THE USE OF PHOTODYNAMIC THERAPY IN DERMATOLOGY: RESULTS OF A CONSENSUS CONFERENCE

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Abstract
Photodynamic therapy (PDT) has significant promise in improving outcomes of patients with a variety of cutaneous conditions. A group of experts met to review the principles, indications, and clinical benefits of PDT with 5-aminolevulinic acid (ALA). They also reviewed PDT with methyl aminolevulinate. The experts established consensus statements for pretreatment, posttreatment, ALA contact time, light sources, and numbers of sessions associated with ALA PDT for actinic keratosis and superficial basal cell carcinoma, photorejuvenation and cosmetic enhancement, acne, sebaceous skin, rosacea, and rhinophyma. They based consensus recommendations on their clinical experience and the medical literature. They also suggested future applications of ALA PDT. Experts concluded that ALA PDT is a safe and effective modality for the treatment of conditions commonly encountered in dermatology. Since downtime is minimal, the technique is suitable for patients of all ages and lifestyles. Appropriate light sources are available in many dermatology offices. The expanding clinical and financial benefits of PDT justify the purchase of an appropriate light source.

Introduction and Objectives
Photodynamic therapy (PDT) using topical 5-aminolevulinic acid (ALA) has significant promise in improving the clinical and cosmetic outcomes of patients with a variety of cutaneous conditions. Although ALA PDT has been explored and expanded by some practitioners, the technique has not been widely adopted by most dermatologists because (1) the 1999 FDA clearance of ALA (as Levulan® Kerastick®, Dusa Pharmaceuticals, Inc.) is limited to the treatment of nonhypertrrophic actinic keratoses (AK) of the face and scalp, (2) patient “downtime” and photosensitivity are concerns, (3) reimbursement for the ALA PDT treatment of AK is poor, (4) the ALA PDT treatment of acne and other conditions are not covered by insurance, and (5) clinical guidelines have not been established.

To address these issues, a group of experts in ALA PDT met to (1) discuss the history, principles, and clinical benefits of ALA PDT; (2) establish an economic model; (3) define indications, patient types, and classifications; (4) establish...
consensus statements for pretreatment, ALA contact time, light sources (preferred and alternative), posttreatment, and number of treatments; (6) suggest future applications of the technique; and (7) prepare a consensus statement. The information in this report is intended for dermatologists and other physician specialists seeking treatment alternatives to skin diseases that we believe can be treated successfully with ALA PDT.

History of Photodynamic Therapy
In 1900, Raab reported that although acridine orange or light was not toxic to paramecia, the cells died in less than 2 hours when exposed to both at the same time. Von Tappeiner and Jesionek later used topical eosin (5%) and light together to treat skin cancer, lupus vulgaris, and condyloma lata. In these cases, acridine and eosin acted as “photosensitizers,” compounds which, when inside cells, could participate in cytotoxic chemical reactions when activated by light. Von Tappeiner and Jodlbauer later reported that oxygen must be present for these photosensitizing reactions to occur.

Subsequent interest in photosensitization focused on porphyrins. In 1911, Hausman described the ability of light-activated hematoporphyrin to photosensitize guinea pigs and mice. In 1913 Meyer-Betz showed that hematoporphyrin could photosensitize humans by injecting himself with hematoporphyrin and noting swelling and pain in parts of his body exposed to light. (Meyer-Betz also endured skin phototoxicity for 2 months, a major drawback in the use of hematoporphyrin as a photosensitizer.) In 1942, Auler and Baner showed conclusively that hematoporphyrin was taken up and retained more in tumors than in surrounding tissue. They also found that fluorescent tumors were necrotic, and this was the first observation of the photodynamic action of hematoporphyrin.

At this stage, the principles of the photodynamic process had been established. Porphyrin-based photosensitizing agents could selectively concentrate in human cancerous tissue and be activated by light in the presence of oxygen to initiate cytotoxic chemical reactions. Hematoporphyrin derivative (HPD), a complex mixture of porphyrin subunits resulting from attempts to purify hematoporphyrin became the standard photosensitizer for studies of photodynamic therapy. The development of photodynamic therapy with systemic HPD in various cancers is largely due to the work of Dougherty and others.

Because skin is accessible to light-based therapy, dermatologists have explored the use of PDT for cutaneous conditions. A major drawback of HPD, however, is that it accumulates in much more so than HPD. Patients with ALA-induced PpIX are at risk for phototoxic reactions for only a few days rather than several months. Another advantage is that aqueous ALA penetrates abnormal but not normal keratin, so PpIX synthesis is confined to abnormal tissue, thus increasing the specificity of photodynamic therapy.

Under ordinary circumstances, heme biosynthesis is under close feedback control, so heme precursors, including PpIX, do not accumulate in most tissues. The clinical consequence of this is that PpIX from exogenous ALA is cleared rapidly from skin, much more so than HPD. Patients with ALA-induced PpIX are at risk for phototoxic reactions for only a few days rather than several months. Another advantage is that aqueous ALA penetrates abnormal but not normal keratin, so PpIX synthesis is confined to abnormal tissue, thus increasing the specificity of photodynamic therapy.

Subsequent research culminated in the 1999 U.S. Food and Drug Administration (FDA) clearance of Levulan Kerastick (delta-aminolevulinic acid HCl, 20%, Dusa Pharmaceuticals, Inc) for the treatment of nonhyperkeratotic AKs on the head and scalp with a 14- to 18-hour skin contact time and activation of ALA-induced PpIX with a blue light source, (2) the FDA clearance of the BLU-U® Blue Light Photodynamic Therapy Illuminator for the AK indication in 2000. Although the original protocol suggests 14- to 18-hour ALA contact time with the treated areas before exposure to light, recent reports show that shorter ALA contact (incubation) times—30 minutes to 1 hour in most cases—are generally sufficient for the treatment of photodamage, acne, and other skin conditions.

