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

Mark S. Nestor MD PhD (chair),[a] Michael H. Gold MD (co-chair),[b]
Arielle N. B. Kauvar MD,[c] Amy F. Taub MD,[d] Roy G. Geronemus MD,[c] Eva C. Ritvo MD,[e]
Mitchel P. Goldman MD,[f] Dore J. Gilbert MD,[g] Donald F. Richey MD[h] (Consensus Panel)

a. Center for Cosmetic Advancement, Aventura, FL
b. Gold Skin Care Center, Nashville, TN
c. New York Laser & Skin Care, New York, NY
d. Advanced Dermatology, Lincolnshire, IL
e. Department of Psychiatry and Behavioral Science, University of Miami, Miami, FL
f. La Jolla Spa MD, La Jolla, CA
g. Newport Dermatology and Laser Associates, Newport Beach, CA
h. North Valley Dermatology Center, Chico, CA

Tina S. Alster MD,[i] R. Rox Anderson MD,[j] David E. Bank MD,[k] Alastair Carruthers MD,[l] Jean Carruthers MD,[l]
David J. Goldberg MD JD,[m] C. William Hanke MD,[n] Nicholas J. Lowe MD,[o] David M. Pariser MD,[p]
Darrell S. Rigel MD,[q] Perry Robins MD,[q] James M. Spencer MD,[r] Brian D. Zelickson MD[s]
(American Society of Photodynamic Therapy Board Members)

i. Washington Institute of Dermatologic Laser Surgery, Washington DC
j. Harvard Medical School, Boston, MA
k. The Center for Dermatology, Cosmetic and Laser Surgery, Mount Kisco, NY
l. University of British Columbia, Vancouver, Canada
m. Skin Laser & Surgery Specialists of New York & New Jersey, Westwood, NJ
n. Laser and Skin Surgery Center of Indiana, Carmel, IN
o. UCLA School of Medicine, Santa Monica, CA
p. Eastern Virginia Medical School Norfolk, VA
q. NYU Medical Center, New York, NY
r. Mt. Sinai School of Medicine, New York, NY
s. Center for Cosmetic Care Minneapolis, MÑ

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.[1,2] 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 nonhypertrophic 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 Tappeimer and Jesionek later used topical eosin (5%) and light together to treat skin cancer, lupus vulgaris, and condylomata lata.[2,3] In these cases, acridine and eosin acted as "photosensitizers,"[1] 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.[3]

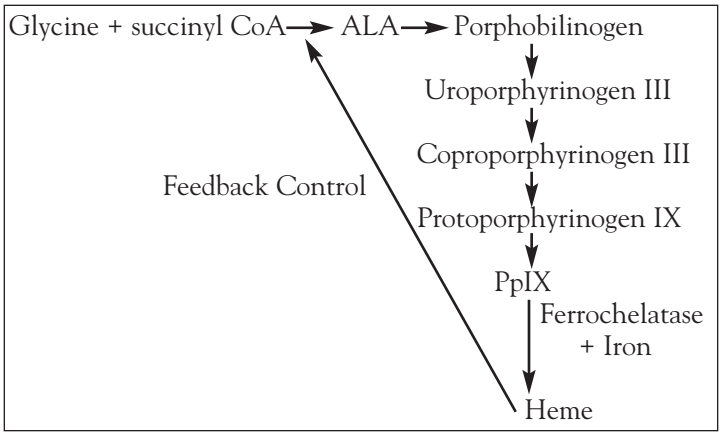
Subsequent interest in photosensitization focused on porphyrins. In 1911, Hausman described the ability of light-activated hematoporphyrin to photosensitize guinea pigs and mice. In 1913 Meyer-Betz showed that hematoporphyrin could photosensitize humans by injecting himself with hematoporphyrin and noting 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 Banzer 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.[3]

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[4] became the standard photosensitizer for studies of photodynamic therapy.[2,5] The development of photodynamic therapy with systemic HPD in various cancers is largely due to the work of Dougherty[6] and others.[7]

