

BRIEF ARTICLES

Photodynamic Therapy with δ -Aminolevulinic Acid and Blue Light for the Treatment of Actinic Cheilitis

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ABSTRACT

Background: Actinic cheilitis is a common precancerous disorder of the lower lip caused by ultraviolet radiation. Photodynamic therapy (PDT) is a potential treatment for actinic cheilitis, however controlled clinical trials regarding this treatment are needed.

Objective: To evaluate the safety and efficacy of PDT with blue light and topical δ -aminolevulinic acid (Levulan®) in the treatment of actinic cheilitis.

Methods: We conducted a single center, investigator-initiated, nonrandomized, open-label, proof of concept study of PDT with blue light for the treatment of actinic cheilitis. We enrolled 24 subjects, 20 meeting inclusion and exclusion criteria. One subject withdrew from the study prior to treatment. The study consisted of a screening visit, one to three scheduled treatments, and two follow-up visits. The primary outcome was clinical improvement in actinic cheilitis from baseline, estimated as no (0%), mild (25%), moderate (50%), marked (75%), or excellent improvement (100%). Post-treatment assessment of swelling, erythema, flaking/scaling, crusting, vesiculation/pustulation, and erosion/ulceration was also recorded. Subjects completed the Dermatological Life Quality Index questionnaire, subject global assessment of improvement, and pain assessment at each visit.

Results: 65% of subjects achieved clinical improvement of 75% or greater and 20% achieved 100% improvement by the end of the study. Treatments were well tolerated with minimal discomfort. Subjects experienced transient mild adverse effects.

Conclusion: Overall, our study supports using PDT for the treatment of actinic cheilitis.

INTRODUCTION

Actinic cheilitis is a common precancerous manifestation of severe photodamage of the lower lip caused by chronic ultraviolet radiation.^{1,2} Conventional therapies, such as cryotherapy, topical 5-fluorouracil or imiquimod, chemical peels, electrodesiccation, laser ablation, and vermilionectomy are accepted treatments.³ However, they can be expensive or time-consuming, can require local or general anesthesia, and can be associated with noncompliance, high recurrence rates, or scars. Alternative treatments for actinic cheilitis would be helpful.

Several reports have shown photodynamic therapy (PDT) to be an effective treatment of actinic cheilitis requiring relatively few PDT treatments and causing minimal cutaneous side effects.^{2,4,5} PDT is based on the combined use of photosensitizers and photoradiation. Topically applied δ -aminolevulinic acid (ALA) is theorized to be taken up by premalignant cells. Upon irradiation with a light source, photoactivated porphyrins produce singlet oxygen and other potent oxidizers, resulting in cell death.^{2,6,7,8} Unfortunately, controlled clinical trials assessing the efficacy of PDT for actinic cheilitis are lacking. We hypothesized that using PDT with blue light and topical ALA treatment is a safe and effective treatment for actinic cheilitis.

METHODS

We conducted a single center, investigator initiated, nonrandomized, open-label, proof of concept study of PDT with blue light and topical ALA in the treatment of actinic cheilitis. We sought to enroll a total of 20 subjects in the study. The study was approved by our institutional review board.

Subject recruitment

Patients at least 18 years of age from the outpatient dermatology clinic with a clinical diagnosis of actinic cheilitis were invited to participate in the study. Exclusion criteria included active herpes labialis lesions, pregnancy or lactation, and use of any treatment for actinic cheilitis within 3 months of study entry.

Visit schedule

The study consisted of a screening visit, up to 3 scheduled treatments 6 weeks apart, and 2 follow-up office visits 12 and 24 weeks after the final treatment. Total study duration was approximately 36 weeks. Treatments were discontinued once the patient achieved clinical clearance. Study medication application, blue light therapy, post-therapy assessments, tolerability assessments, and photographs were performed at each visit.

Treatment Parameters

Levulan® Kerastick® (supplied by DUSA Pharmaceuticals, Inc.) containing 354 milligrams of aminolevulinic acid HCl at 20% concentration was applied topically to the pre-cleaned designated treatment area. After an incubation period of 90 minutes, the area was cleaned, and BLU-U® blue light (417 nanometers) was administered to the target area for 16 minutes and 40 seconds, resulting in approximately 10 J/cm² delivered at 10 mW/cm². Subjects were given post-treatment instructions on aftercare (gentle cleansing, petrolatum application, and sun protection for at least 48 hours after each treatment).

