Title: Treatment of moderate to severe inflammatory acne vulgaris: photodynamic therapy with 5-aminolevulinic acid and a novel Advanced Fluorescence Technology pulsed light source.(Clinical report)

Date: 3/1/2007; **Publication**: Journal of Drugs in Dermatology; **Author**: Gold, Michael H.;Biron, Julie A.;Boring, Molly;Bridges, Tancy M.;Bradshaw, Virginia L.

Abstract

The use of photodynamic therapy (PDT) with 20% 5-aminolevulinic acid (ALA) for the treatment of acne vulgaris has been explored. This study evaluates the safety and efficacy of a new Advanced Fluorescence Technology (AFT) pulsed light source (420-950 nm) for photoactivation in ALA PDT for the treatment of moderate to severe inflammatory facial acne vulgaris. Nineteen subjects received 4 ALA PDT treatments with the AFT pulsed light source. Treatments were spaced 2 weeks apart. ALA was incubated for 15 to 30 minutes. At the end of the fourth treatment, the total reductions in inflammatory and noninflammatory lesion counts were 54.5% and 37.5%, respectively. Median Global Severity Scores suggest a trend toward reduction after several treatments. Investigator and subject assessments show moderate to marked improvement in most patients. The new AFT pulsed light source with ALA PDT appears to be a safe and effective modality for the treatment of moderate to severe inflammatory acne vulgaris.

Introduction

The use of photodynamic therapy (PDT) with 20% 5-aminolevulinic acid (ALA) for the treatment of mild to severe acne vulgaris has been explored by many investigators. The rationale for this approach is based on the update of exogenous ALA by pilosebaceous units, the conversion of ALA to photosensitive

protoporphyrin IX (PpIX), the production of porphyrins by Propionibacterium acnes, and the photoexitation of PpIX and bacterial porphyrins to form cytotoxic singlet oxygen. A variety of light sources and lasers have been used for photoactivation of ALA-induced PpIX (1-3) and methyl aminolevulinate (MAL) has also been used as photosensitizing agent. (4) A panel of experts has recently agreed that ALA PDT is generally more effective against inflammatory and cystic acne than comedonal acne. (3)

This study evaluates the safety and efficacy of a new pulsed light source (420-950 nm) with Advanced Fluorescent Technology (AFT) for photoactivation in ALA PDT for the treatment of moderate to severe inflammatory acne vulgaris of the face.

Materials and Methods

Nineteen healthy subjects (aged 19 to 46 years, skin types II-VI, all women) with moderate to severe inflammatory acne of the face (at least 20 inflammatory lesions and a Global Severity Score of 2) participated in the study. The study was approved by the Essex Institutional Review Board, Inc., and all subjects gave signed informed consent to treatment. Subjects were excluded if their histories included previous treatment with laser or light devices or ALA to areas to be treated, severe comedonal acne, autoimmune disease, porphyria or allergy to porphyrins, abnormal photosensitivity, mental illness, topical acne medications within the previous 2 weeks, systemic antibiotics or steroids within the previous 4 weeks, systemic retinoids within the previous 6 months, treatment with an investigational drug within the previous 30 days, dermal filler treatments, botulinum toxin, chemical peels, dermabrasion, keloid or scar formation, uncorrected coagulation defects, or any condition which, in the investigator's opinion, would make it unsafe to participate in this study. Pregnancy or unacceptable methods of birth control were also grounds for exclusion.

At the beginning of the study subjects were given a cleanser to use throughout the study and beginning at least 7 days prior to the first study medication application. Subjects were instructed to avoid other cleansers or prohibited topical medications other than the study medications on their face.

[FIGURE 1 OMITTED]

The study flow chart is shown in Table 1. Patients received 4 ALA PDT treatments with the AFT pulsed light source (420-950 nm, Harmony, Alma Lasers, Inc., Fort Lauderdale, Fla). The ALA was Levulan[R] Kerastick[R] (Dusa Pharmaceuticals, Wilmington, Mass). Treatments were spaced 2 weeks apart. ALA incubation times varied from 15 to 30 minutes. Fluences were 5 to 7 J/[cm.sup.2], pulse width was 30 to 50 ms, and light treatment was for 5 to 10 minutes. The 420 handpiece was used throughout the study and subjects typically received 2 passes at each treatment session.

Results were evaluated by lesion counts, Global Severity Score, improvement scores, and adverse effects.

Acne lesions were counted on visits 1 through 6. Comedones (open and closed), papules, and pustules, and nodules were counted and recorded on the face vertically from the hairline to mandible rim and horizontally from ear to ear.

A Global Severity Score was assigned to each subject on visits 1 through 6. The scale was 0 to 3 in which 0 = clear, no lesions; 1 = mild, less than 10 inflammatory lesions; 2 = moderate, around 20 inflammatory lesions; and 3 = severe, greater than 40 inflammatory lesions localized or scattered. Enrolled subjects had a Global Severity Score at least 2 at visit 1.

Improvements were assessed by comparing facial acne to observations at visit 1. Improvement grades were assigned as follows: 0 = none; 1 = slight (25%); 2 = moderate (50%); 3 = marked (75%); 4 = complete clearing (95%).

Adverse effects (mottled hyperpigmentation, erythema, edema, stinging [before and after treatment], crusts, and erosions) were graded on a scale of 0 to 3 with 3 as most severe.