Treatment variables that affect PDT results include the ALA concentration, volume of ALA applied per unit of skin area, ALA incubation time, time between application of ALA and light treatment, delivery vehicle for ALA into tissue, temperature of the area being treated, wavelength(s) of light used in treatment, light dose (fluence in J/cm²), rate at which light is delivered (mW/cm²), and the availability of molecular oxygen at the treatment site. The accumulation and clearance of PpIX in tissue as well as photobleaching also affects outcomes.

**Figure 1.** Simplified pathway of heme biosynthesis and negative feedback control. Heme synthesis occurs in the mitochondria. PpIX is the only photosensitive intermediate in this pathway.

![Simplified pathway of heme biosynthesis](image-url)
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Methyl Aminolevulinate

Due to its low lipophilicity, ALA diffuses slowly through cell membranes. A large amount of ALA must therefore be applied to skin to ensure that enough ALA accumulates in diseased tissue.

To enhance diffusion rate, researchers have prepared ALA derivatives of higher lipophilicity. They hypothesized that these ALA prodrugs would enter cells more rapidly and be enzymatically hydrolyzed to ALA, leading to the formation of PpIX.15,16 This theory was explored by Fritsch and colleagues,17 who compared porphyrin accumulation (in both solar keratoses and adjacent normal skin) due to topically applied ALA with accumulation due to its methyl ester, methyl aminolevulinate (MAOP). With both ALA and MAOP, porphyrin levels were higher in solar keratoses than in the adjacent normal skin. Results also indicated that MAOP was a more specific sensitizer of keratotic cells than ALA.

These early studies led to prospective randomized trials18-20 of the use of MAOP PDT for the treatment of AK (Table 1). Two18,20 showed that clinical responses and tolerability with MAOP PDT were comparable to those of cryotherapy and all 3 trials showed that cosmetic outcome and patient satisfaction were high with MAOP PDT. In a prospective, randomized trial comparing MAOP PDT with surgery for 97 patients with nodular basal cell carcinoma (BCC), Rhodes and colleagues21 obtained 91% and 98% response rates (3 months after treatment) for MAOP PDT and surgery, respectively.

MAOP PDT has also been used successfully in the treatment of actinic cheilitis,22 erythroplasia of Queyrat,23 “difficult to

Table 1. Treatment of actinic keratoses (AK) by photodynamic therapy with topical methyl aminolevulinate (MAOP) and red light (570-670 nm) activation.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients/Lesions</th>
<th>MAOP Contact Time (hr)</th>
<th>No. of Treatments</th>
<th>Complete Response Rate (%)</th>
<th>Follow-Up (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szeimies et al18</td>
<td>193/699</td>
<td>3</td>
<td>1*</td>
<td>69</td>
<td>3</td>
</tr>
<tr>
<td>Freeman et al20</td>
<td>204/-</td>
<td>3</td>
<td>2</td>
<td>91</td>
<td>3</td>
</tr>
<tr>
<td>Pariser et al19</td>
<td>80/502</td>
<td>3</td>
<td>2</td>
<td>89</td>
<td>3</td>
</tr>
</tbody>
</table>

*Two treatments for areas not on face or scalp.
CR=Complete response

Figure 2. Absorption spectrum of PpIX and wavelengths associated with the blue light device, potassium titanyl phosphate (KTP) laser, pulsed dye laser (PDL), and intense pulsed light (IPL) device.
treat" BCC, and AKs in transplant recipients. Details of MAOP use and applications have been reviewed.

Research led to the European approval of MAOP cream (Metvix™, PhotoCure ASA, Norway) for the treatment of AKs of the face and scalp and basal cell carcinoma unsuitable for conventional therapy in 2001, and the FDA clearance of Metvix for the treatment of AKs in 2004. Metvix is not available in the US at the time of this writing.

Although clinical responses and cosmetic outcomes have been favorable, MAOP has drawbacks. Before applying MAOP cream, the authors of 5 large studies had to (1) use a dermal curette to remove loose crusts, scales, and other debris from lesions to be treated and (2) roughen lesional surfaces to enhance access of the cream and red light. They also had to allow MAOP to incubate 3 hours under occlusion before activation with red light.

Allergies to ALA and MAOP, though rare, have been reported.

Mechanism of Photodynamic Therapy
With ALA PDT, (1) photosensitizing agent (ALA) must penetrate the stratum corneum of the target area and (2) ALA-induced PpIX must accumulate in sufficient quantity to have a therapeutic effect.

Since PpIX fluoresces when exposed to UV light (Wood's lamp), the penetrating ability of ALA can be studied by observing the fluorescence of ALA-induced PpIX. Fluorescence studies show that ALA penetration decreases with skin thickness and increases in the presence of photo-damage, AKs, psoriasis, BCC, or other skin abnormalities. Once inside, ALA diffuses through the epidermis to the dermis, but very little PpIX fluorescence is found in the dermis. As a result, ALA PDT can eradicate epidermal cancers without seriously damaging the dermis, thus avoiding scarring. The time for ALA to diffuse to 2.5 to 3.0 mm has been estimated at 3 to 15 hours.

When enough PpIX has accumulated, the treatment area is exposed to wavelength(s) of light absorbed by PpIX (Figure 2). In general, the longer the wavelength (up to 850 nm), the deeper its penetration into tissue. Depending on the type of tissue, the optical penetration depth is less than 1 mm at 400 nm, 0.5 to 2 mm at 514 nm, 1 to 6 mm at 630 nm, and maximal at 700 to 800 nm.