Because skin is accessible to light-based therapy, dermatologists have explored the use of PDT for cutaneous conditions.[8] A major drawback of HPD, however, is that it accumulates in skin and may take several months to clear. During this time, phototoxic reactions may occur in patients.[4]

To overcome the prolonged risk of phototoxicity, Kennedy and colleagues[4] introduced topically applied ALA, a new photosensitizing "prodrug" that can penetrate the stratum corneum of actinically damaged cells, solar keratoses, basal cell carcinomas, squamous cell carcinomas, and pilosebaceous units.[2,9] When ALA enters epidermal cells, it is converted to

Figure 1. Simplified pathway of heme biosynthesis and negative feedback control. Heme synthesis occurs in the mitochondria.[11] PpIX is the only photosensitive intermediate[10] in this pathway.



protoporphyrin IX (PpIX) because ALA is the natural precursor of PpIX in the biosynthesis of heme (Figure 1). ALA is a photosensitizing agent while PpIX is a photosensitizer which can be activated by either blue or red light.[2]

Under ordinary circumstances, heme biosynthesis is under close feedback control, so heme precursors, including PpIX, do not accumulate in most tissues.[10] 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.[1,11,12]

Subsequent research culminated in the 1999 U.S. Food and Drug Administration (FDA) clearance of Levulan Kerastick (δ-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.[2,13]

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/cm^2), rate at which light is delivered (mW/cm^2), and the availability of molecular oxygen at the treatment site.[14] The accumulation and clearance of PpIX in tissue as well as photobleaching also affects outcomes.

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 trials[18-20] of the use of MAOP PDT for the treatment of AK (Table 1). Two[18,20] 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 colleagues[21] obtained 91% and 98% response rates (3 months after treatment) for MAOP PDT and surgery, respectively.

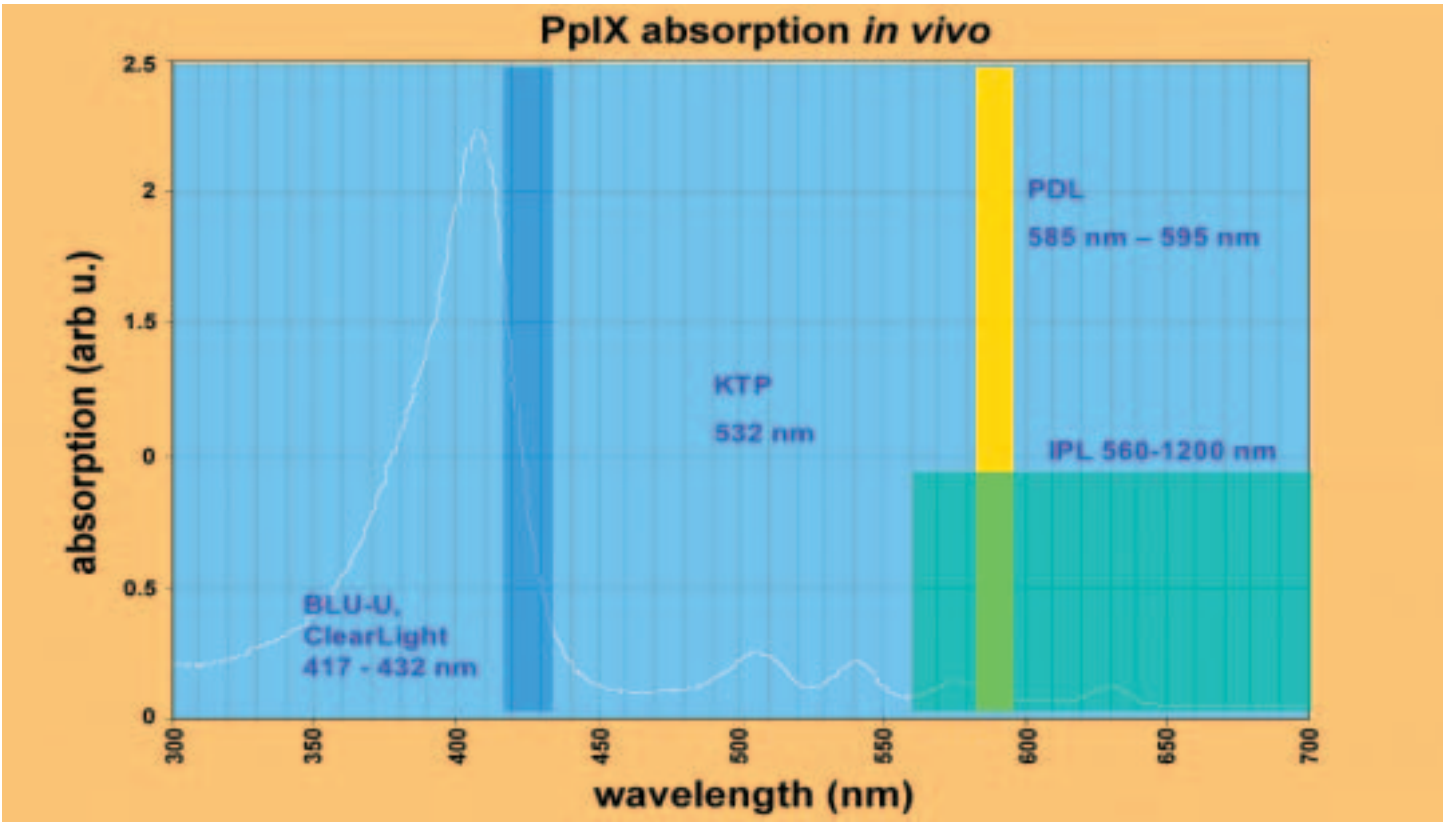
MAOP PDT has also been used successfully in the treatment of actinic cheilitis,[22] erythroplasia of Queyrat,[23] "difficult to

