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The Use of a Novel Intense Pulsed Light and Heat Source and ALA-PDT in the Treatment of Moderate to Severe Inflammatory Acne Vulgaris

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Abstract

The use of lasers and noncoherent light sources is becoming more commonplace in the treatment of inflammatory acne vulgaris. Topical 5-aminolevulinic acid (ALA) is finding its niche as an enhancer to these laser and light sources. Twenty patients with moderate to severe inflammatory acne vulgaris were enrolled in a clinical trial to evaluate the efficacy of ALA-PDT with activation by a SkinStation® LHE® (Radiancy, Inc., Orangeburg, NY), a novel intense pulsed light (IPL) and heat source that emits 430-nm to 1100-nm radiation at 3 to 9 J/cm2 fluences. Patients were given topical ALA (Levulan® Kerastick®, Dusa Pharmaceuticals, Inc., Wilmington, MA) photosensitizing agent that remained in contact with skin for one hour before irradiation. Fifteen patients completed the trial and 12 responded to the treatment. Among respondents, reduction in active inflammatory acne lesions was, on average, 50.1% at the end of the 4-week treatment period, 68.5% 4 weeks after the final treatment, and 71.8% 12 weeks after the final treatment. ALA-PDT with IPL activation was well-tolerated by all patients. No treated lesion recurred at the end of the follow-up period. ALA-PDT with IPL activation is a treatment option for patients with moderate to severe inflammatory acne vulgaris.

Introduction

A difficult disease to treat, acne vulgaris (acne) accounts for more than 30% of all visits to dermatologists. Approximately 80% of the population will suffer from this condition at some time[1]. Acne affects more than 40 million American adolescents and approximately 25 million American adults[2].

Acne is a multifactorial disease. Both genetics and hormonal changes that begin during puberty play a role in its development. In its simplest form, acne is a disorder of the sebaceous glands where hormonal activity results in glandular dilation, obstruction, and proliferation of *Propionobacterium Acnes (P. Acnes)* bacteria. This is clinically evident as the papules, pustules, and cystic lesions characteristic of inflammatory acne vulgaris.

Treatment options for acne include topical and systemic antibiotics, topical benzoyl peroxides, topical salicylic acid, and topical and systemic retinoids. Use of these agents, however, is often difficult and frustrating. Topical medications may irritate the skin and require several months for a positive response. Antibiotic resistance rates up to 60% have been reported [1,3] and long-term use of tetracycline may increase the risk of breast cancer[4]. Finally, lay press reports of teratogenic and psychological problems associated with systemic retinoid therapy have raised concerns about these drugs.

Exposure to ultraviolet (UV) light has been reported effective against acne vulgaris by researchers[5] and patients. Although not fully understood, the mechanism of the UV effect presumably involves destruction of *P. Acnes* in the sebaceous gland, leading to lesional resolution. The potential of UV exposure to cause photoaging and skin cancer preclude its regular use in the treatment of acne.

Photodynamic therapy (PDT) requires a photosensitive compound, light, and molecular oxygen to kill cells[6,7]. As *P. Acnes* proliferates in sebaceous glands, they produce protoporphyrin IX (PpIX) and coproporphyrin III, both of which demonstrate an absorption maximum at 415 nm, in the range of blue light with a second peak in the red light range (630 nm) and several smaller peaks in between blue and red light[8]. When these

