the face and scalp.

Design: Randomized, placebo-controlled, uneven parallel-group study.

Interventions: Patients (N=243) were randomized to receive vehicle or ALA followed within 14 to 18 hours by PDT. Follow-up visits occurred 24 hours and 1, 4, 8, and 12 weeks following PDT. Target lesions remaining at week 8 were re-treated.

Main Outcome Measure: Clinical response based on lesion clearing by week 8.

Results: Most patients in both groups had 4 to 7 lesions. Complete response rates for patients with 75% or more of the treated lesions clearing at weeks 8 and 12 were 77% (128/166) and 89% (133/149), respectively, for the drug group and 18% (10/55) and 13% (7/52), respectively, for the vehicle group ($P<.001$, Cochran-Mantel-Haenszel general association test). The 95% confidence interval for the difference in response rates at week 8 was 46.9% to 71.0% and at week 12, 65.3% to 86.3%. The week 12 response rate includes 30% of patients who received a second treatment. Most patients experienced erythema and edema at the treated sites, which resolved or improved within 1 to 4 weeks after therapy, and stinging or burning during light treatment, which decreased or resolved by 24 hours after light treatment.

Conclusion: Findings indicate that topical ALA PDT is an effective and safe treatment for multiple actinic keratoses of the face and scalp.

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ACTINIC KERATOSES (AKs) are the most common epithelial precancerous lesions among light-complexioned individuals.[1] It is widely accepted that a small percentage of AKs progress to invasive squamous cell carcinoma,[2,3] but some authors believe that an AK actually *is* a squamous cell carcinoma at an early stage of development.[4,5] Patients with mutliple AKs are usually advised to seek treatment. Current modalities of treatment include cryosurgery, curettage, electrosurgery, excision, dermabrasion, laser surgery, and topical chemotherapy.[6]

Photodynamic therapy (PDT) is a cytotoxic process dependent on the simultaneous presence of a photosensitizing agent, light, and oxygen.[7] When aminolevulinic acid hydrochloride (hereinafter "ALA") is applied to skin, it is converted to the endogenous photosensitizer protoporphyrin IX (PpIX) in skin cells by enzymes in the heme biosynthetic pathway.[8] Selectivity of photosensitization may be due in part to the ability of photodamaged or rapidly proliferating skin cells to convert more ALA to PpIX than can less rapidly proliferating normal epidermal cells[8] and may also be due to altered cutaneous permeability caused by aberrantly differentiated keratinocytes. The relatively tissue-specific phototoxic effects of the topical administration of exogenous ALA provides a basis for using ALA-induced PpIX for PDT.

See also pages 17, 26, 33, and 116

Treatment with ALA PDT using a cream formulation and 630-nm laser light

Author affiliations are listed at the end of this article. *The authors have no relevant financial interest in this article.*

is an effective therapy for AKs.[9] Blue light has been shown to be more potent than red light for activating PpIX,[10] and ALA PDT using a solution formulation and visible blue light has also been shown to be an effective treatment for multiple AKs.[11] The phase 3 multicenter studies described herein evaluated the efficacy and safety of treating multiple AKs of the face and scalp with topical 20% ALA solution followed 14 to 18 hours later by photoillumination using a nonlaser fluorescent blue light at a dose of 10 J/cm^2 delivered at 10 mW/cm^2.

METHODS

This was a multicenter, investigator-blinded, randomized, vehicle-controlled, uneven parallel-group study. The results from 2 independent, identical, phase 3 clinical trials are presented as a single research effort.

The study was conducted under an investigational new drug application and was approved by the institutional review board of each institution. Written informed consent was obtained from each patient before enrollment. Safety was assessed by analyses of adverse events, PDT response, pigmentary changes, and laboratory results. Efficacy was assessed using (1) the complete response rate or clearing of individual AK lesions, (2) the percentage of patients who experienced 75% or greater clearance of all target AKs treated (75% response rate), and (3) the percentage of patients who experienced 100% clearance of all target AKs treated (100% response rate).