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

Reference	No. of Patients/ Lesions	MAOP Contact Time (hr)	No. of Treatments	Complete Response Rate (%)	Follow-Up (mo.)
Szeimies et al[18]	193/699	3	1*	69	3
Freeman et al[20]	204/—	3	2	91	3
Pariser et al[19]	80/502	3	2	89	3

*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,[24] and AKs in transplant recipients.[25] Details of MAOP use and applications have been reviewed.[26,27]

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[18-21,24] 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[28] and MAOP,[29] 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 photodamage, 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.[11] The time for ALA to diffuse to 2.5 to 3.0 mm has been estimated at 3 to 15 hours.[30]

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),[8] the deeper its penetration into tissue.[5] 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.[31]

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.[32,33] 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).[34] Death of actinic keratotic cells after ALA PDT has been shown to involve an apoptotic mechanism.[35]

The first direct evidence that PDT-induced skin damage is related to the production of singlet oxygen was reported by Niedre and colleagues.[33] 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.[36] 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.[37] Destructive and topical treatments of AK are shown in Table 2.

Table 2. Destructive and topical treatments of actinic keratosis.

Destructive	
	Cryosurgery
	Curettage
	Electrosurgery
	Excisional surgery
	Photodynamic therapy
Topical	
	5-fluorouracil
	Imiquimod
	Diclofenac
	Tretinoin
	Adalpene
	Tazarotene

Photodynamic Therapy with 5-Aminolevulinic Acid

In 1990 Kennedy and colleagues[4] introduced topical ALA as a photosensitizing agent. This report stimulated researchers to experiment with a variety of light sources to activate ALA-induced PpIX.[1] 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[38] and the long-pulse pulsed dye laser[39] have been shown to provide efficacy and safety with minimal discomfort in the ALA PDT treatment of AK[39] as well as certain superficial BCCs.[38]

Clinical Trials

The encouraging results of early studies led to phase 1,[40] 2,[41] and 3[42] 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.[43] No noncutaneous effects were

