

Therapeutic and Aesthetic Uses of Photodynamic Therapy

Part two of a five-part series

Lasers and Light Treatments for Acne Vulgaris Promising Therapies

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ABSTRACT

Acne vulgaris remains one of the most common dermatologic disorders. Clinicians are always searching for new therapies to utilize in their therapeutic armamentarium for this common skin concern. We have many medical therapies at our disposal and these have proven useful in many cases in controlling the disease process. However, some patients need or want other therapies, and laser and light treatments for acne vulgaris have become popular over the past several years. This manuscript will review some of these promising therapies.

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As dermatologists, we have known that exposure to ultraviolet (UV) light is effective in the treatment of acne vulgaris.¹ This phenomenon has been described as a natural photodynamic therapy (PDT) response in that there is selective destruction of the *Propionibacterium acnes* (*P. acnes*) bacteria within the pilosebaceous unit, the bacteria responsible for the inflammatory phase of acne vulgaris. Dermatologists, well aware of the potential damages associated with excessive UV exposure, do not regularly recommend this type of therapy for acne vulgaris because of the potential long-term adverse effects that are associated with this kind of therapy. These adverse effects include an increase in skin aging and in premalignant and malignant skin lesions.

The PDT reaction seen in acne vulgaris lesions involves the production of porphyrins by the *P. acnes* bacteria themselves during their growth and proliferation in the follicular units as noninflammatory acne lesions become inflammatory in nature. The porphyrins produced are known as protoporphyrin IX (PpIX) and coproporphyrin III. These porphyrins have an absorption spectrum in the near UV and visible spectrum of light, as shown in Figure 1. This figure demonstrates the absorption spectrum of PpIX; the absorption spectrum for coproporphyrin III is similar. The major absorption peak for these porphyrins is at 415nm,

known commonly as the Soret Band, and is in the blue range of the visible light spectrum. A second peak, seen at 630nm, is also seen and corresponds to red light. Therefore, phototherapy devices have been developed that utilize either blue light or red light PDT for the treatment of inflammatory acne vulgaris lesions. The PDT process seen in this reaction involves the photo-excitation of the *P. acnes* porphyrins after exposure to the appropriate light source. This will then form singlet oxygen within the bacteria and the selective destruction of the bacteria. The reaction occurs rapidly and has been demonstrated *in vivo*. In addition, by utilizing a topical photosensitizer to the reaction, a synergistic effect has been demonstrated, making PDT a viable option for many suffering from inflammatory acne vulgaris.^{2–4}

Lasers and light sources that have been developed to treat acne vulgaris are usually divided into two classes—those that destroy the sebaceous glands and the entire pilosebaceous unit and those that destroy *P. acnes*. Those that destroy the *P. acnes* bacteria include blue and red light sources, green light lasers, yellow light lasers, and intense pulsed light (IPL) sources. Those medical devices that destroy sebaceous glands include lasers in the near infrared spectrum of light and radiofrequency (RF) devices. Over the past several years, many of us have had an interest in

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utilizing PDT for inflammatory acne vulgaris, via a mechanism of destruction of *P. acnes* and a partial destruction of the sebaceous glands.

LASERS AND LIGHT SOURCES THAT DESTROY *P. ACNES* BACTERIA

Blue light systems. The first of the blue light devices approved by the FDA for the treatment of inflammatory acne vulgaris was a high-intensity, narrow-band, blue light source, known as the ClearLight Acne Photoclearing System (CureLight, Yokneam, Israel) as shown in Figure 2. It has Food and Drug Administration (FDA) approval for the treatment of mild-to-moderate inflammatory acne vulgaris. Its success in the treatment of inflammatory acne vulgaris is well documented in the medical literature in various open-labeled trials. Kawada et al⁵ reported a 64-percent reduction in mild-to-moderate inflammatory acne vulgaris in 30 patients who received twice weekly therapy for five weeks. Shalita et al⁶ treated 35 patients with this system and found that 80 percent noted significant improvement in their acne vulgaris lesions. Adverse events were not seen and all skin types were able to be treated with this high-intensity blue light source. Gold et al⁷ treated 40 patients and found a 43-percent reduction in inflammatory acne vulgaris lesion counts.