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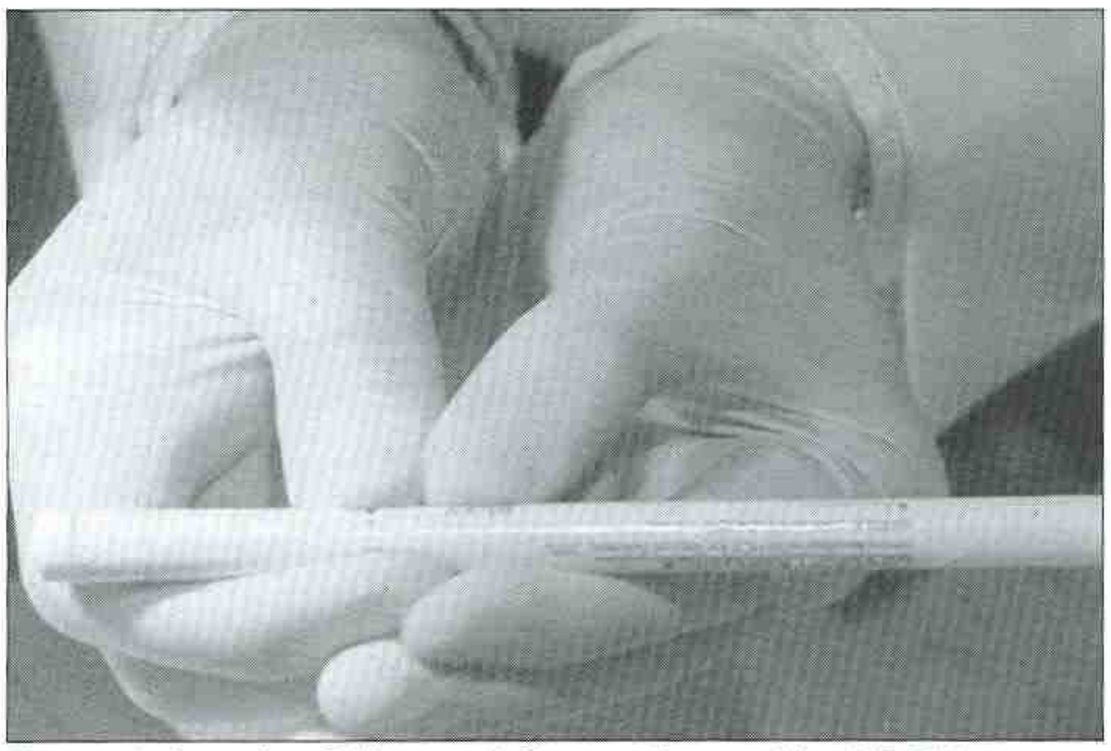

Figure 1. Levulan® Kerastick® manufactured by DUSA Pharmaceuticals, Inc.