In PDT, activation of photosensitizer generates products that can destroy cells. The primary cytotoxic agent is believed to be singlet oxygen, a metastable intermediate produced when photosensitizer is activated. The cytotoxic process occurs in 3 steps: (1) ALA diffuses through the stratum corneum to the epidermis and dermis, (2) tissues synthesize PpIX, and (3) optical radiation of PpIX generates singlet oxygen (or possibly radicals). Death of actinic keratotic cells after ALA PDT has been shown to involve an apoptotic mechanism.

The first direct evidence that PDT-induced skin damage is related to the production of singlet oxygen was reported by Niedre and colleagues. Using a method to detect singlet oxygen in vitro, these researchers exposed hairless mouse skin photosensitized with ALA to 635-nm laser radiation. They found that skin damage was related to cumulative oxygen production. Although other reactive intermediates are produced, most phototoxicity in ALA PDT was attributable to singlet oxygen.

Actinic Keratoses
Actinic keratosis is considered by some to be an in situ cancer that may regress, remain stable, or progress. Although the natural history of a specific lesion is unpredictable, all AKs should be treated to avoid progression to invasive SCC and more expensive treatment. Destructive and topical treatments of AK are shown in Table 2.

Table 2. Destructive and topical treatments of actinic keratosis.

<table>
<thead>
<tr>
<th>Destructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryosurgery</td>
</tr>
<tr>
<td>Curettage</td>
</tr>
<tr>
<td>Electrosurgery</td>
</tr>
<tr>
<td>Excisional surgery</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>Imiquimod</td>
</tr>
<tr>
<td>Diclofenac</td>
</tr>
<tr>
<td>Tretinoin</td>
</tr>
<tr>
<td>Adaplene</td>
</tr>
<tr>
<td>Tazarotene</td>
</tr>
</tbody>
</table>

Photodynamic Therapy with 5-Aminolevulinic Acid
In 1990 Kennedy and colleagues introduced topical ALA as a photosensitizing agent. This report stimulated researchers to experiment with a variety of light sources to activate ALA-induced PpIX. ALA incubation times ranged from 3 to 24 hours. In most cases, CR rates for AK lesions exceeded 75% with a single treatment. Adverse effects included localized edema and erythema as well as mild stinging and burning during light treatment. A large-field source of incoherent light and the long-pulse pulsed dye laser have been shown to provide efficacy and safety with minimal discomfort in the ALA PDT treatment of AK as well as certain superficial BCCs.

Clinical Trials
The encouraging results of early studies led to phase 1, 2, and 3 trials. Treatment parameters and results are presented in Table 3.

In phase 3 trials, 94% of patients considered their cosmetic outcome as good to excellent. No noncutaneous effects were
associated with treatment. A variety of temporary local side effects were found in both the ALA and vehicle groups. Cosmetic results were rated good or excellent by 92% of investigators and by 94% of patients.

The efficacy and recurrence rate of AK lesions treated with ALA PDT has been studied by Fowler and colleagues. These investigators reported that 4 years after treatment, 69% of 32 lesions in 4 patients were still clear, 9% recurred, and 22% were “uncertain.”

**Short Incubation**
Having established the safety and efficacy of ALA PDT, researchers turned their attention to making the procedure more practical for patients seen in the dermatology practice (Table 4). These studies collectively showed that short-contact and/or wide field ALA PDT provides efficacy and safety in the treatment of nonhyperkeratotic AKs.

**Large-Surface Application**
Early studies on the use of ALA PDT for the treatment of extensive AKs of the scalp, multiple AKs, photodamage, and acne, suggested that ALA PDT might be effective over large skin surfaces. Smith and colleagues reported that ALA PDT with 1-hour ALA incubation and blue light activation cleared AK lesions as effectively as topical 5-fluorouracil (5-FU), the standard treatment of AK over large surfaces, and was better tolerated. At the same time, encouraged by an early report that ALA PDT delayed UV-induced skin tumors in hairless mice, Bissonette and colleagues reported that skin tumors did not develop for up to 10 months in hairless mice treated weekly with ALA alone, blue light alone, or ALA PDT with blue light. Liu and colleagues reported that weekly ALA PDT with blue light delayed induction of skin tumors in hairless mice exposed daily to UV radiation. These studies collectively showed that ALA PDT might be an alternative to 5-FU for the treatment of multiple AKs over large skin surfaces. In human patients, Touma and colleagues reported significant AK reduction over broad skin areas treated by ALA PDT.

In a recent study, 14 of 15 patients with multiple diffuse AKs maintained 90% lesion clearance 1 year after receiving 5-FU for 5 days followed by a single session of ALA PDT with IPL (Table 4). The rationale of this approach was to substitute ALA PDT for 5-FU before the appearance of skin irritation associated with 5-FU treatment.

**Photorejuvenation**
By a mechanism not well understood, photoaging occurs when UV radiation triggers the production of reactive oxygen species (ROS) which alter DNA, proteins, lipids, and other cellular components in skin by oxidation. The clinical symptoms of prolonged sun exposure—telangiectases, dyschromias, lentigines, rhytids, and rough elastotic skin—are collectively known as chronic actinic damage. Shielding skin from solar radiation by clothing, UV-blocking sunscreen, or other agents are effective in the treatment and prevention of photoaging. Topical treatments include retinoic acid, alpha-hydroxy acids, antioxidants, and estrogens.