Other blue light trials have supported the efficacy of blue light. Papageorgiou et al⁸ described their experiences with phototherapy comparing a mixed blue and red light system (415 and 660nm) with blue light therapy alone and white light therapy. The results showed that the combination of blue and red light decreased inflammatory acne vulgaris lesions by 76 percent versus 58 percent in the blue light alone group, which were both better than white light (25%). Meffert et al⁹ reported experiences with a high-energy, broad-spectrum, blue light source that combined blue light and UVA with a wavelength of 410 to 420nm and noted marked improvement in patients with pustular acne vulgaris after 10 treatments.

A second blue light source, known as the BluU (DUSA Pharmaceuticals, Wilmington, Massachusetts) is shown in Figure 3. Goldman et al¹⁰ reported its effectiveness in inflammatory acne vulgaris lesions in 12 patients. Lesion counts performed two weeks after the final treatment showed a 40-percent reduction in papular acne lesions, a 65-percent reduction in pustular acne lesions, and a 62-percent reduction in comedonal acne lesions. A second study compared this blue light system to topical 1% clindamycin use. This study showed that the blue light therapy was more effective than the topical clindamycin in reducing inflammatory acne vulgaris lesions.¹¹

A third blue light system, the OmniLux Blue (Photo Therapeutics, Manchester, United Kingdom) has also shown effectiveness in the treatment of inflammatory acne vulgaris lesions. This LED blue system has demonstrated reductions in inflammatory acne vulgaris lesions by an average of 74 percent.¹² Other forms of this medical device are also available, which may increase the efficacy even further by adding additional wavelengths of light to the

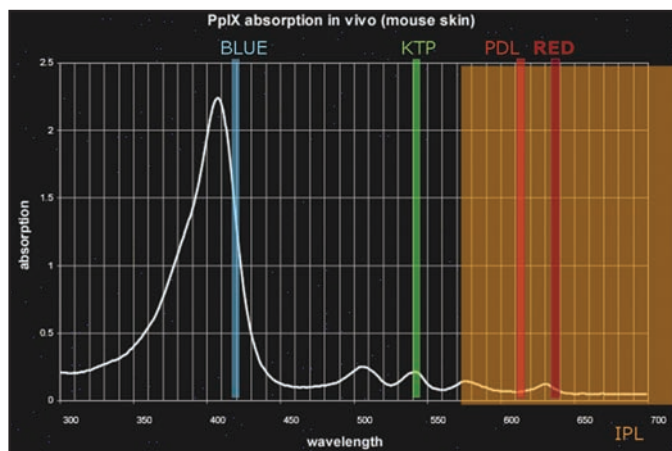


Figure 1. Protoporphyrin IX absorption spectrum



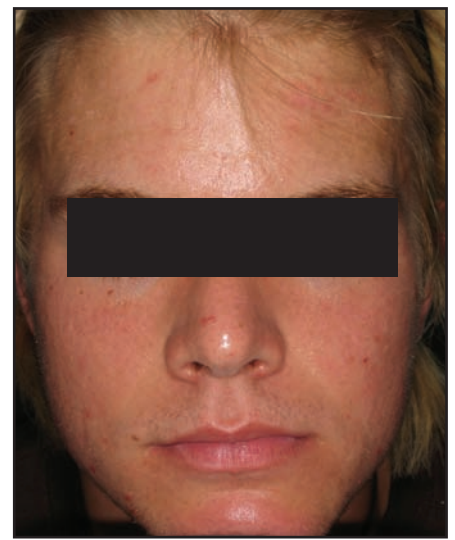
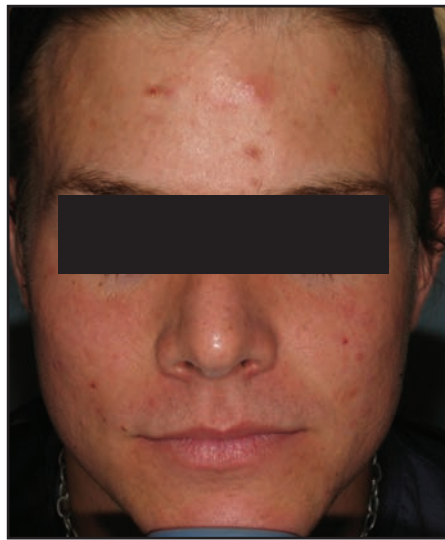
Figure 2. ClearLight Acne Photoclearing system (CureLight, Yokneam, Israel)



Figure 3. BluU blue light source (DUSA Pharmaceuticals, Wilmington, MA)



Figure 4. Isolaz (Aesthera, Pleasanton, CA)



Figures 5a and 5b. Clinical example of acne treated with Isolaz (Aesthera, Pleasanton, CA). Photos courtesy of Michael H. Gold, MD, Tennessee Clinical Research Center, Nashville, TN.

therapeutic options available.