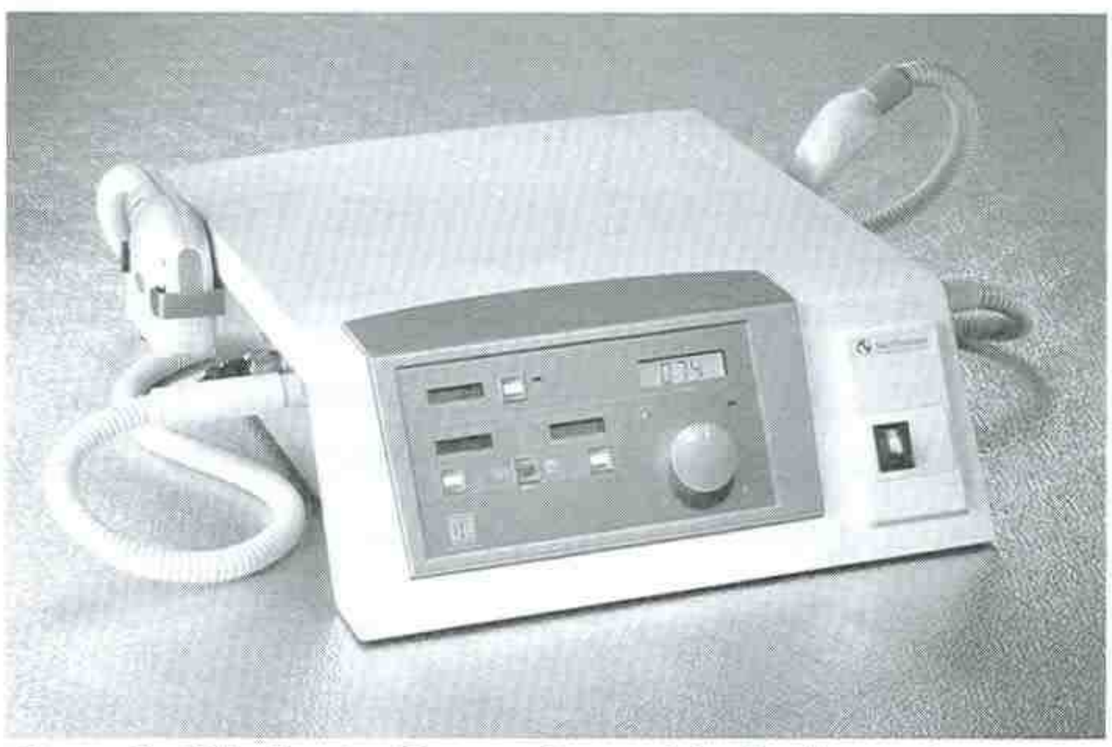

Figure 2. SkinStation® manufactured by Radiancy, Inc.

photosensitive porphyrins are irradiated with blue light, the singlet oxygen produced selectively destroys the bacterial cells and clears the acne lesions. Clinical trials[9-14] have shown the effectiveness of endogenous PDT with blue light in mild to moderate inflammatory acne. Several laser and light-based systems, including an intense pulsed light (IPL) and heat source (LHE®), have also been shown to be effective in the treatment of mild to moderate inflammatory acne[15-18].

To enhance the photodynamic reaction and potentially treat moderate to severe inflammatory acne, investigators began to use an exogenous form of PDT in which a photosensitizing agent, 5-aminolevulinic acid (ALA), is topically applied to the area to be treated before light treatment[19]. As part of the natural biosynthetic pathway for heme, topical ALA enters the skin and is converted to the photosensitive PpIX. Activation of PpIX, again by light of an appropriate wavelength, leads to the formation of cytotoxic singlet oxygen[6,7]. The use of the exogenous ALA is thought to act in a synergistic manner to enhance the photodynamic reaction.

The applications of ALA-PDT in dermatology—including actinic keratoses, superficial basal cell carcinoma, squamous cell carcinoma, Bowen's disease, and other cutaneous conditions—have been thoroughly reviewed[6,7,20-23]. More recent uses are in the treatment of recalcitrant verrucae vulgaris and molluscum contagiousum[24] as well as hidradenitis supporitiva[25].

Since reports suggest that acne vulgaris[26-31] and sebaceous gland hyperplasia[29,32,33] respond to ALA-PDT, we evaluated the efficacy of short-contact, full-face ALA-PDT with a novel light and heat (LHE) technology for the treatment of moderate to severe inflammatory acne vulgaris.

Materials and Methods

The clinical trial was performed at the Tennessee Clinical Research Center under the auspices of the Western Institutional Review Board (WIRB), Seattle, Washington. All patients gave signed informed consent before participating in this research program. Patients receiving topical and/or systemic medications for treatment of their acne or those with a history of light-based treatments for their acne were excluded. Patient participants had a minimum of 15 facial inflammatory acne lesions, consisting of papules, pustules, and cysts, as determined by a board-certified dermatologist or registered nurse practitioner. All patients were more than 18 years of age and cleansed their faces with only Cetaphil™ liquid cleanser during the study.

Twenty patients received one ALA-PDT (with IPL activation) treatment per week for 4 weeks and returned for evaluation 4 and 12 weeks after the final treatment. Clinical photographs were taken and patients were questioned in detail for adverse effects during each treatment session and follow-up visit.

ALA (Levulan® Kerastick®, Dusa Pharmaceuticals, Inc., Wilmington, MA) was prepared and applied to the full face as described[16] and remained in contact with skin for one hour before removal with Cetaphil™ cleanser and treatment with IPL. Levulan® Kerastick® is shown in Figure 1.

IPL activation was accomplished with the SkinStation® (Figure 2, Radiancy, Inc., Orangeburg, NY), a table-top device with a ClearTouch™ system of two flash lamps that emit 430-nm to 1100-nm radiation at 3 to 9 J/cm^2 fluences. The SkinStation uses the proprietary LHE technology of both light and heat energy—light for the targeted indications (porphyrins and sebaceous glands) and heat to potentially stimulate further photodynamic reactions and to reduce inflammation. The SkinStation light pulse duration is 35 msec and the spot size is 22 x 55 mm. Treatments were administered at power settings throughout the 3 to 9 J/cm^2 range. Topical and/or systemic anesthesia was not used during the course of the project, nor any extra cooling devices.