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**Table 3. Clinical trial data for the treatment of nonhyperkeratotic actinic keratosis by photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA).**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients/Lesions</th>
<th>Treatment Parameters</th>
<th>Results</th>
<th>Side Effects (Temporary)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeffes et al (Phase 1, single treatment)</td>
<td>40/218</td>
<td>Argon pumped dye laser (630 nm); 10-150 J/cm²; up to 150 mW/cm²; ALA (10%, 20%, 30%) incubation 3 hr</td>
<td>91% CR rate for face, scalp; 45% CR rate trunk, extremities; 8-wk follow-up</td>
<td>Erythema, edema (localized), mild stinging, burning during light exposure</td>
<td>Clinical responses with 10%, 20%, 30% ALA similar; best response with non-hypertrophic AKs; well-tolerated</td>
</tr>
<tr>
<td>Jeffes et al (Phase 2, single treatment)</td>
<td>36/70</td>
<td>Blue light (417 nm); 2-10 J/cm²; 3-10 mW/cm²; ALA (20%) incubation 14-18 hr.</td>
<td>CR 66%, 8-wk follow-up</td>
<td>Burning/stinging during light exposure; itching, pain; erythema, edema, vesiculation</td>
<td>re-treatment increased CR rate from 66% to 88%; well-tolerated</td>
</tr>
<tr>
<td>Piacquadio et al (Phase 3, single treatment)</td>
<td>243/1909</td>
<td>Blue light (417 nm); 10 mW/cm²; ALA (20%) incubation 14-18 hr.</td>
<td>CR 83%, 8-wk follow-up</td>
<td>Burning/stinging during light exposure; erythema, edema</td>
<td>re-treatment increased CR rate from 83% to 91%; safe and effective</td>
</tr>
</tbody>
</table>

*Levulan Kerastick, Dusa Pharmaceuticals. CR=complete response.*
were excellent. Avram confirmed these findings with the use of 34 of 38 AK lesions had been removed and cosmetic results.

Photodamage and AK lesions. After 2 treatments, with IPL at a 615-nm cutoff filter to treat skin with both photodamage and AK lesions. Touma and colleagues showed that at 1 and 5 months after treatment, (1) improvement in photodamage (and AK clearance) with 1-hour ALA incubation was comparable to that obtained with 14- to 18-hour ALA incubation and (2) broad-area treatment was effective against multiple AKs and significantly reduced wrinkles, sallowness, and dyspigmentation. More than 80% of patients reported good to excellent satisfaction with results, despite moderate phototoxicity for 1 week.

The results of subsequent reports using ALA PDT with IPL or blue light are shown in Table 5. In the split face studies, results on the ALA PDT with IPL are generally superior to those on the IPL alone side, indicating that ALA enhances the effects of IPL. Side effects were mild and temporary. Avram and colleagues showed clearly that ALA PDT with IPL was effective against both AK and symptoms of photodamage.

In a recent pilot study, Lowe and colleagues activated ALA-induced PpIX with a 633-nm light-emitting diode device (Omnilux revive, Photo Therapeutics Ltd. Manchester, UK) in 6 patients with photodamaged skin. In this study, 5% ALA in Unguentum M was applied to the periocular areas and incubated under occlusion for 30 minutes before irradiation. (The 5% concentration was chosen to minimize erythema, ulceration, scaling, pigmentation, roughness, and phototoxic reactions.) The authors noted a reduction in fine lines in 4 patients and improved skin softness in all patients. The treatment was well-tolerated with no adverse effects.

Recent work by Hall and colleagues suggests that ALA/PDT may also be used in conjunction with radiofrequency (RF) energy to enhance photorejuvenation and treat both dermal and epidermal actinic changes.

To provide guidelines for the treatment of photoaging, investigators have categorized photoaging as type A, type B, and type C (Table 6) and treatment techniques as type I, type II, and type III (Table 7).

Photodynamic Therapy Consensus

ALA PDT (type III) is the preferred treatment for type C photodamage. IPL is more appropriate for patients with skin types I-III because it acts on brown and red pigment. For patients with skin types IV-VI, blue light is appropriate because tissue effects are minimal.

Consensus panel members recommend a minimum of 3 ALA PDT treatments at 2- to 4-week intervals. ALA PDT can also be part of a standard 5-treatment IPL regime for photorejuvenation.

Acne

Determining an appropriate course of treatment of acne vulgaris depends on the severity, extent, and duration of the acne; the nature of the lesions; and psychological factors. Current medical therapies include topical, systemic, and hormonal agents. Numerous light- and laser-based treatments—blue light, red and blue light, diode lasers, pulsed-dye laser, and ALA PDT—have been explored, and radiofrequency has been introduced. Blue light (420 nm) alone or in combination with topical agents is effective against mild to moderate acne, but not against severe acne. The Global Alliance to Improve Outcomes in Acne has developed recommendations for acne management.

Acne is a rapidly emerging application for ALA PDT. The ALA PDT approach is based on (1) the proven efficacy of light- and laser-based therapies against acne, (2) uptake of ALA by pilosebaceous units and its conversion to PpIX, and (3) photoexcitation of endogenous bacterial porphyrins to produce cytotoxic singlet oxygen.