Because of the reactive nature of PDT, safety and efficacy assessments were performed by different investigators. Drug application and activation, light treatment, and all safety evaluations were performed by an unblinded investigator, and evaluation of response of AKs to treatment was performed by a blinded investigator.

PATIENTS AND TREATMENT

To enroll, men and nonpregnant, nonlactating women had to be at least 18 years old with 4 to 15 discrete target lesions on either the face or scalp. Women were postmenopausal, surgically sterile, or using a medically acceptable form of birth control and had a negative urine pregnancy test result. Major criteria for exclusion from the studies were (1) a history of cutaneous photosensitization or porphyria, hypersensitivity to porphyrins, or photodermatosis; (2) use of photosensitizing drugs within a given time frame of study start; (3) very hyperkeratotic, grade 3 (on a 0-3 scale) AK lesions among the target lesions; (4) use of topical medications such as corticosteroids, α-hydroxy acids, or retinoids on the face or scalp within 2 weeks before study entry; (5) systemic steroid therapy within 4 weeks before study entry; (6) cryotherapy to the target lesions; (7) laser resurfacing, chemical peels, topical application of fluorouracil or masoprocol for the treatment of AKs within 2 months before study entry; and (8) systemic treatment with chemotherapeutic agents, psoralens, immunotherapy, or retinoids within 2 months before study entry.

The studies were conducted at 16 sites. Randomization was performed separately for each center in a 3:1 drug-vehicle ratio. After randomization, patients had ALA or vehicle applied by an unblinded investigator 14 to 18 hours prior to light treatment. Patients returned for follow-up visits 24 hours and 1, 4, 8, and 12 weeks after light treatment. Remaining target lesions were re-treated at week 8 according to the original randomization. Re-treated patients returned 24 hours and 1 week after light treatment.

Efficacy assessments were performed by a blinded investigator at weeks 4, 8, and 12. Laboratory tests were performed at baseline and 24 hours after initial light treatment and again at week 8 and 24 hours after retreatment. Events associated with phototoxic effects such as erythema, edema, stinging or burning, and changes in pigmentation were assessed at every visit by an unblinded investigator. Adverse events were assessed before, during, and after treatment and at each visit during the study period.

ALA AND VEHICLE APPLICATION

Aminolevulinic acid hydrochloride (20% wt/vol) or vehicle was applied to individual AK lesions using a unit-dose applicator. Just prior to application by the unblinded investigator, the appropriate randomized test article was thoroughly mixed for 3 minutes. The resultant topical solution was applied to each lesion twice, and the solution was allowed to dry between applications.

LIGHT SOURCE

Each patient was treated with visible blue light (Blu-U; DUSA Pharmaceuticals Inc, Wilmington, Mass). The device was designed to provide a uniform distribution of blue light (peak output, 417 ± 5 nm) to the facial or scalp areas of a patient for 1000 seconds. The power density of light produced by the device was designed to be fixed at 10 mW/cm^2. Final adjustment to this value was performed by a DUSA technician at the time the device was installed at the clinical trial site. A power meter was used just prior to the treatment to verify the output (acceptable power density range, 9-11 mW/cm^2). Blue-blocking goggles were worn by the patient during PDT.

STATISTICAL METHODS

Demographic and Baseline Characteristics

Comparability of the treatment groups with respect to demographic and baseline characteristics was assessed using a univariate analysis of variance with treatment effect for continuous variables or the Cochran-Mantel-Haenszel test (general association version), stratified by investigator, for discrete variables. Descriptive statistics (mean, SD, and frequency) were used to summarize demographic and baseline characteristics for all patients.

Efficacy

An observed-value per-protocol analysis of the clinical response as assessed by the blinded investigator was performed at weeks 8 and 12. Patients were excluded from the per-protocol efficacy analysis if they did not return for light treatment within 14 to 18 hours or if their light treatment did not last half of the prescribed course (1000 seconds). Patients who did not meet requirements for retreatment were excluded from visit 9 (week 12) analysis. Patients whose visits fell outside of the predefined window or had missing responses were excluded from analysis of that visit. The percentage of individual lesions showing complete response or clearing, the percentage of patients who experienced 75% clearance or greater of target AKs (75% response rate), and the percentage of patients who experienced 100% clearance of target AKs (100% response rate) were analyzed using the Cochran-Mantel-Haenszel test to evaluate any treatment differences.