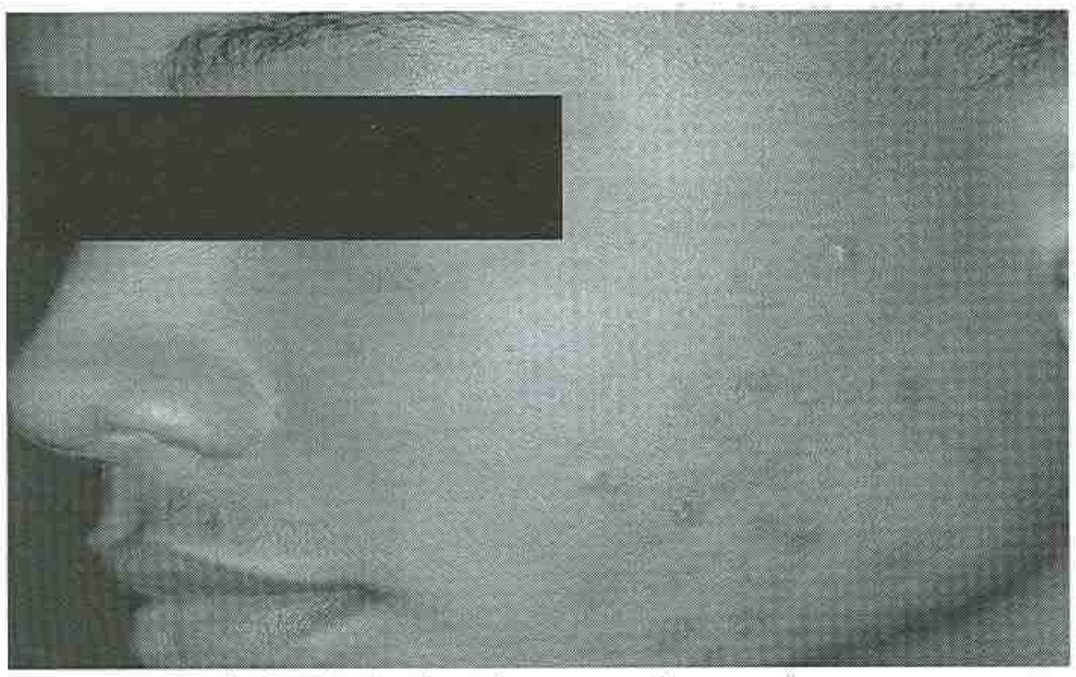

Figure 3a. Left cheek of a female patient shows inflammatory acne lesions before treatment with ALA (Levulan Kerastick) PDT and IPL (SkinStation) activation.