Green light systems. Green light lasers with a wavelength of 532nm have been reported to be effective in treating inflammatory acne vulgaris lesions. They are effectively absorbed by *P. acnes* porphyrins, as shown in Figure 1. Bowes et al¹³ evaluated 11 patients with mild-to-moderate inflammatory acne vulgaris lesions in a split-face, prospective, randomized, clinical trial with a 532-nm laser. Four total treatments were given with this laser and at the one-month follow-up evaluation, acne lesion counts decreased by 35.9 percent versus 11.8 percent on the control side. Sebum measurements were decreased by 28.1 percent on the laser-treated side versus 6.4 percent on the control side.

Yellow light systems. Yellow light pulsed dye lasers (585-595nm) can also be used by clinicians to treat inflammatory acne vulgaris. The first clinical trial¹⁴ evaluated 41 individuals and showed the effectiveness of a low-fluence pulsed dye laser (PDL) in the treatment of inflammatory acne vulgaris lesions. This was a double-blind, randomized, clinical trial where 31 individuals received PDL and 10 patients received a placebo treatment. All of the patients in this trial received one treatment with the PDL or the placebo device and were followed for three months. Acne severity decreased from 3.8 to 1.9 in the PDL group versus 3.6 to 3.5 in the placebo group (using a modified Leeds grading system). Total lesion counts were 53 percent (49% inflammatory reduction) versus nine percent in the placebo group. A second clinical trial did not confirm these results.¹⁵ This trial was a randomized, single-blind, controlled, split-face analysis of 40 individuals receiving 1 to 2 treatments with the PDL. No significant differences were achieved in Leeds grading scores or in lesional counts. More clinical work in this regard is needed; most clinicians who utilize PDLs are comfortable with its efficacy and safety profile.

Intense pulsed light systems. A variety of intense pulsed light (IPL) sources have been used to treat inflammatory acne vulgaris lesions. The first IPL system

reported as being useful in the treatment of acne vulgaris was called the ClearTouch (Radiancy Inc, Orangeburg, New York), now known as SkinStation. This system uses light and heat energy, known as "LHE technology," to trigger the destruction of the *P. acnes* bacteria. Elman et al¹⁶ treated 19 patients and showed that 85 percent of the individuals had a greater than 50 percent improvement in their acne vulgaris lesions following therapy. The patients had twice weekly therapy for four weeks.

Other IPLs, although commonly used for acne, have little documented evidence. Dierickx¹⁷ reported on the use of the Lux V handpiece on the Palomar Medical Technologies (Burlington, Massachusetts) IPL systems (EsteLux, MediLux, and StarLux Systems). Fourteen patients with mild-to-moderate inflammatory acne vulgaris lesions received five treatments, given every 2 to 4 weeks. Two to three passes were given with an average fluence of 10J/cm². At six months post-therapy, clearance rates of 72 percent for non-inflammatory acne vulgaris lesions were seen and 73 percent were seen for inflammatory acne vulgaris lesions.

Photopneumatic system. A new light source, known as the Isolaz (Aesthera, Pleasanton, California), utilizes photopneumatic therapy, which involves a vacuum apparatus to bring the tissue closer to the light source. Several recent articles^{18,19} support its use, including a recent clinical trial by Gold et al¹⁹ in which 11 patients received four treatments at three-week intervals and were followed for three months after their last treatment. They found a 78-percent reduction in inflammatory acne lesions ($p=0.0137$) and a 57.8-percent reduction in non-inflammatory acne lesions ($p=0.0383$). The Isolaz (Figure 4) is FDA-approved for inflammatory and noninflammatory acne lesions. Figures 5a and 5B show a patient with acne who received treatment with Isolaz.

