41 - The Ever-Increasing Role of ALA-PDT, Part 1 of 2

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Author:
By Michael H. Gold, M.D.

P hotodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA) photosensitizing agent and a variety of lasers and light sources has changed how dermatologists and laser surgeons approach the clinical concerns of patients. Since the Levulan Kerastick (DUSA Pharmaceuticals, Inc,) formulation of 20% ALA with blue light activation received FDA clearance in 1999 for the treatment of non-hyperkeratotic actinic keratoses (AKs) of the face and scalp,1 ALA-PDT off-label uses have expanded to include photodamage, AKs, sebaceous disorders and hidradenitis suppurativa. In Europe, ALA-PDT's primary use is for treating superficial non-melanoma skin cancer. (See table 1 below.) In this first article, I'll review how ALA-PDT therapy is being used and what the research is showing. In part two, I'll share insights from other experts in the field of photodynamic therapy on the practical aspects of Levulan into today's world — from new entities being treated to how to make Levulan an everyday part of your practice. Overnight ALA incubation The original protocol for ALA-PDT with Levulan Kerastick calls for applying Levulan to lesions and allowing it to remain in contact with skin for 14 to 18 hours before exposure to blue light for 16.7 minutes. Phase II and III trials leading to FDA approval showed a high degree of efficacy with this protocol (see photo 1).3 Burning, pain, erythema during exposure to blue light, crusting and peeling occurred in most patients. Healing required up to 1 week, a phenomenon known as the PDT effect.4 Lesion recurrences were infrequent after 4 years.5 Of interest to physicians participating in the trials were the cosmetic improvements observed in the skin of 94% of patients after Levulan-PDT (see photos 2a and 2b). Reducing ALA Contact Time To make ALA-PDT easier for dermatologists, investigators focused on reducing the ALA contact time and using a variety of laser and light sources to activate protoporphyrin IX (PpIX). Touma et al.6 found that with 1-hour ALA incubation in 18 patients with moderate facial photodamage, improvements in sallowness, fine wrinkles and mottled hyperpigmentation were comparable to improvements observed with 14- to 18-hour incubation. Ruiz-Rodriquez et al.7 used intense pulsed light (IPL) in 17 patients with AKs and varying degrees of photodamage. Two IPL sessions with 3-hour ALA incubation yielded 87% improvement in the signs of photodamage — wrinkling, skin texture, pigmentation and telan- giectasias — and resolution of AKs. Cosmetic results were excellent. In my own research,8 I treated patients three times using 1-hour ALA incubation and 30 to 60 minutes exposure to IPL. Three months after the final treatment, patients showed 90% improvement in crow's feet appearance, 100% improvement in tactile skin roughness, 90% improvement in mottled hyperpigmentation, 70% improvement in facial erythema, and clearance of 83% of targeted AKs. (See photos 3a, 3b, 4a and 4b.) Other trials expanded on these results. Goldman et al.9 used short-contact ALA-PDT with blue light activation in 32 patients with AKs and moderate photodamage. One treatment achieved