The first major evaluation of ALA PDT for acne was reported by Hongcharu and colleagues in 2000. In this landmark study, investigators treated 22 subjects (with acne of the back) at 4 sites with (1) ALA (20%) and red light (550-700 nm), (2) ALA alone, (3) red light alone, and (4) no treatment. ALA was incubated for 3 hours under occlusion before treatment. Eleven subjects were treated once and the remaining 11 were treated 4 times. The authors studied changes in sebum excretion rate and auto-fluorescence from bacteria in follicles, protoporphyrin synthesis in pilosebaceous units, and histologic changes associated with treatment. They found that with ALA PDT, (1) multiple treatments were associated with reduced sebum excretion rates, (2) porphyrin fluorescence was suppressed in bacteria, (3) sebaceous glands were damaged, and (4) inflammatory acne was cleared for 10 weeks and 20 weeks after a single treatment and multiple treatments, respectively. Side effects with ALA PDT included transient hyperpigmentation, superficial exfoliation, and crusting, all of which cleared without scar formation.

The results of subsequent studies are summarized in the Table 8. In these studies, acne ranging from mild to severe was treated by ALA PDT. Improvement was measurable and effective treatment of acne with disease-free periods of up to 13 months.
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In the experience of one author (Dr. Nestor), clearance of moderate to severe acne has been achieved and maintained for more than 2 years in 50% to 60% of patients receiving 3 ALA PDT treatments.59

Consensus panel members agreed that ALA PDT provides (1) the best results when used to treat inflammatory and cystic acne and (2) modest clearance when used to treat comedonal acne, although recent data shows that ALA PDT was effective against comedonal acne when the long-pulsed pulsed dye laser is used. They also agreed that (1) acneiform flares may occur after any treatment, including ALA PDT, and (2) although not supported by extensive documentation, PDL activation provides the best results in ALA PDT for acne. One member (Dr. Nestor) stated that only PDL with ALA PDT has maintained clearance of acne lesions for up to 2 years, even in patients resistant to other treatments.

### Table 4. Single treatment of actinic keratoses by photodynamic therapy with short-incubation 5-aminolevulinic acid (ALA).

<table>
<thead>
<tr>
<th>Reference</th>
<th>ALA Contact Time (hr)</th>
<th>Light Source</th>
<th>Clearance (%)</th>
<th>Follow-Up (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldman et al12</td>
<td>1</td>
<td>Blue light</td>
<td>90 (6 mo.)</td>
<td>6</td>
</tr>
<tr>
<td>Gold45</td>
<td>0.5-1</td>
<td>IPL</td>
<td>&gt;85*</td>
<td>3</td>
</tr>
<tr>
<td>Smith et al46</td>
<td>1</td>
<td>Blue light</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>Avram et al47</td>
<td>1</td>
<td>IPL</td>
<td>68</td>
<td>3</td>
</tr>
<tr>
<td>Touma et al13</td>
<td>1</td>
<td>Blue light</td>
<td>90</td>
<td>5</td>
</tr>
<tr>
<td>Gilbert56†</td>
<td>0.5-0.75</td>
<td>IPL</td>
<td>90</td>
<td>12</td>
</tr>
</tbody>
</table>

*Three treatments.
†Patients received 5-fluorouracil for 5 days, followed by a single treatment of ALA PDT.
IPL=intense pulsed light.

### Table 5. Results of ALA PDT with IPL or blue light for the treatment of photoaging.

<table>
<thead>
<tr>
<th>Reference</th>
<th>ALA Contact Time (hr)</th>
<th>Light Source</th>
<th>No. of Treatments</th>
<th>Improvement or Clearance</th>
<th>Follow-Up (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold45</td>
<td>1</td>
<td>IPL</td>
<td>3</td>
<td>90 (crow’s feet); 100 (tactile skin roughness); 90 (mottled hyperpigmentation); 70 (facial erythema); 83 (AK)</td>
<td>3</td>
</tr>
<tr>
<td>Goldman et al12</td>
<td>Short-contact</td>
<td>Blue light</td>
<td>1</td>
<td>90 (AK); 72 (skin texture); 59 (skin pigmentation)</td>
<td>—</td>
</tr>
<tr>
<td>Avram et al47</td>
<td>1</td>
<td>IPL</td>
<td>1</td>
<td>68 (AK); 55 (telangiectasias); 48 (pigment irregularities); 25 (skin texture)</td>
<td>1,3</td>
</tr>
<tr>
<td>Bhatia et al46†</td>
<td>—</td>
<td>IPL</td>
<td>3*, 2†</td>
<td>80 (ALA-PDT-IPL) vs. 50 (IPL) photoaging; 95 vs. 65 (mottled hyperpigmentation); 55 vs. 20 (fine lines)</td>
<td>1</td>
</tr>
<tr>
<td>Gold et al47</td>
<td>—</td>
<td>IPL</td>
<td>3*</td>
<td>80 (ALA-PDT-IPL) vs. 50 (IPL) crow’s feet; 55 vs. 29.5 (tactile skin roughness); 60.3 vs. 37.2 (mottled hyperpigmentation); 84.6 vs. 53.8 (facial erythema); 78 vs. 53.6 (AK)</td>
<td>3</td>
</tr>
<tr>
<td>Alster et al71</td>
<td>1</td>
<td>IPL</td>
<td>2*</td>
<td>1.65† (ALA PDT IPL) vs. 1.28‡ (IPL)</td>
<td>6</td>
</tr>
<tr>
<td>Dover et al49§</td>
<td>0.5-1</td>
<td>IPL</td>
<td>3*, 2†</td>
<td>80 (ALA-PDT-IPL) vs. 45 (IPL) global score; 95 vs. 60 (mottled hyperpigmentation); 80 vs. 80 (fine lines); 95 vs. 90 (tactile roughness); 75 vs. 75 sallowness</td>
<td>1</td>
</tr>
</tbody>
</table>

*Split face, ALA PDT-IPL vs IPL.
†Full face, IPL alone.
1 Mean clinical grade (1=<25% improvement, 2=25%-50%; 3=51%-75%; 4=76%-100%).
‡Prospective, randomized, controlled split-face study.
IPL= intense pulsed light; AK=actinic keratosis; RF=radiofrequency.