LASERS THAT DESTROY SEBACEOUS GLANDS

Several laser systems have been reported to destroy the sebaceous glands to treat inflammatory acne vulgaris.

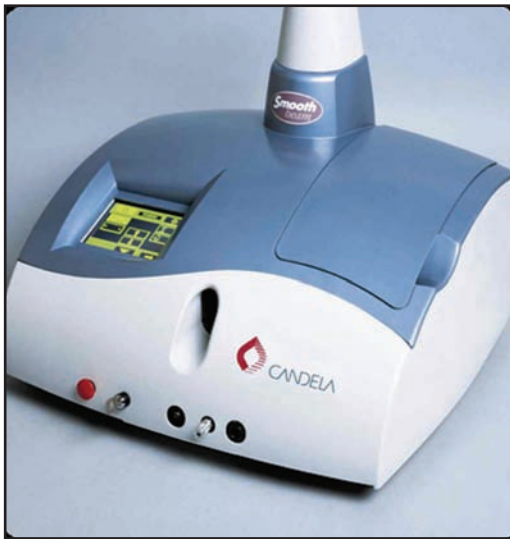


Figure 6. SmoothBeam (Candela, Wayland, MA)



Figures 7a and 7b. Clinical example of acne treated with Accent (Alma Lasers, Caesarea, Israel). Photos courtesy of Martin Braun, MD.

These systems include the near-infrared lasers and possibly the radiofrequency devices currently used for skin tightening, which may also be useful for other indications. A new concept—partial destruction of the sebaceous glands along with the destruction of *P. acnes*—which utilizes 20-percent 5-aminolevulinic acid (ALA) with a variety of lasers and light sources has been found to be useful in the treatment of inflammatory acne vulgaris. This therapy is one of the more exciting new therapies being studied for moderate-to-severe inflammatory acne vulgaris at this time.

The near-infrared lasers being studied for acne vulgaris are the 1320nm CoolTouch CT3 (CoolTouch Inc, Roseville, California), the 1450nm SmoothBeam (Candela, Wayland, Massachusetts), and the 1540nm erbium glass Aramis (WaveLight-Quantel, Clermont-Ferrand, France).

Paithankar et al²⁰ used the 1450nm SmoothBeam laser with its patented dynamic cooling device in 27 patients with inflammatory acne lesions on the back. Four treatments were given at three-week intervals and patients were followed for six months after their last treatment. Results showed a 98-percent reduction in inflammatory acne vulgaris lesions after four treatments. At the follow-up, 100-percent lesion clearance was seen in all but one of the study participants. A second study by Friedman et al²¹ studied facial acne vulgaris. Nineteen patients were evaluated and lesion counts decreased by 37 percent after one treatment, 58 percent after two treatments, and 83 percent after three treatments. Transient erythema and edema were seen with the treatments, and topical anesthetics were utilized to minimize the discomfort routinely observed with these treatments. The SmoothBeam is an effective acne treatment, limited on occasion by pain associated with the treatment. Recent advances and protocols of lower energies and multiple passes are achieving good results and may be a new option for future use with this device. The SmoothBeam is shown in Figure 6.

Tuchin et al²² and Lloyd et al²³ have reported their experiences with indocyanine green (ICG) and a diode laser

for the destruction of the sebaceous glands and the reduction of inflammatory acne vulgaris. ICG, indocyanine green, used as a sensitizing agent, targets the sebaceous glands and was able to show a decrease in inflammatory acne vulgaris lesions with the use of diode lasers (810–900nm). Lloyd et al²³ studied 22 patients with face or back acne. The areas were stained with the ICG for 5 to 15 minutes and then irradiated with a diode laser. Multiple treatments were required to decrease the acne vulgaris activity. ICG is not a readily available photosensitizer and, therefore, not routinely utilized in clinical practice.

The 1540-nm laser has also been reported effective in the treatment of inflammatory acne vulgaris.²⁴

Ruiz-Esparza et al²⁵ reported a preliminary observation with the use of monopolar RF in the treatment of inflammatory acne vulgaris. Twenty-two patients were evaluated with the ThermanCool device (Thermage, Hayward, California). All of the patients were treated twice with the RF device. Follow-ups ranged from 1 to 8 months and excellent responses were seen in 82 percent, modest responses in nine percent, and no response in nine percent of patients. Further clinical trials are needed to evaluate the effectiveness of RF in the treatment of moderate-to-severe inflammatory acne vulgaris, although other RF devices, such as the Alma Lasers Accent (Caesarea, Israel), have also been used to treat inflammatory acne as shown in Figure 7.