Safety

All randomized patients who received study medication were included in the safety analysis. The safety variables (adverse events, phototoxic reactions, pigmentation, and laboratory results) were summarized by descriptive statistics.

Table 1. Patient Demographics*

Characteristic	ALA Group (n = 181)	Vehicle Group (n = 62)
Mean age (range), y	67.1 (34-89)	64.5 (35-85)
Sex		
Female	34 (19)	6 (10)
Male	147 (81)	56 (90)
Fitzpatrick skin type		
I	52 (29)	20 (32)
II	90 (50)	23 (37)
III	36 (20)	17 (27)
IV	3 (2)	2 (3)
White race	181 (100)	62 (100)

Abbreviations: ALA, aminolevulinic acid hydrochloride at 20% wt/vol.
*Unless otherwise indicated, data are number (percentage) of subjects.

RESULTS

Results from the independent trials were similar and showed significant differences between treatment groups when analyzed separately and using the combined data. Randomization was done separately for each center, and analysis of the data included stratification by investigator.

Patient demographics are summarized in **Table 1**. A total of 243 patients (40 women and 203 men) were randomized to receive ALA (n=181) or vehicle (n=62) and blue light treatment. There were no statistically significant differences in patient demographics between the treatment groups.

No patients had a medical history that influenced any potential effect of the treatment. Ninety-six percent (233/243) of patients completed the study. Reasons for not completing the study were patient noncompliance (4 patients in the ALA group, 2 in the vehicle group), patient request for withdrawal (1 in the ALA group), death (1 in the ALA group), and other (1 patient in each group).

ANALYSIS OF EFFICACY

A typical lesion clearance response is seen in **Figure 1**. The response rates by patient and lesion are summarized in **Table 2**. The significance of all lesion response rates was calculated with the Cochran-Mantel-Haenszel general association test. The differences in response rates for patients with 75% or more of their AKs cleared were significant ($P<.001$) at week 8 (77% [128/166] for ALA vs 18% [10/55] for vehicle) and week 12 (89% [133/149] for ALA vs 13% [7/52] for vehicle). The 95% confidence interval for the difference in response rates at week 8 was 46.9% to 71.0% and at week 12, 65.3% to 86.3%. The complete response rates for patients with 100% of AKs clearing at weeks 8 and 12 were 66% (109/166) and 73% (109/149), respectively, for ALA and 11% (6/55) and 8% (4/52), respectively, for vehicle ($P< .001$ at weeks 8 and 12). The 95% confidence interval for the difference in response rates at week 8 was 43.8% to 65.7% and at week 12, 55.3% to 75.6%. The ALA week 12 response rates include 30% (55/181) of patients who received a second treatment.