In the experience of one author (Dr. Nestor), clearance of moderate to severe acne has been achieved and maintained for more than 2 years in 50% to 60% of patients receiving 3 ALA PDT treatments.60
Table 6. Characteristics of types A, B, C skin damage.

<table>
<thead>
<tr>
<th>Photodamage Type</th>
<th>Characteristics</th>
<th>Treatment Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Superficial changes in complexion, including vascular and pigmentary changes,</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>lentigines, telangiectasias, erythema, symptoms of rosacea and melasma</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Structural changes in the dermis and epidermis resulting in rhytides,</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>large pores, lax and actinically damaged skin</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Severe elastosis associated with AK, early skin cancer, type A damage,</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>type B damage</td>
<td></td>
</tr>
</tbody>
</table>

ALA=5-aminolevulinic acid; PDT=photodynamic therapy; AK=actinic keratosis; IPL=intense pulsed light.

Table 7. Characteristics of types I, II, III treatment modalities.

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (IPL alone or in combination with topical treatments*)</td>
<td>Pigmentary changes, posttreatment (laser) dyschromia, vascular changes</td>
</tr>
<tr>
<td>I1 (IPL in combination with 1064-nm, 1320-nm Nd:YAG laser)</td>
<td>Elastosis, enlarged pores, rhytides</td>
</tr>
<tr>
<td>III (ALA PDT with IPL)</td>
<td>AK, severe acne, rosacea</td>
</tr>
</tbody>
</table>

*Metronidazole topical cream, fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%.

Table 8. Studies on the use of ALA PDT for acne vulgaris.

<table>
<thead>
<tr>
<th>Reference</th>
<th>ALA Incubation Time (hr)</th>
<th>No. of Treatments</th>
<th>Light Source</th>
<th>Results</th>
<th>Follow-up (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itoh et al*80</td>
<td>(intractable acne) 4</td>
<td>1</td>
<td>Pulsed excimer-dye</td>
<td>laser (635 nm)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treated areas clear for 8 mo.; temporary edematous erythema, crusting</td>
<td></td>
</tr>
<tr>
<td>Itoh et al*81</td>
<td>(intractable acne) 4</td>
<td>1</td>
<td>Halogen (600-700 nm)</td>
<td>New lesions reduced 1, 3, 6 mo. after treatment; improved facial appearance; temporary edematous erythema, epidermal exfoliation; acne lesions returned in 6 months</td>
<td>6</td>
</tr>
<tr>
<td>Gold et al*86</td>
<td>(moderate to severe) 1</td>
<td>4</td>
<td>IPL</td>
<td>50% reduction in lesions at end of final treatment; 68% reduction 4 weeks after final treatment, 72% reduction at 12 weeks; no adverse events or recurrences</td>
<td>1,3</td>
</tr>
<tr>
<td>Goldman et al*52</td>
<td>(mild to moderate) 2</td>
<td></td>
<td>Blue</td>
<td>32% (ALA PDT) vs 25% (light only) improvement; 68% (ALA PDT) vs 40% (light only) reduction in papule counts; no significant adverse effects</td>
<td>0.5</td>
</tr>
<tr>
<td>Gold*41</td>
<td>(moderate to severe) 0.5-1</td>
<td>4</td>
<td>Blue</td>
<td>58% reduction in inflammatory lesions, 55% with &gt;75% improvement in global severity score; no adverse reactions</td>
<td>1,3</td>
</tr>
<tr>
<td>Taub*88</td>
<td>(moderate to severe) 0.25-0.5</td>
<td>2-4</td>
<td>Blue or 580-1000 nm with RF (ELOS)</td>
<td>1.75 average improvement*; 11 of 12 patients with improvement had 50% improvement and 5 had 75% or more; temporary erythema, peeling</td>
<td>4</td>
</tr>
<tr>
<td>Alexiades-Armenakas*82</td>
<td>(mild to severe) 0.75</td>
<td>Mean 2.9, range 1-6</td>
<td>LP PDL (595 nm)</td>
<td>Clearance in all patients</td>
<td>Mean 6.4, range 1-13</td>
</tr>
</tbody>
</table>

*Acne improvement graded on a scale of 0 to 4.
ALA=5-aminolevulinic acid; PDT=photodynamic therapy; IPL=intense pulsed light; RF=radiofrequency;
ELOS=Electro-Optical Synergy, Syneron Medical Ltd., Yokneam, Israel; LP PDL=long pulsed, pulsed dye laser.
Sebaceous Skin
Traditional treatments of sebaceous skin (SS) include cautery, cryotherapy, topical medications, oral tretinoin, surgical excision, and ablative laser vaporization. With these treatments, the risks of dyspigmentation, scar formation, intra- and postoperative bleeding, and lesion recurrence are substantial. In addition, recovery times may be long and the number of lesions treated in one session is limited. A pulsed dye laser (PDL) and a 1450-nm diode laser have shown encouraging results.

The efficacy and safety of ALA PDT in the treatment of SS has been evaluated and the results of 5 reports are shown in Table 9.