ALA-PDT IN THE TREATMENT OF INFLAMMATORY ACNE VULGARIS

The use of ALA-PDT in the treatment of inflammatory acne vulgaris has become a very exciting and new therapeutic option for the treatment of moderate-to-severe inflammatory acne vulgaris. ALA-PDT is FDA approved for the treatment of nonhyperkeratotic actinic keratoses (AKs) of the face and scalp with a blue light source for 16 minutes and 40 seconds. ALA is known to accumulate in actinically damaged skin cells, nonmelanoma skin cancer cells, and in



Figure 8. Levulan Kerastick (DUSA Pharmaceuticals, Wilmington, MA)

the pilosebaceous unit. In the United States, the only currently available ALA at the time of this writing is known as Levulan® Kerastick™ (DUSA Pharmaceuticals, Wilmington, Massachusetts) (Figure 8). The European equivalent is the methyl ester of ALA (MAL) known as Metvix®, (manufactured by PhotoCure ASA, Norway, and distributed by Galderma, Fort Worth, Texas). Metvix® has FDA clearance in the United States for the treatment of nonhyperkeratotic AKs of the face and scalp and will be known as Metvixia®. PhotoCure ASA has retained the marketing rights for this compound in the treatment of acne vulgaris.

The first reported clinical trial utilizing ALA in the treatment of acne vulgaris was reported by Hongcharu et al.²⁶ They studied 22 individuals utilizing ALA and a 550 to 570-nm broad-band light source. The ALA was incubated on the skin for three hours without occlusion. Significant clinical clearance was evident after four weekly ALA-light treatments. The patients in this study experienced downtime prior to healing, known commonly today as the "PDT effect," which has come to mean downtime associated with PDT. The PDT effect consisted of acneiform folliculitis, post-inflammatory hyperpigmentation, superficial peeling, and crusting. The mechanism of action for this improvement was felt to be through partial destruction of the sebaceous glands. Itoh et al²⁷ reported their experience with ALA-PDT for acne vulgaris in utilizing a 635-nm pulsed excimer dye laser and a four-hour ALA drug incubation in a single patient with intractable acne vulgaris on the face. The treated area remained disease free for the eight months of the follow-up time period. The patient did experience a PDT effect manifested by erythema, edema, and crusting immediately after the therapy. In a subsequent study, Itoh et al²⁸ reported their experience with 13 patients utilizing ALA-PDT and a 600- to 700-nm light from a halogen light source. All patients showed improvement in their inflammatory acne vulgaris lesions with new acne vulgaris lesions reduced at one, three, and seven months following their therapy. A PDT effect once again was seen and some

recurrence was noted after the following six months.

A group of investigators began looking at short-contact, full-face ALA-PDT therapies with a variety of different lasers and light sources. Goldman²⁹ reported his experience treating acne vulgaris and sebaceous gland hyperplasia utilizing a one-hour ALA incubation and therapy with either an IPL or blue light activation. Relative clearing of the inflammatory acne vulgaris lesions was seen after 2 to 4 once-weekly ALA-PDT treatments. Treatments were noted to be pain free and no PDT effect was seen.

Gold³⁰ used a 30- to 60-minute ALA drug incubation and the high-intensity blue light source to evaluate moderate-to-severe inflammatory acne vulgaris lesions. The study used once-weekly ALA-blue light treatments and patients were evaluated at one and three months following their final therapies. Response rates of 60 percent were found. The treatments were well tolerated and no adverse events were observed in any of the treated patients.

Goldman et al³¹ treated 22 patients with moderate-to-severe inflammatory acne vulgaris with blue light with and without the ALA. There was a greater response in the ALA-PDT blue light group than the blue light group alone. No adverse events were seen. Taub³² reported her experience with short-contact, full-face therapy utilizing blue light sources (ClearLight or Blu-U) or an IPL with RF (Aurora®, Syneron, Yokneam, Israel). Eighteen patients were evaluated. The patients received 2 to 4 treatments over a 4- to 8-week time period. Improvement was noted at four months following the last treatment. Of the 18 patients, 11 showed 50-percent improvement, and five had greater than 75-percent improvement.