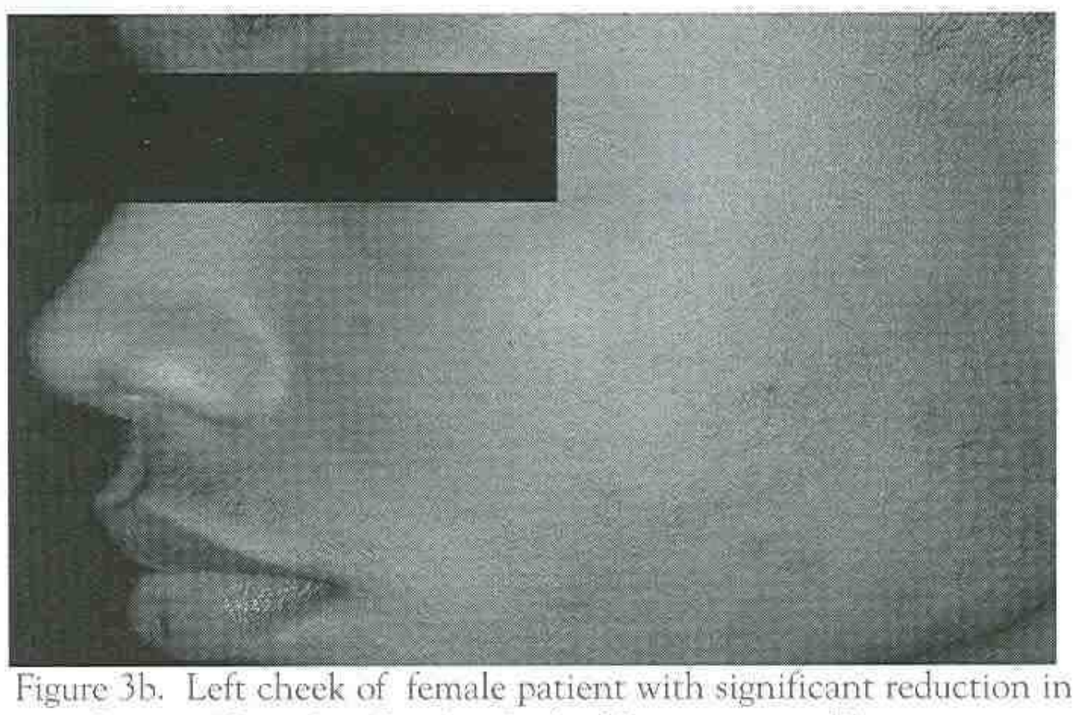

Figure 3b. Left cheek of female patient with significant reduction in acne lesions 12 weeks after the final of four once-weekly treatments.