AL-A-5-aminolevulinic acid; PDT=photodynamic therapy

### Table 9. Studies on the use of ALA PDT for sebaceous skin.

<table>
<thead>
<tr>
<th>Reference</th>
<th>ALA Incubation Time (hr)</th>
<th>No. of Treatments</th>
<th>Light Source</th>
<th>Results</th>
<th>Follow-up (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horio et al</td>
<td>4</td>
<td>3</td>
<td>Halogen, &gt;620 nm</td>
<td>Small and large lesions decreased in size and reduced sizes persisted for 12 months; temporary erythema, edema, hyperpigmentation</td>
<td>12</td>
</tr>
<tr>
<td>Alster et al</td>
<td>1</td>
<td>1,2</td>
<td>PDL (595 nm)</td>
<td>7 of 10 patients cleared with 1 treatment, 3 patients cleared after 2 treatments; transient erythema, edema, focal crusting</td>
<td>3</td>
</tr>
<tr>
<td>Goldman</td>
<td>0.25</td>
<td>2-4</td>
<td>IPL or blue</td>
<td>Acne and SS lesions cleared after 2-4 treatments</td>
<td>—</td>
</tr>
<tr>
<td>Richey et al</td>
<td>0.75-1</td>
<td>3-6</td>
<td>Blue</td>
<td>70% lesion clearance after 6 mo.; 10%-20% recurrence 3-4 months after final treatment; temporary erythema, edema, hyperpigmentation</td>
<td>6</td>
</tr>
<tr>
<td>Gold et al</td>
<td>0.5-1</td>
<td>4</td>
<td>Blue, IPL</td>
<td>55% reduction in lesions with blue light, 53% with IPL; temporary mild erythema and blisters</td>
<td>1,3</td>
</tr>
</tbody>
</table>

### Table 10. Emerging applications of ALA PDT.

<table>
<thead>
<tr>
<th>Dermatologic Condition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>Coors et al, Umegaki et al</td>
</tr>
<tr>
<td>Cutaneous leishmaniasis</td>
<td>Gardlo et al, Enk et al, El-On et al</td>
</tr>
<tr>
<td>Extramammary Paget’s disease</td>
<td>Shieh et al, Mikasa et al</td>
</tr>
<tr>
<td>Hailey-Hailey disease</td>
<td>Ruiz-Rodriguez et al</td>
</tr>
<tr>
<td>Hidradenitis suppurativa</td>
<td>Gold et al, Strauss et al</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>Radakovic-Fijan et al</td>
</tr>
<tr>
<td>Keratosis pilaris</td>
<td>Clark et al</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>Moir, Gold et al</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>Edstrom et al, Markham et al</td>
</tr>
<tr>
<td>Nevus sebaceous</td>
<td>Dierickx et al</td>
</tr>
<tr>
<td>Perioral dermatitis</td>
<td>Richey et al</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Bissonnette et al, Yim et al, Radakovic-Fijan et al</td>
</tr>
<tr>
<td>Rhinophyma</td>
<td>Amari et al</td>
</tr>
<tr>
<td>Scleroderma (localized)</td>
<td>Karrer et al</td>
</tr>
<tr>
<td>Warts</td>
<td>Wang et al, Smucler et al, Schroeter et al</td>
</tr>
</tbody>
</table>

ALA PDT with a halogen slide projector, PDL, IPL, and blue light appear to be safe and effective treatments of SS without the adverse effects and long recovery times of traditional treatments. ALA PDT with PDL appears to require the fewest treatments to clear SS lesions. Focal crusting may be needed to destroy lesions completely.

Consensus panel members agreed that (1) ALA should be incubated at least 1 hour before irradiation and (2) PDL with multiple stacked pulses provides the best results in ALA PDT for SS.

Emerging Applications
Hidradenitis suppurativa (HS) and molluscum contagiosum are 2 of many other applications of ALA PDT. In one
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study,95 4 patients with chronic HS unresponsive to standard treatments received 3 to 4 ALA PDT sessions at 1- to 2-week intervals. ALA remained in contact with skin for 15 to 30 minutes before irradiation with blue light. All patients showed 75% to 100% clearance 3 months after the final treatment. Adverse effects were not observed.

Other conditions responsive to ALA PDT are shown in Table 10.

Table 11. Consensus recommendations for light sources, number of treatments, and treatment intervals for photodynamic therapy with 5-aminolevulinic acid.

<table>
<thead>
<tr>
<th>Dermatologic Condition</th>
<th>Light Source (Preferred/Alternate/Other)</th>
<th>No. of Treatments (interval)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinic keratoses, superficial basal cell carcinoma</td>
<td>Blue/PDL,* IPL/green, yellow, red</td>
<td>1-2 (3-5 or 2 wk)†</td>
<td></td>
</tr>
<tr>
<td>Photodamage/cosmetic enhancement</td>
<td>IPL† (blue for skin type VI) /Blue, PDL*/green, yellow‡</td>
<td>At least 2 (2-4 or 1 wk),‡ depending on severity of damage</td>
<td>Typically 5 treatments at 2-3 wk intervals; 3 treatments include ALA§</td>
</tr>
<tr>
<td>Acne</td>
<td>PDL→blue (5 min)/blue (8 min)/green, red, IPL, yellow</td>
<td>1-3 (2-3 wk)‖</td>
<td>Treat flares immediately; 6-12 mo. clearance typical</td>
</tr>
<tr>
<td>Sebaceous skin, rosacea, rhinophyma</td>
<td>PDL,* blue/IPL/green,* yellow, red</td>
<td>1-2 (3-5 or 2 wk)‡</td>
<td></td>
</tr>
</tbody>
</table>

* Fluences that avoid bruising.
† Standard photorejuvenation settings by patient type.
‡ Increase ALA incubation time if necessary in second and subsequent treatments.
§ Optimum is IPL, PDL, or green (532 nm) followed by blue light for 5 minutes.
‖ For skin types IV-VI, ALA incubated 30 min. for first treatment.
# Double or triple pulsing on lesion recommended.
PDL=pulsed dye laser; IPL=intense pulsed light.