Gold et al³³ reported their experience with short-contact (30 minutes), full-face therapy utilizing ALA and an IPL device (Harmony, Alma Lasers, Buffalo Grove, Illinois). Patients received once-weekly ALA-IPL treatments and were followed for up to three months following their final treatment. A 72-percent reduction in acne lesions was seen. No PDT effects were observed. From the previous open-labeled studies, both blue light and IPL therapies were efficacious in treating inflammatory acne vulgaris. Clinical trials have not been performed comparing blue light and IPLs.

Two recent split-face IPL treatments with ALA-PDT have recently been reported in the literature. Santos et al³⁴ reported their experience with ALA-PDT in moderate-to-severe inflammatory acne vulgaris lesions utilizing ALA-PDT and the Quantum IPL device (Lumenis, Santa Clara, California). Thirteen patients were treated with short-contact, full-face therapy. The IPL was used with a 560-nm filter, double pulsed with 2.4/6.0msec, a 25-msec pulse delay, and fluences of 26 to 34J/cm². In this split-face analysis, 10 of 13 patients showed a marked response in the ALA-IPL-treated side versus the IPL side alone after a single treatment. A second split-face clinical trial, performed by Rojanamatin et al,³⁵ confirmed the results described by Santos et al. They evaluated 14 patients in a split-face fashion with an IPL and found that the ALA-IPL-treated

area was superior to treatment with the IPL alone.

Alexiades-Armenakas³⁶ reported her experience with the PDL and ALA in inflammatory acne vulgaris. A drug-incubation average time of 45 minutes and an average of three PDL sessions cleared all of the 14 patients. Miller and Van Camp³⁷ reported on the successful use of ALA and the KTP (potassium-titanyl-phosphate) laser in patients with inflammatory acne vulgaris. Clinical examples of inflammatory acne vulgaris treated with ALA-PDT can be seen in Figures 9a and 9b.

At the time of this writing, a large, multicenter, controlled, clinical trial is underway in the United States, which will further evaluate the use of ALA in the treatment of moderate-to-severe inflammatory acne vulgaris. The trial is studying the effectiveness of the blue light source in an FDA pivotal trial to determine what role ALA might have in the United States in the future. Also, ALA-PDT is now being utilized by clinicians in Central and South America as well as several countries in Asia, as Levulan® is becoming available in these markets.

In Europe, MAL has been evaluated in several small clinical trials for the treatment of inflammatory acne vulgaris. Wiegall and Wulf⁴¹ evaluated 21 patients with moderate-to-severe inflammatory acne vulgaris. Two treatments were given two weeks apart. Twelve weeks after the treatments, there was a 68-percent reduction in inflammatory acne lesion counts, with no change in the control group. All patients in the study experienced a PDT effect consisting of severe erythema, pustular eruptions, and exfoliation of the skin. Moderate-to-severe pain during the treatments was also noted. A second clinical trial by Horfelt et al⁴² looked at 30 individuals with moderate-to-severe inflammatory acne vulgaris lesions. This was a split-face analysis, with a three-hour, under-occlusion-drug-incubation exposure to red light and two treatments given at two-week intervals. At 12 weeks after the last treatment, there was a statistical reduction in acne lesions of 54 percent versus 20 percent in the control group. Pain and a PDT effect were once again seen in the patients treated. Additional clinical trials are underway in Europe to further evaluate what role the methyl ester of ALA will have in the treatment of moderate-to-severe inflammatory acne vulgaris.

CONCLUSION

The use of ALA-PDT in the treatment of moderate-to-severe inflammatory acne vulgaris has become a useful modality for many patients suffering from this disease. Some clinicians use this as first-line therapy in the treatment of moderate-to-severe inflammatory acne vulgaris and still others add this therapy if routine medical



Figures 9a and 9b. Clinical example of inflammatory acne vulgaris; before treatment and after three ALA-PDT with Isolaz treatments. Noticeable improvement in lesions (forehead and perioral area) and overall redness. Photos courtesy of Michael H. Gold, MD, Gold Skin Care Center, Nashville, TN.

therapy does not provide the clinical results expected. Lasers and light sources, as well as ALA-PDT, are changing how acne vulgaris is treated.

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