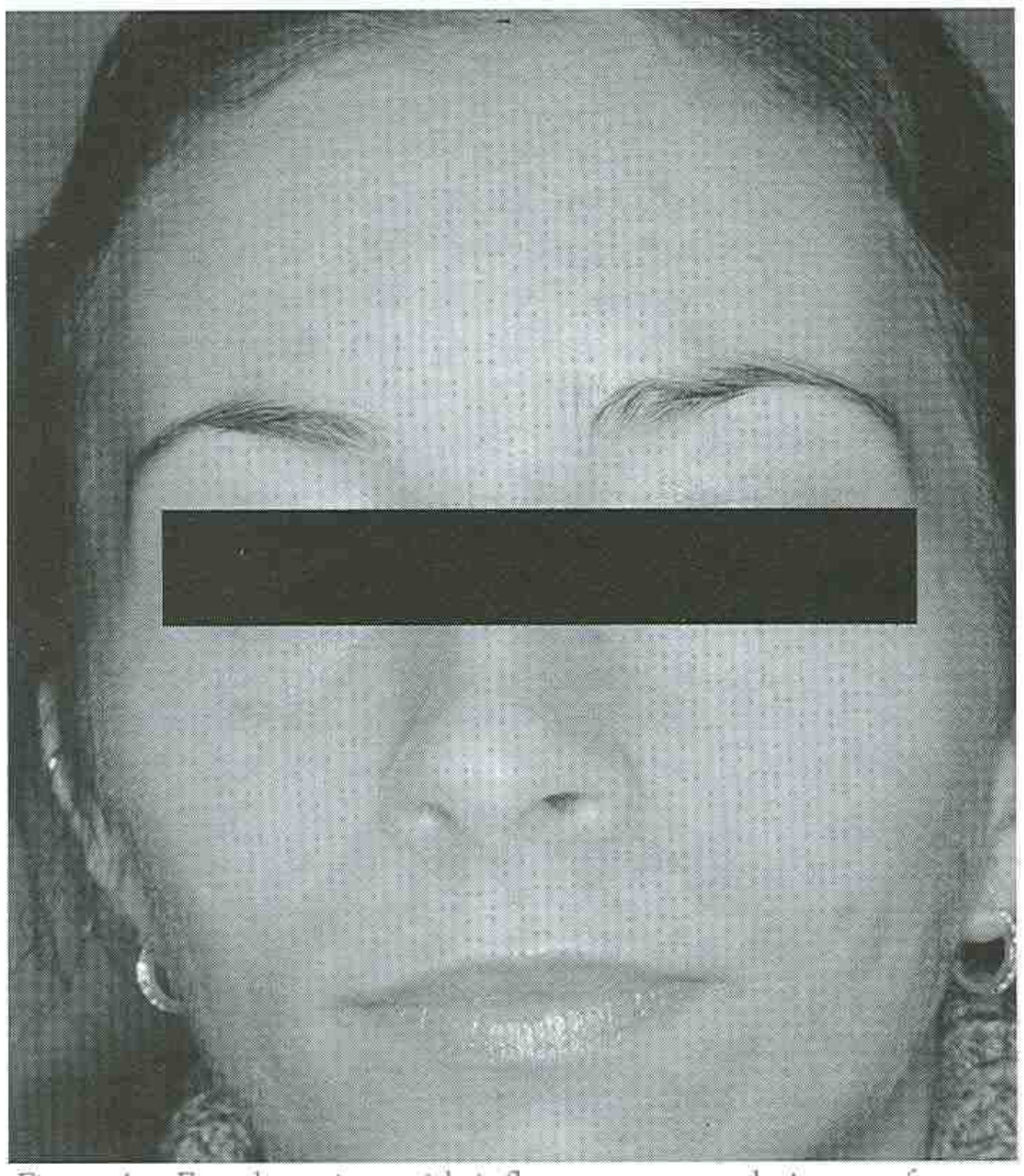

Figure 4a. Female patient with inflammatory acne lesions on forehead, nose, cheeks, nasolabial area, and chin before treatment with ALA (Levulan Kerastick) PDT and IPL (SkinStation) activation.