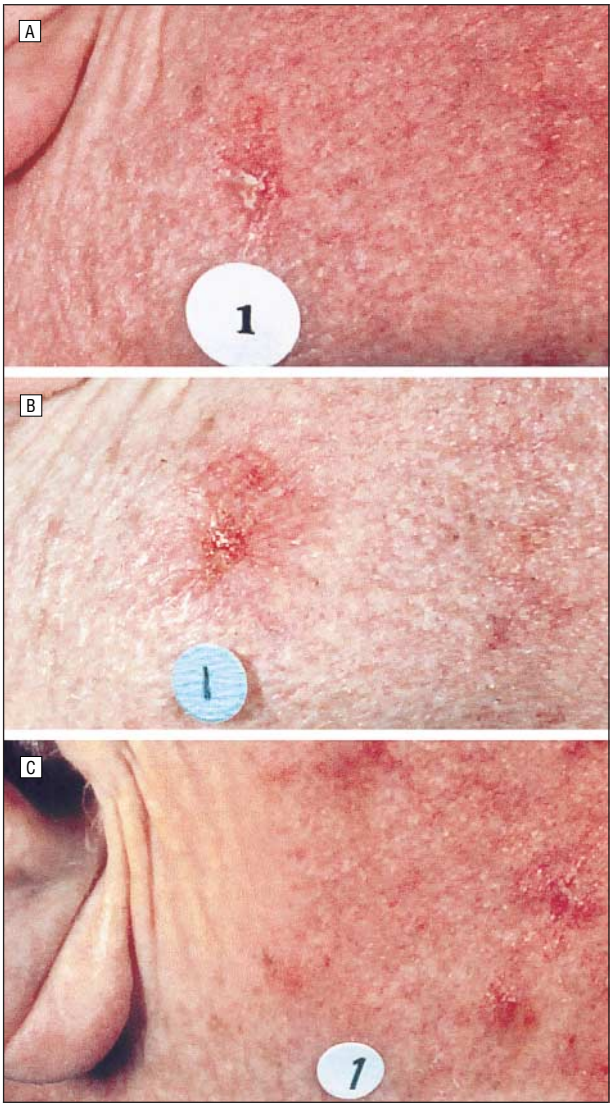

Figure 1. Case example from the phase 3 clinical trial. Pictured is a single actinic keratosis lesion before treatment (A), 24 hours after treatment (B), and 8 weeks after treatment (C).

Individual AK lesion response rates independent of how many individual lesions treated cleared at weeks 8 and 12 were 83% (1046/1258) and 91% (1019/1114), respectively, for ALA and 31% (139/455) and 25% (109/428), respectively, for vehicle ($P<.001$ at weeks 8 and 12). The 95% confidence interval for the difference in response rates at week 8 was 47.9% to 57.3% and at week 12, 61.6% to 70.4%.

SAFETY

Similar incidences of adverse events were seen for patients treated with either ALA or vehicle. However, the ALA-treated patients appeared to have higher incidences of headache (6.6% vs 3.2%), injury (5.0% vs 1.6%), hypertension (1.7% vs 0), and skin hypertrophy (1.7% vs 0).

Of 113 adverse events, 104 (92%) were judged to be of mild or moderate severity; 8 (7%) were rated as severe. One life-threatening adverse event occurred in a patient who was diagnosed with hepatocellular carcinoma

Table 2. Summary of Patient and Lesion Complete Response Rate*

	ALA Group	Vehicle Group
Total No. of patients treated	181	62
≥75% Treated AKs clearing		
Week 8	128/166 (77)	10/55 (18)
Week 12†	133/149‡(89)	7/52 (13)
100% Treated AKs clearing		
Week 8	109/166 (66)	6/55 (11)
Week 12†	109/149§(73)	4/52 (8)
Total No. of lesions treated	1403	506
Lesion complete response rate		
Week 8	1046/1258 (83)	139/455 (31)
Week 12	1019/1114 (91)	109/428 (25)

Abbreviations: AK, actinic keratosis; ALA, aminolevulinic acid hydrochloride at 20% wt/vol.

*Unless otherwise indicated, data are number of responding patients/number of possible responding patients (percentage of responding patients).

†The ALA week 12 response rates include 55 (30%) of 181 patients who received a second treatment.

‡Week 12 response rate for patients with only 1 treatment was 95%; week 12 response rate for patients with 2 treatments was 76%.

§Week 12 response rate for patients with only 1 treatment was 87%; week 12 response rate for patients with 2 treatments was 41%.

Table 3. Clinical Adverse Events Related to ALA Treatment*

Treated with ALA	181 (100)
Total No. of adverse events	3 (2)
Headache	1 (<1)
Dry skin	1 (<1)
Conjunctivitis	1 (<1)
Relationship to treatment	
Definite	0
Probable	1 (<1)
Possible	2 (1)

Abbreviation: ALA, aminolevulinic acid hydrochloride at 20% wt/vol.

*Data are number (percentage) of patients.

and who eventually died, an event deemed unrelated to study treatment. Ninety-seven percent of adverse events in the ALA group were unrelated to treatment. Adverse events related to ALA were headache, dry skin, and conjunctivitis (**Table 3**). No patient withdrew from either study owing to an adverse event.