90% clearance of AKs, 72% improvement in skin texture, and 59% improvement in skin pigmentation. Of note, 62.5% of patients found the therapy less painful than previous cryotherapy. In a study using 1-hour ALA incubation and IPL activation, Avram and Goldman10 reported responses in 68% of AKs with a single treatment. Photodamage parameters also showed improvement — 55% in telangiectasias, 48% in pigment irregularities, and 25% in skin texture. Adverse effects in all these trials were minimal, and the PDT effect was not seen. Alexiades-Armenakas et al., using 1- to 3-hour ALA incubation and a 595 nm long-pulsed dye laser, reported responses in lesions of both AK11 and actinic cheilitis.12 Investigators have shown that short-contact, full-face ALA-PDT is safe and effective, giving us a new way to approach our patients with multiple AKs, photodamage, or both. Split-Face Clinical Trials Two recent split-face trials have confirmed the foregoing results. Bhatia et al.13 treated 20 photoaged patients with ALA-PDT-IPL on one side of patients' faces and IPL alone on the other side. Patients received three split-face treatments followed by two full-face treatments with IPL alone. One month after the final treatment, improvements in ALA-PDT-IPL vs. IPL alone sides were 80% vs. 50% in global score for photoaging, 95% vs. 65% in mottled hyperpigmentation, and 55% vs. 20% in fine lines, respectively. I (Gold et al.14) recently reported a similar split-face comparison in which patients received three treatments. Three months after the final treatment, improvements in ALA-PDT-IPL vs. IPL alone sides were 55% vs. 28.5% in crow's feet, 55% vs. 29.5% in tactile skin roughness, 60.3% vs. 37.2% in mottled hyperpigmentation, and 84.6% vs. 53.8% in facial erythema, respectively. Clearance rates for AKs were 78% and 53.6%. (See photos 5a, 5b, 6a and 6b.) These now commonly used short-contact, full-face ALA-PDTs with activation by various lasers and light sources (including blue light sources, IPLs and vascular lasers) allow us to treat patients with virtually no adverse effects. With these therapies, the PDT effect is not routinely seen, and pain during irradiation can be reduced by cooling the skin during treatment and using more rapid protocols of the new lasers and light sources. In the original trial I conducted, not one patient reported downtime as a result of short-contact, full-face treatment. Patients must still, however, avoid sunlight and use sunblock for 24 to 48 hours after treatment. Metvix The discussion so far has focused on ALA (Levulan Kerastick). The methyl ester of ALA, called Metvix (PhotoCure), is available in Europe as a photosensitizing agent used in PDT for non-hyperkeratotic AKs of the face and scalp and for superficial non-melanoma skin cancers unsuitable for conventional therapy. Metvix is recommended for use after gentle curettage of the affected area. When used this way, Metvix is incubated for 3 hours under occlusion before red (635 nm) light activation. Reports15-17 indicate that the use of Metvix in PDT is effective against AKs and superficial skin cancers. One case of contact dermatitis to the methyl ester has been reported.18 Applications in Sebaceous Disorders The potential of short-contact, full-face ALA-PDT is not limited to the routine treatment of AKs and photodamage. Treatments of moderate to severe inflammatory acne, sebaceous gland hyperplasia (SGH), hidradenitis suppurativa, and other dermatologic entities have also been reported. Since ALA localizes in sebaceous glands, it appears quite natural that ALA-PDT would be useful in treating inflammatory acne vulgaris. Hongcharu et al.19 first reported success in the use of ALA-PDT for acne. These workers incubated ALA for 3 hours under occlusion before irradiating with broadband light. They reported significant lesion clearance lasting up to 10 weeks with a single treatment and up to 20 weeks with multiple treatments. Patients

experienced a significant PDT effect. Itoh et al.20 used 4-hour ALA incubation under occlusion and irradiation with a 635-nm pulsed excimer-dye laser on a single patient with acne vulgaris. Despite a classic PDT effect, the treated area remained disease-free for 8 months. In a subsequent 13-patient study, Itoh et al.21 used polychromatic visible light (600 nm to 700 nm) and 4-hour ALA incubation under occlusion. Facial appearance improved in all patients and acne lesion counts were reduced at 1 month, 3 months and 6 months. Once again, a PDT effect was seen in all patients. Having succeeded with photorejuvenation and AK clearance, investigators are evaluating the effectiveness of short-contact, full-face ALA-PDT in the treatment of moderate to severe inflammatory acne vulgaris. In another study,22 10 patients were incubated with ALA for 30 to 60 minutes before exposing acne lesions to high-intensity blue light for 15 minutes. Patients were treated once weekly for 4 weeks. Three months after the final treatment, acne lesion counts were reduced by 58% compared to 43% with blue light alone. In a more recent 14-patient study, we (Gold et al.23) used IPL rather than blue light activation. This time, there was more than a 70% reduction in lesion counts 3 months after the final treatment (see photos 7a and 7b). Adverse effects were minimal, and the PDT effect was not seen in any patient. Other investigators report similar results in treating acne (see photos 8a and 8b). The treatment of SGH remains difficult for most clinicians. Using a slide projector light source, Horio et al.24 first reported the use of ALA-PDT for the treatment of SGH. These researchers treated lesions of a single patient once weekly for 3 weeks. Lesions became smaller, flattened or disappeared. Alster and Tanzi25 treated 10 patients with short-contact ALA-PDT and 595-nm pulsed-dye laser activation. A single treatment cleared the lesions of seven patients, and two treatments cleared the lesions of the remaining three. In a 10-patient study, Richey and Hopson26 obtained 70% clearance with short-contact ALA-PDT and blue light activation. In a recent study, we (Gold et al.27) used blue light or IPL activation with ALA-PDT in 11 patients with SGH. Four weekly treatments showed a 55.3% improvement in the blue light group and 53.4% improvement with the IPL group. Again, a short-contact approach was used and a PDT effect was not encountered in any patient (see photos 9a and 9b). Finally, using short-contact ALA-PDT with blue light activation, we (Gold et al.28) reported 75% success in four patients who had recalcitrant hidradenitis suppurativa. (See photos 10a and 10b.)

Fewer Treatments and Safe to Use

ALA-PDT is an exciting new development for dermatologists and laser surgeons. With this technique we can more effectively treat patients and use lasers and light sources already in many offices. ALA-PDT is safe and requires fewer treatments than the devices we currently use. Next month, look for part two in this series for expert advice on using AL-PDT in your practice.