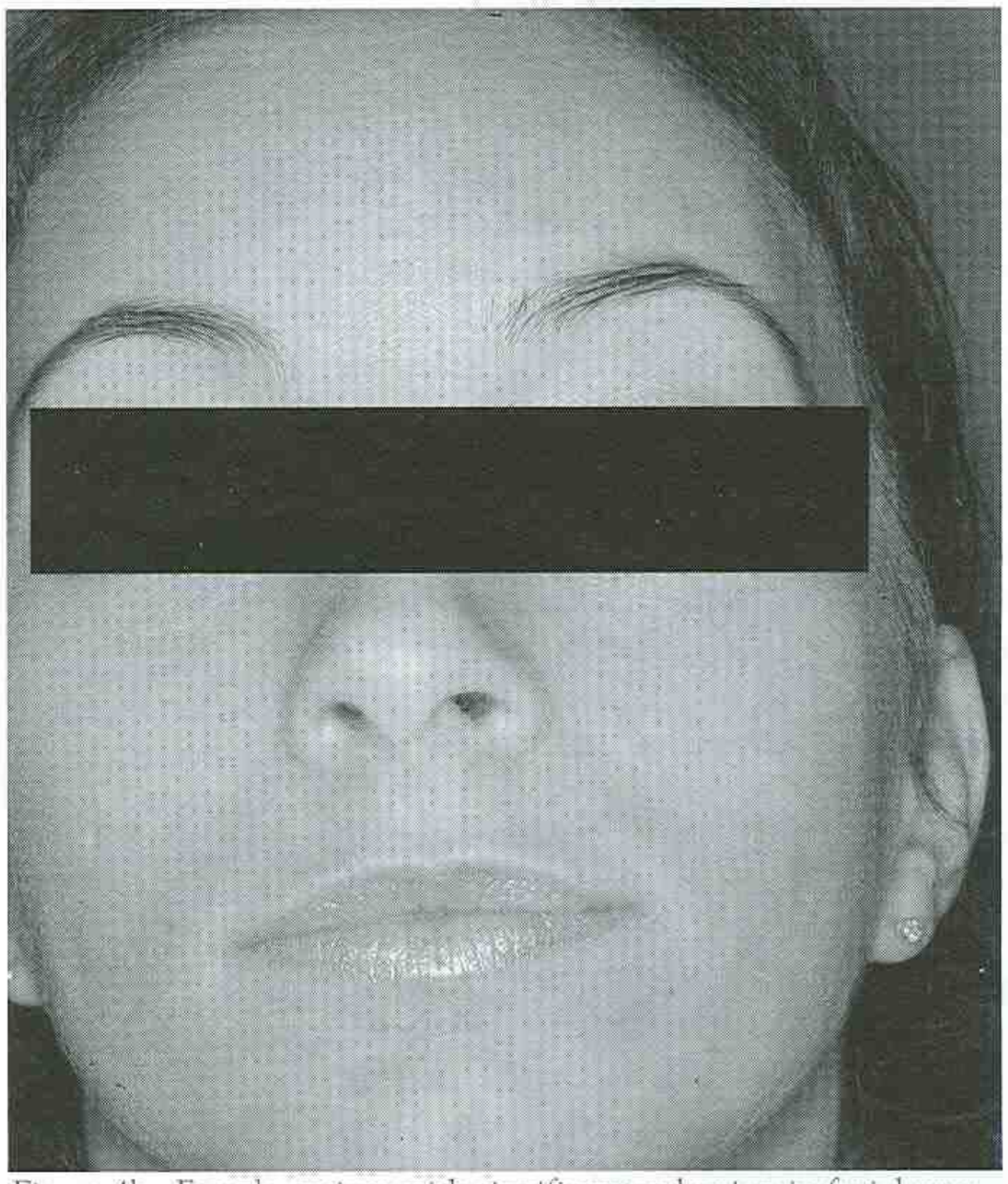

Figure 4b. Female patient with significant reduction in facial acne lesions 12 weeks after the final of four once-weekly treatments.

Figures 3 and 4. Patients reported no adverse events, recurrences, or changes during the treatment or follow-up periods.

Results

Fifteen of the 20 trial participants completed the study. Five patients were lost to follow-up during the clinical trial. Three (20%) did not respond to the treatment leaving 12 evaluable patients (10 women, 2 men) 20 to 54 years of age (mean 32.7 years).

Among these 12 patients, reduction in acne lesions was, on average, 50.1% at the end of the 4-week treatment period, 68.5% 4 weeks after the final treatment, and 71.8% 12 weeks after the final treatment. Clinical examples are shown in

Discussion

Our results show that ALA-PDT with SkinStation IPL activation is an effective and safe treatment for moderate to severe inflammatory acne vulgaris.

Early investigators[26-28] used a variety of light sources and long ALA incubation times to treat acne. In the first reported trial of ALA-PDT in the treatment of moderate to severe acne during a 22-patient study, Hongcharu et al[26] used 550- to 570-nm

broadband light to activate ALA incubated three hours. Significant clinical clearance was evident after four once-weekly treatments. Adverse effects included acneform folliculitis, post-inflammatory hyperpigmentation, superficial peeling, and crusting. Itoh et al[27] used ALA-PDT with 635-nm pulsed excimer-dye laser activation and 4-hour ALA incubation to treat a single patient with intractable acne vulgaris on the face. The treated area remained clear for at least 8 months. Classical PDT reactions—erythema, edema, and crusting—appeared after treatment. In a later study, Itoh et al[28] treated 13 patients with ALA-PDT, this time using 600-nm to 700-nm visible light from a less expensive halogen source. All patients showed improvement and new acne lesions were reduced at 1, 3, and 7 months after treatment. During the following 6 months, acne lesions reappeared and seborrhea returned in most patients. Again, erythema, edema, and crusting were evident after ALA-PDT.

Later investigators used blue light activation and shorter ALA incubation times. Goldman[29] treated acne and sebaceous gland hyperplasia with one-hour ALA drug incubation and either IPL or 15-minute blue light activation. Relative clearing of acne lesions occurred after 2 to 4 once-weekly treatments. Treatments were reported to be pain free and without adverse effects.

In a full-face study of 10 patients with moderate to severe acne, Gold[30] used 30- to 60-minute drug incubation time and high-intensity blue light activation once weekly for 4 weeks. Response rates averaged 60% with ALA-PDT compared to 43% with blue light alone. Treatments were well tolerated with no adverse effects.