PATIENT DISCOMFORT

Figure 2 shows the severity of stinging or burning during initial ALA PDT treatment at 1, 6, and 11 minutes after initiation of light treatment. The sensation of stinging or burning appeared to reach a plateau at 6 minutes into the treatment, with moderate-severe discomfort reported by at least 90% of patients treated with ALA. In 3% of patients, light treatment was discontinued before the full dose of light was given owing to the severity of the stinging or burning. Five patients terminated blue light treatment at fluences lower than 5 J/cm^2.

The percentage of patients who reported severe levels of stinging or burning discomfort decreased by at least half immediately after light treatment (from 37% after 6 minutes of treatment to 14% immediately after treatment completion), with most (81%) reporting only minimal to moderate discomfort. By 24 hours after light treatment, only 2 patients reported severe sensations of stinging or burning, and only 28% of patients reported any discomfort. This number decreased to 7% by 1 week after light treatment.

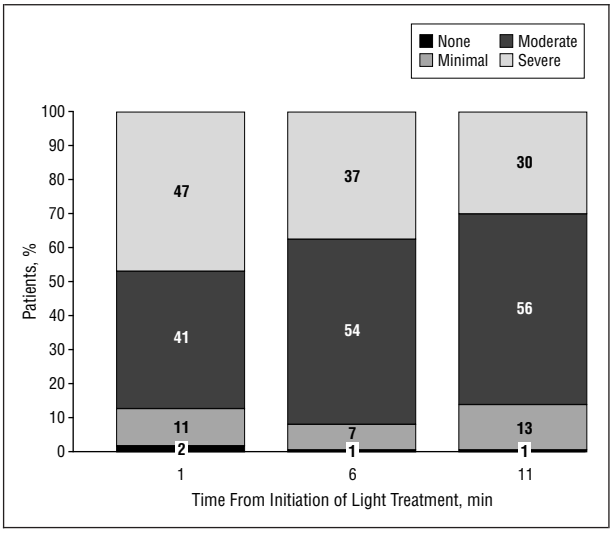

Figure 2. Severity of stinging or burning discomfort during initial photodynamic therapy of 181 patients with topical aminolevulinic acid at 20% wt/vol. The numbers inside the bars indicate the number of patients in the given discomfort category.

The most common changes in lesion appearance after ALA PDT were erythema and edema, which resolved or improved within 1 to 4 weeks after therapy. Erythema was seen in 76% of ALA-treated patients at baseline, and increased to 93% after drug application (before light treatment). The percentage of patients with erythema increased to 99% immediately after light treatment. One and 4 weeks after light treatment, erythema was observed in 83% and 57%, respectively, of ALA-treated patients. Incidence of erythema did not increase after treatment with vehicle. Seventy-nine percent of patients in the vehicle group had erythematous lesions at baseline and after light treatment. One week after light treatment, 65% of patients still had erythematous lesions.

One patient presented with edema at baseline. Incidence of edema in the ALA group increased to 13% just prior to light treatment and peaked at 38% twenty-four hours after light treatment. One week later, the incidence of edema decreased to 5%. One patient in the vehicle group reported edema (at baseline only).

The most common local responses to ALA PDT were (1) crusting, observed in 49% of patients and 34% of lesions; (2) pruritis, which was observed in 30% of patients and 22% of lesions; and (3) scaling, which was observed in 31% of patients and 19% of lesions. Other very rare findings such as blister or vesicle formation were reported in about 1% of all lesions treated.

Pigmentary changes of lesions, classified as hyperpigmentation or hypopigmentation, were uncommonly seen. In the ALA group, 1403 lesions were treated, and 1340 were evaluated for pigmentation. In the vehicle

group, 506 lesions were treated, and 483 were evaluated for pigmentation. At week 12, 95% of the ALA-treated lesions and 90% of the vehicle-treated lesions had no pigmentary changes. Compared with baseline, there was no change in hyperpigmentation or hypopigmentation noted throughout the study in either group. Treatment with ALA PDT using blue light therefore does not appear to promote significant pigmentary changes in AKs.

COMMENT

The results of this study demonstrate that ALA PDT using blue light is a highly effective therapy for facial and scalp AKs, with positive results persisting over the 12-week follow-up period. A phase 4 study with a 1-year follow-up period is currently under way to determine if the high response rates seen in this study are maintained over a prolonged time period.