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

Reference	No. of Patients/ Lesions	Treatment Parameters	Results	Side Effects (Temporary)	Comment
Jeffes et al[40] (Phase 1, single treatment)	40/218	Argon pumped dye laser (630 nm); 10-150 J/cm^2; up to 150 mW/cm^2; ALA (10%, 20%, 30%) incubation 3 hr	91% CR rate for face, scalp; 45% CR rate trunk, extremities; 8-wk follow-up	Erythema, edema (localized), mild stinging, burning during light exposure	Clinical responses with 10%, 20%, 30% ALA similar; best response with non-hypertrophic AKs; well-tolerated
Jeffes et al[41] (Phase 2, single treatment)	36/70	Blue light (417 nm); 2-10 J/cm^2; 3-10 mW/cm^2; ALA (20%) incubation 14-18 hr.	CR 66%, 8-wk follow-up	Burning/stinging during light exposure; itching, pain; erythema, edema, vesiculation	re-treatment increased CR rate from 66% to 88%; well-tolerated
Piacquadio et al[42] (Phase 3, single treatment)	243/1909	Blue light (417 nm); 10 mW/cm^2; ALA (20%) incubation 14-18 hr.	CR 83%, 8-wk follow-up	Burning/stinging during light exposure; erythema, edema	re-treatment increased CR rate from 83% to 91%; safe and effective

*Levulan Kerastick, Dusa Pharmaceuticals.
CR=complete response.

associated with treatment. A variety of temporary local side effects were found in both the ALA and vehicle groups.[2] 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.[44] 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[12,13,45-47] 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,[48] multiple AKs,[49] photodamage,[12,47,50] and acne,[51,52] suggested that ALA PDT might be effective over large skin surfaces. Smith and colleagues[46] 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[53] that ALA PDT delayed UV-induced skin tumors in hairless mice, Bissonette and colleagues[54] 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[55] 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[13] reported significant AK reduction over broad skin areas treated by ALA PDT.

In a recent study,[56] 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.[57,58] The clinical symptoms of prolonged sun exposure—telangiectases, dyschromias, lentigines, rhytids, and rough elastotic skin—are collectively known as chronic actinic damage.[59] Shielding skin from solar radiation by clothing, UV-blocking sunscreen, or other agents are effective in the treatment and prevention of photoaging.[60,61] Topical treatments include retinoic acid, alpha-hydroxy acids, antioxidants, and estrogens.

Regarding procedures, initial studies showed that (1) IPL improves wrinkling, coarse skin texture, pigmentation changes, and telangiectasia with epidermal ablation[62,63] and (2) ALA PDT with red light is effective against AKs and nonmelanoma skin cancers.[8,17] Encouraged by these results, Ruiz-Rodriguez and colleagues[64] used compounded ALA PDT with IPL at a 615-nm cutoff filter to treat skin with both photodamage and AK lesions. After 2 treatments, 34 of 38 AK lesions had been removed and cosmetic results were excellent. Avram[47] confirmed these findings with the use of Levulan ALA PDT and standard IPL settings. The treatment, coined "photodynamic photorejuvenation,"[65] was well-tolerated.

Other investigators evaluated the efficacy and safety of PDT with blue light. Gold[37] reported (1) reductions of skin thickening and inelasticity in areas of multiple nonhyperkeratotic AKs, (2) complete healing of the treatment area, and (3) additional improvement over time in 2 patients with AKs and moderate to severe photodamage. Touma and colleagues[13] 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,[66-68] 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[47] showed clearly that ALA PDT with IPL was effective against both AK and symptoms of photodamage.

In a recent pilot study,[69] 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 periorbital 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[70] 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).[65] 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.[72] Current medical therapies include topical,[73] systemic,[74] and hormonal[75] agents. Numerous light- and laser-based treatments—blue light, red and blue light, diode lasers, pulsed-dye laser, and ALA PDT—have been explored,[76] and radiofrequency has been introduced.[77] Blue light (420 nm) alone or in combination with topical agents is effective against mild to moderate acne,[78] but not against severe acne.[59] The Global Alliance to Improve Outcomes in Acne has developed recommendations for acne management.[79]