Outcomes

The primary outcome was assessed by the investigators as clinical improvement in actinic cheilitis from baseline to the end of the study (approximately week 36) and was estimated as none (0%), mild (25%), moderate (50%), marked (75%), or excellent (100%). Post-treatment investigator assessments of swelling, erythema, flaking/scaling, crusting, vesiculation/pustulation, and

erosion/ulceration were graded on a scale of 0 to 4 (none, mild, moderate, severe). Adverse events were assessed at every visit.

Subjects completed the Dermatological Life Quality Index (DLQI) questionnaire every visit except during screening.⁹ The subject global assessment was also performed to assess the subjects' impression of their overall improvement as compared to baseline, defined as none (0%), mild (25%), moderate (50%), marked (75%), and excellent (100%). Pain was assessed at each treatment visit using a Visual Analogue Scale (VAS) from 0 to 10, 0 indicating no pain and 10 indicating the worst possible pain. Two days after each treatment, patients were contacted by telephone and asked to assess redness, swelling, and dryness (graded on a scale of 0 to 4).

RESULTS

The primary outcome is shown in Table 1. Of the 20 subjects that participated in the study, 65% achieved clinical improvement of 75% or greater at the end of the study according to the investigators' assessment. Four of these subjects (20%) achieved 100% improvement. Five subjects (25%) discontinued the study prior to week 36 - one of whom was lost to follow-up before any assessment of clinical improvement was performed. If all available subjects' results are included in the analysis as of the time of their last assessment, 80% achieved clinical improvement of at least 75%, and five subjects (25%) achieved 100% improvement (mean improvement 75%, standard deviation (SD) 24% for those present for assessment). Based on the subjects' assessment of improvement, 60% achieved improvement of at least 75% by the final assessment. Based on a concordance analysis using kappa calculation and McNemar's test, investigator and subject

assessments of improvement were concordant overall (Concordance (kappa) = 0.7814; McNemar P-value = 0.01431).

Side effects are depicted in Table 2. In general, treatments were well tolerated with minimal discomfort. Many subjects had transient side effects including swelling, erythema, and flaking. Very few subjects had more serious side effects, such as vesiculation, pustulation, or crusting. No subjects experienced erosion or ulceration. Pain during treatment averaged 3.2 on a scale of 0 to 10 (SD 1.8) on the VAS. Quality of life, as assessed by the DLQI, remained relatively unaffected throughout the study (mean DLQI 0.75, SD 1.29). There were no significant adverse events attributable to participation in the study.

Table 1. Primary Outcome: Clinical Improvement

Improvement at week 36 (%)	Number of participants (%)
Excellent (100)	4 (20)
Marked (75)	9 (45)
Moderate (50)	1 (5)
Mild (25)	0 (0)
None (0)	1 (5)
Discontinued/Lost to Follow-Up	5 (25)

Table 2. Side Effects (graded 0 to 4)

Local skin reaction	Immediately post-treatment: mean (SD)	2 days post-treatment: mean (SD)*
Swelling	1.33 (0.74)	2.10 (1.12)
Erythema	1.92 (0.80)	2.53 (1.14)
Flaking/Scaling or Dryness	0.55 (0.61)	2.41 (1.21)
Crusting	0.08 (0.27)	n/a
Vesiculation/Pustulation	0.04 (0.20)	n/a
Erosion/Ulceration	0 (0)	n/a

*subject reported

DISCUSSION

Overall, our study supports using PDT for the treatment of actinic cheilitis. Based on investigator assessment, 65% of subjects

had improvement of at least 75% at week 36. Eighty percent of subjects (including those that discontinued early) had improvement of at least 75% by the time of their last assessment. Treatments were well-

Figure 1. One study subject (A) pre-treatment 1 and (B) 7 weeks post-treatment 3



tolerated with minimal pain and transient side effects; swelling, erythema, and scaling were most common. Limitations of this study include its small sample size, lack of blinding or randomization, and a subjective rather than objective (e.g. histological) assessment of outcomes. In conclusion, PDT therapy for actinic cheilitis achieves significant improvement or clearance at 36 weeks. A follow up study to assess recurrence after treatment would be beneficial.

Conflict of Interest Disclosures and Funding:

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