Pretreatment
1. Continue topical or systemic medications.
2. For patients with severe actinic damage and hypertropic actinic keratosis consider treating individual lesions or areas with a short course of imiquimod or 5-fluorouracil.
3. Wash area to be treated with soap and water or alcohol swab.
4. Perform either microdermabrasion, single pass, and/or scrub area with acetone. Microdermabrasion removes the keratin layer and increases the even penetration of ALA.
5. Prepare 20% ALA by crushing ampoules with the fingers and shaking the Kerastick for 3 minutes.
6. Apply ALA liberally with extra pressure to lesions; avoid mucous membranes.
7. Allow ALA to incubate for at least 30 to 60 minutes.
8. Remove ALA with soap and water, wipe with alcohol.

Light Source
- Preferred: Most significant response for lesion type; may cause response without ALA (ie, IPL for photodamage, PDL for acne).
- Alternate: Substantial effectiveness against lesion type.
- Other: Unproven effectiveness against lesion type (ie, 532 nm light for acne).
- Blue light (5-8 min): (15 min): as a single light source or (5-8 min): when used in addition to IPL or laser for activation of remaining ALA (photobleaching).

Posttreatment
- Apply titanium dioxide-zinc oxide to block UVA and UVB light.
- Instruct patient to avoid direct sun exposure for 24 to 48 hours.
- Tell patient to expect desquamation and sunburn-like reaction with mild to moderate redness and erythema for 48 to 72 hours.
- Apply moisturizers as needed.

Number and Timing of Treatments
- Since number of treatments and timing depend upon indication, give 2 to 5 treatments, 2 to 4 weeks apart as a general rule.
- Vary drug incubation time(s) and light source energy/time to achieve desired clinical response in second and subsequent ALA PDT treatments.

Erythema
Panel members agreed that results of ALA PDT improve with the amount of posttreatment redness and peeling. Although responses vary among patients, the absence of redness for 24
to 48 hours after treatment generally indicates that the ALA incubation time was not long enough to achieve a therapeutic effect, and that the ALA incubation time should be increased in the next session. Alternatively, this suggests that skin preparation may not have been vigorous, implying that a stronger acetone scrub and/or microdermabrasion is necessary. With more aggressive treatment (ie, longer ALA incubation times), fewer treatment sessions may be required to achieve the clinical endpoint of 48 to 72 hours of redness and peeling after treatment. ALA incubation time may be gradually increased to 60 to 90 minutes, depending on patient tolerance.59 Some patients may prefer more treatments with less redness and swelling.

Panelists agreed that physicians should tell patients to expect mild to moderate redness, swelling, and desquamation after treatment.

Carcinogenic Potential of ALA PDT
In 1997, Stender and colleagues53 reported that topical ALA delayed UV photocarcinogenesis in hairless mice, an early indication that repetitive ALA PDT might be used to prevent skin cancer. Other studies of the potential roles of blue light121,122 and ALA123 in carcinogenesis led Bissonette and colleagues54 to search deeper for possible carcinogenic effects of multiple ALA PDT sessions with blue light activation in hairless mice. Eighty mice were divided into 4 treatment groups: (1) ALA, (2) blue light, (3) ALA PDT with blue light activation, and (4) no treatment. Each group was treated once weekly for 10 months. Skin tumors were not observed in any of the treatment groups, indicating the ALA, blue light, and ALA PDT with blue light activation can be used safely in human patients. The low risk of ALA PDT-induced skin cancer has been reviewed in detail.124

Prevention of Non-Melanoma Skin Cancer
One author (Dr. Nestor) has tracked the occurrence rate of active facial non-melanoma skin cancer (NMSC) in 5 patients followed since 2001 (Figure 3). Five or six new NMSCs developed in these patients each year. When these patients received ALA PDT with IPL activation at the end of 2003, the occurrence rate dropped to 1 NMSC per patient, suggesting that ALA PDT with IPL activation has a photochemoprotective effect in patients with active facial NMSC.

Research Goals
ALA PDT parameters—ALA incubation times, light source settings, multiple treatments, and treatment intervals—should be continually refined to ensure maximum efficacy, safety, and patient comfort during the treatment of acne (including moderate to severe), photodamage, nonmelanoma skin cancers, actinic cheilitis, and new applications. The use of ALA PDT in combination with other treatment modalities has shown encouraging results in the treatment of photodamaged skin and acne. The technique has been explored in structural skin smoothing,125 onychomycosis, and hair removal and may ultimately reduce the risk of skin cancers.59

Figure 3. Occurrence of non-melanoma facial skin cancer (NMSC) in patients followed during 2001, 2002, 2003, and 2004. At the end of 2003, the 5 patients received 5 treatment sessions of photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) and intense pulsed light (IPL) activation, leading to a decrease in NMSCs of approximately 80% by the time of this writing.
Conclusions
ALA PDT is a safe and effective modality for the treatment of conditions commonly encountered in a dermatology practice. Since downtime is minimal, the technique is suitable for patients of all ages and lifestyles. The combined effect of light and activation of ALA-induced PpIX results in clinical and cosmetic improvement exceeding that of either modality alone and with little risk of pigmentary alterations. Visible light, lasers, and pulsed light can be used to activate photosensitizer with the added benefit of improvement in the quality of treated skin. Appropriate light sources are already available in many dermatology offices. If not, the expanding clinical and financial benefits of ALA PDT justify the purchase of an appropriate light source.

Disclaimer
Due to the variability of responses among patients, the ASPDT does not guarantee that the consensus recommendations for ALA PDT will apply to all patients.

Disclosure
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References

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