Acne is a rapidly emerging application for ALA PDT.[1,9,45,52,80-82] The ALA PDT approach is based on (1) the proven efficacy of light- and laser-based therapies against acne,[76] (2) uptake of ALA by pilosebaceous units and its conversion to PpIX,[11,83,84] and (3) photoexcitation of endogenous bacterial porphyrins to produce cytotoxic singlet oxygen.[84,85]

The first major evaluation of ALA PDT for acne was reported by Hongcharu and colleagues in 2000.[9] 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 visible and adverse effects were minimal and temporary, showing that ALA PDT with a variety of light sources is a safe and effective treatment of acne with disease-free periods of up to 13 months.[82]

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

Reference	ALA Contact Time (hr)	Light Source	Clearance (%)	Follow-Up (mo.)
Goldman et al[12]	1	Blue light	90 (6 mo.)	6
Gold[45]	0.5-1	IPL	>85*	3
Smith et al[46]	1	Blue light	50	1
Avram et al[47]	1	IPL	68	3
Touma et al[13]	1	Blue light	90	5
Gilbert[56†]	0.5-0.75	IPL	90	12

*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.

Reference	ALA Contact Time (hr)	Light Source	No. of Treatments	Improvement or Clearance	Follow-Up (mo.)
Gold[45]	1	IPL	3	90 (crow's feet); 100 (tactile skin roughness); 90 (mottled hyperpigmentation); 70 (facial erythema); 83 (AK)	3
Goldman et al[12]	Short-contact	Blue light	1	90 (AK); 72 (skin texture); 59 (skin pigmentation)	—
Avram et al[47]	1	IPL	1	68 (AK); 55 (telangiectasias); 48 (pigment irregularities); 25 (skin texture)	1,3
Bhatia et al[66]	—	IPL	3*, 2†	80 (ALA-PDT-IPL) vs. 50 (IPL) photoaging; 95 vs. 65 (mottled hyperpigmentation); 55 vs. 20 (fine lines)	1
Gold et al[67]	—	IPL	3*	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)	3
Alster et al[71]	1	IPL	2*	1.65‡ (ALA PDT IPL) vs. 1.28‡ (IPL)	6
Dover et al[68§]	0.5-1	IPL	3*, 2†	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)	1

*Split face, ALA PDT-IPL vs IPL.
†Full face, IPL alone.
‡ 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.[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[82] 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 6. Characteristics of types A, B, C skin damage.

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

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

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

Treatment Type	Applications
I (IPL alone or in combination with topical treatments*)	Pigmentary changes, posttreatment (laser) dyschromia, vascular changes
11 (IPL in combination with 1064-nm, 1320-nm Nd:YAG laser)	Elastosis, enlarged pores, rhytides
III (ALA PDT with IPL)	AK, severe acne, rosacea

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

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

Reference	ALA Incubation Time (hr)	No. of Treatments	Light Source	Results	Follow-up (mo.)
Itoh et al[80] case study	(intractable acne) 4	1	Pulsed excimer-dye	laser (635 nm) Treated areas clear for 8 mo.; temporary edematous erythema, crusting	8
Itoh et al[81] (intractable acne)	4	1	Halogen (600-700 nm)	New lesions reduced 1, 3, 6 mo. after treatment; improved facial appearance; temporary edematous erythema, epidermal exfoliation; acne lesions returned in 6 months	6
Gold et al[86] (moderate to severe)	1	4	IPL	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	1,3
Goldman et al[52] (mild to moderate)		2	Blue	32% (ALA PDT) vs 25% (light only) improvement; 68% (ALA PDT) vs 40% (light only) reduction in papule counts; no significant adverse effects	0.5
Gold[87] (moderate to severe)	0.5-1	4	Blue	58% reduction in inflammatory lesions, 55% with >75% improvement in global severity score; no adverse reactions	1,3
Taub[88] (moderate to severe)	0.25-0.5	2-4	Blue or 580-1000 nm with RF (ELOS)	1.75 average improvement*; 11 of 12 patients with improvement had 50% improvement and 5 had 75% or more; temporary erythema, peeling	4
Alexiades-Armenakas[82] (mild to severe)	0.75	Mean 2.9, range 1-6	LP PDL (595 nm)	Clearance in all patients	Mean 6.4, range 1-13

*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 cauterization, 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.[89,90] In addition, recovery times may be long and the number of lesions treated in one session is limited.[90] A pulsed dye laser (PDL)[89] and a 1450-nm diode laser[91] have shown encouraging results.