Goldman and Boyce[31] treated 22 patients with moderate to severe inflammatory acne vulgaris with blue light with and without ALA photosensitizing agent. Blue light therapy was performed twice per week for 2 weeks with follow-up at 2 weeks; blue light plus ALA was performed two times at 2-week intervals with a follow-up at 2 weeks after the final treatment. There was a greater response in the ALA-PDT/blue light group than blue light alone with no significant adverse effects seen in either group of patients.

Concurrently, other investigators used blue light alone to treat inflammatory acne. Papageorgiou et al[9] reported a 63% response rate for inflammatory lesions and 45% for comedonal lesions, while Kawada et al[10] reported a 65% response rate for inflammatory lesions with blue light therapy. A high-intensity blue light source (ClearLight™, CureLight, Lumenis) has been shown to provide 60% to 75% improvement and a 20% average non-response rate in patients with acne[11,12]. Most of the trials described above used two treatments per week for 4 weeks with 1- and 3-month follow-up times.

In a study of 40 patients with mild to moderate inflammatory acne, Gold[13] obtained an average 43% improvement (including non-responders) with 4 weeks of twice-weekly treatments with a high-intensity blue light source. Patients were evaluated at 1 and 3 months after the final treatment. Improvement was maintained throughout the 3-month follow-up period.

Also FDA-cleared for the treatment of mild to moderate acne, the BLU-U® (Dusa Pharmaceuticals, Inc.), has been reported more effective than topical clindamycin (1%) in the treatment of inflammatory acne. Treatments were given over 4 weeks and patients were followed for 1 month[14].

Other investigators have used IPL for the treatment of acne vulgaris. Elmam et al[2] evaluated the ClearTouch™ acne clearance system. Eighty-five percent of their patients showed greater than 50% improvement in their acne lesions following a treatment regimen of bi-weekly treatments for 4 weeks and two follow-up visits after 1 and 2 months. Further improvement was observed at the 2-month follow-up, 85% versus 79%. Fifteen to 20% of the patients, however, were non-responders.

Gregory et al[17] reported similar results after a 1-month treatment phase and 1-month follow-up. In 75% of treated areas, a reduction in the number of inflamed lesions of 50% or more was achieved. The mechanism of action for IPLs is similar to that of blue light therapy except perhaps with an additional mode of action found – the radiation may attack and destroy the sebaceous glands themselves as well as destroying the P. acnes bacteria, leading to successful PDT[17].

Lasers are also effective against sebaceous glands. After preloading enlarged sebaceous glands with indocyanin green (ICG), Lloyd and Mirkov[15] directed 810-nm laser radiation at the ICG-loaded glands. Histological examination showed that the laser-treated glands had become necrotic and that acne in the treated areas had decreased at 3, 6, and 10-month follow-up visits. Longer wavelength laser radiation is also effective, as shown by the study of Paithankar et al[16] The authors showed histologically that 1450-nm laser radiation with cyogen cooling resulted in damage to the dermal layer containing the sebaceous glands with no damage to the epidermis of animal skin. They also showed that the same treatment reduced the lesion counts on the backs of human patients with few adverse effects. Recently, Friedman et al[34] demonstrated the usefulness of the 1450-nm diode laser on facial acne.

Our report further documents the effectiveness of lasers and light therapy on the treatment of moderate to severe inflammatory acne vulgaris. The SkinStation LHE source was shown to be an effective IPL light source in the group of patients we studied in the treatment of moderate to severe inflammatory acne. Our patients tolerated the procedure and the majority responded well to the therapy.

Overall, the combination of short-contact, full-face ALA-PDT with blue light, IPL, lasers, and other light sources appears to be effective against moderate to severe inflammatory acne. The

ALA-PDT combination is safe and appears to work faster than laser or light therapy alone. Fewer treatments are also required. In some patients, the combination may eliminate the need for more intensive systemic therapies.

Dr. Gold is a consultant for DUSA Pharmaceuticals, Inc. Dr. Gold performs research, speaks for, and owns stock in DUSA Pharmaceuticals, Inc. The SkinStation® LHE® from Radiancy, Inc., was loaned to Dr. Gold for use during the research project. Dr. Gold has no conflicts of interests with Radiancy.

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