Safety analyses revealed no treatment-emergent systemic signs or symptoms or clinically significant changes in laboratory parameters. The most common changes in lesion appearance were erythema and edema, with the application of ALA resulting in a slight increase in mild to moderate erythema and edema in the 14- to 18-hour interval prior to light treatment. Incidence of erythema and edema peaked during the 24-hour period after light treatment, with improvement and resolution occurring within 1 to 4 weeks after therapy. Additionally, no treatment-related pigmentation effects were found. The most common adverse experience was stinging or burning during light treatment. The stinging or burning sensation resolved in virtually all patients by 24 hours after light treatment. This can be significant in some patients and postmarketing experience has shown that the use of topical anesthetics and cooling with a fan, sprays, or other means has markedly improved the discomfort associated with the therapy.

The results of this study are consistent with previous observations of a good clinical response of typical AKs to PDT using ALA.[11-14] In an early study, Wolf et al[13] treated a small number of lesions and found that 9 of 9 completely responded to the treatment. Calzavara-Pinton[14] treated 50 AKs on the face, which required an average of 2 treatments (range, 1-3), and achieved 100% apparent clinical complete responses. Of 33 AKs observed for 24 to 36 months, 5 (15%) of 33 developed recurrences at 3, 6, 15, 19, and 32 months.

Most PDT studies with ALA for treatment of cutaneous lesions have used red light because of deeper light penetration in human skin.[12] Jeffes et al[11] reported an 85% complete response rate after a maximum of 2 treatments in a light dose-ranging study where a blue light source was used. Since PpIX has a maximum absorption at 410 nm (Soret band) and blue light is approximately 50 times more effective in activating PpIX than is red light, these shorter wavelengths were considered effective in treating superficial AKs.[10] Recently, the long pulsed–dye laser was shown to produce results similar to incoherent broadband lamp light in the activation of ALA for PDT of AKs,[15] suggesting that light sources already present in some dermatology practices may prove useful for photodynamic activation.

Esters of ALA have also been synthesized and evaluated as potential PDT drugs. A comparative study of methyl-ALA and cryotherapy was conducted by Szeimies et al.[16] They performed a multicenter comparison of 193 patients (699 AKs) randomized for treatment with either m-ALA or cryotherapy. Overall response rates were similar between the groups at 3 months (69% cleared for PDT and 75% for cryotherapy), but the cosmetic outcome was superior for the PDT group.

Topical ALA PDT treatment clearly offers a significant clinical benefit, but the time required for treatment makes it a more practical consideration for patients with multiple AKs. Anecdotally, the therapeutic benefit of ALA PDT is comparable to cryotherapy and may offer a better safety profile, but there are no controlled comparison trials. Photodynamic therapy with ALA may also be better than other AK treatments with respect to ease of treatment of multiple identifiable AKs, especially when home-based therapies such as fluorouracil are the treatments of choice.[17,18] Typically, home therapies like fluorouracil require 2 to 4 weeks of treatment followed by an additional 4 to 8 weeks for healing.[19] The physician-controlled nature of ALA PDT as well as its demonstrated safety and efficacy and the rapid healing of erythema and edema within 1 to 4 weeks make it an attractive alternative for both the patient and the physician.

In summary, ALA PDT offers a safe and effective therapeutic alternative for the treatment of AK. The treatment is particularly appropriate for patients with multiple nonhyperkeratotic AKs and offers physicians a new alternate to home application therapy for these patients.

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News and Notes

The National Registry for Ichthyosis and Related Disorders is seeking enrollment of all patients with inherited disorders of keratinization (except ichthyosis vulgaris). Serum testing for X-linked recessive ichthyosis, as well as molecular diagnosis of selected disorders, is available without charge. We are eager to assist with research efforts, and we welcome proposals. Information and enrollment forms can be downloaded from our Web site. Please contact us to enroll your affected patients or discuss research interests: phone: 1-800-595-1265; e-mail: info@skinregistry.org; Web site: www.skinregistry.org.