Overall improvement was assessed by the investigator and by subjects on visits 5 and 6.

Results

Fifteen of the 19 subjects completed the study up to visit 5. One was lost to follow-up and the remaining 3 withdrew consent. Since 4 of the 15 patients who completed the study up to visit 5 provided data for all parameters at visit 6 (week 19), the data from visit 6 was not included in the analyses.

The reductions in both inflammatory and noninflammatory lesion counts is shown in Figure 1.

The median Global Severity Score at weeks 1, 3, and 5 was 2.0 (2.0-2.0) (96.6% CI, n=15). At weeks 7 and 11 the median Global Severity Score was 2.0 (1.0-2.0) (96.6% CI, n= 15). The extension of the lower limit of the range from 2.0 to 1.0 at weeks 7 and 11 suggests a trend toward reduction in Global Severity Score, although the medians remain constant.

[FIGURE 2 OMITTED]

Improvements in acne for two patients are shown in Figures 2 and 3.

[FIGURE 3 OMITTED]

The median (96.5% CI) investigator-assessed improvement score was 2.0 (1.0-2.0), slightly lower than the corresponding subject-assessed 2.5 (2.0-3.0) at visit 5.

The adverse effect data are shown in Table 2.

Mottled hyperpigmentation increased slightly by the third treatment (visit 3) and again by visit 5, 4 weeks after the final treatment as suggested by the extension of the upper limit of the 96.5% CI from 1.0 to 2.0. Erythema and pretreatment stinging (while ALA incubated) were slight (0.0 and 1.0, respectively) and did not change throughout the course of treatment. Post-treatment stinging was greater (2.0 [1.0-2.0]) than pretreatment stinging, but did not become more severe with continued treatment.

Discussion

The results show that ALA PDT with the novel AFT pulsed light source (420-950 nm) for photoactivation is a safe and effective treatment of moderate to severe acne. As in earlier studies with ALA PDT for acne, lesion count reduction is greater for inflammatory lesions than for noninflammatory lesions. (3)

The use of pulsed light with ALA PDT for the treatment of acne vulgaris has been reported in 2 studies. (5,6) In the study of Gold and colleagues, (5) 12 patients responded to ALA PDT with intense pulsed light (IPL) and a heat source. Reduction in inflammatory lesions was 50.1% after 4 once-weekly treatments, 68.5% 4 weeks later, and 71.8% 12 weeks after the final treatment. In the present study, the reduction in inflammatory lesion counts was 54.5%, slightly higher than the 50.1% reported earlier. Unlike the present study, a heat source was also used and the treatments were given one week apart rather than 2 weeks apart. ALA contact time was 1 hour, more than twice as long as the 15- to 30-minute ALA contact time in the present study. Fluences and pulse durations used in the earlier study were 3 to 9 J/[cm.sup.2] and 35 ms, respectively, similar to 5 to 7 J/[cm.sup.2] and 30- to 50-ms settings used in the present study. In both studies, the treatments were well-tolerated.

In a split-face study of patients with various degrees of acne, Santos and colleagues (6) treated one side of the faces with ALA PDT and IPL and the other side with IPL alone. Two treatments were given spaced 2 weeks apart. ALA was

incubated 3 hours and fluences started at 26 J/[cm.sup.2] and were increased to 34 J/[cm.sup.2]. Treatment was given in double pulses (2.0 and 6.0 ms). After 2 treatments, visible improvement was apparent in most patients on both sides of the face with the ALA PDT side showing greater improvement. Results were evaluated by a subjective grading system and lesion counts were not reported.

Conclusion

The new AFT pulsed light source (420-950 nm) for photoactivation in ALA PDT appears to be a safe and effective modality for the treatment of moderate to severe acne vulgaris of the face.

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Table 1. Study flow chart.

Procedure	Screening	Visit 1 (wk 1)	Visit 2 (wk 3)	Visit 3 (wk 5)	Visit 4 (wk 7)
Clinical evaluation	X	X	X	X	X
Treatment		X	X	X	X
Adverse events		X	X	X	X
Subject evaluation					X

Procedure	Visit 5 (wk 11)	Visit 6 (wk 19)
Clinical evaluation	X	X
Treatment		
Adverse events	X	X
Subject evaluation	X	X

Table 2. Median (96.5% CI) severity of adverse effects during visits 1-5
(weeks 1-11).

Adverse effects	Visit (wk) 1 (1)	2 (3)	3 (5)
Mottled hyperpigmentation	0.0 (0.0-1.0)	0.0 (0.0-1.0)	1.0 (0.0-1.0)
Erythema	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
Stinging (pretreatment)*	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Stinging (post-treatment) ([dagger])	2.0 (1.0-2.0)	2.0 (1.0-2.0)	2.0 (1.0-2.0)

Adverse effects	Visit (wk) 4 (7)	5 (11)
Mottled hyperpigmentation	1.0 (0.0-1.0)	1.0 (0.0-2.0)
Erythema	0.0 (0.0-1.0)	0.0 (0.0-1.0)
Stinging (pretreatment)*	1.0 (1.0-1.0)	--
Stinging (post-treatment) ([dagger])	2.0 (1.0-2.0)	--

*Before light treatment. ([dagger]) After light treatment.