The efficacy and safety of ALA PDT in the treatment of SS has been evaluated[2,90,92,93] and the results of 5 reports are shown in Table 9.

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.[90]

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.[95-97] In one

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

Reference	ALA Incubation Time (hr)	No. of Treatments	Light Source	Results	Follow-up (mo.)
Horio et al[92]	4	3	Halogen, >620 nm	Small and large lesions decreased in size and reduced sizes persisted for 12 months; temporary erythema, edema, hyperpigmentation	12
Alster et al[90]	1	1,2	PDL (595 nm)	7 of 10 patients cleared with 1 treatment, 3 patients cleared after 2 treatments; transient erythema, edema, focal crusting	3
Goldman[94]	0.25	2-4	IPL or blue	Acne and SS lesions cleared after 2-4 treatments	—
Richey et al[93]	0.75-1	3-6	Blue	70% lesion clearance after 6 mo.; 10%-20% recurrence 3-4 months after final treatment; temporary erythema, edema, hyperpigmentation	6
Gold et al[86]	0.5-1	4	Blue, IPL	55% reduction in lesions with blue light, 53% with IPL; temporary mild erythema and blisters	1,3

Table 10. Emerging applications of ALA PDT.

Dermatologic Condition	Reference
Cutaneous T-cell lymphoma	Coors et al,[98] Umegaki et al[99]
Cutaneous leishmaniasis	Gardlo et al,[100] Enk et al,[101] El-On et al[102]
Extramammary Paget's disease	Shieh et al,[103] Mikasa et al[104]
Hailey-Hailey disease	Ruiz-Rodriguez et al[105]
Hidradenitis suppurativa	Gold et al,[95] Strauss et al[106]
Keratoacanthoma	Radakovic-Fijan et al[107]
Keratosis pilaris	Clark et al[108]
Molluscum contagiosum	Moiin,[97] Gold et al[96]
Mycosis fungoides	Edstrom et al,[109] Markham et al[110]
Nevus sebaceus	Dierickx et al[111]
Perioral dermatitis	Richey et al[112]
Psoriasis	Bissonnette et al,[113] Yim et al,[114] Radakovic-Fijan et al[115]
Rhinophyma	Amari et al[116]
Scleroderma (localized)	Karrer et al[117]
Warts	Wang et al,[118] Smucler et al,[119] Schroeter et al[120]

ALA-5-aminolevulinic acid; PDT=photodynamic therapy

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

Dermatologic Condition	Light Source (Preferred/Alternate/Other)	No. of Treatments (interval)	Comment
Actinic keratoses, superficial basal cell carcinoma	Blue/PDL,* IPL†/green, yellow, red	1-2 (3-5 or 2 wk)‡	
Photodamage/cosmetic enhancement	IPL† (blue for skin type VI) /Blue, PDL*/green, yellow§	At least 2 (2-4 or 1 wk),‡ depending on severity of damage	Typically 5 treatments at 2-3 wk intervals; 3 treatments include ALA[59]
Acne	PDL→blue (5 min)/blue (8 min)/green, red, IPL, yellow	1-3 (2-3 wk) ||	Treat flares immediately; 6-12 mo. clearance typical
Sebaceous skin, rosacea, rhinophyma	PDL,# blue/IPL†/green,# yellow, red	1-2 (3-5 or 2 wk)‡	

* 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.

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.

Treatment Algorithms

Consensus panel members agreed to the following algorithms (pretreatment, light sources, posttreatment) for the use of ALA PDT. Light sources, number of treatments, treatment intervals, and comments are presented in the Table 11.

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

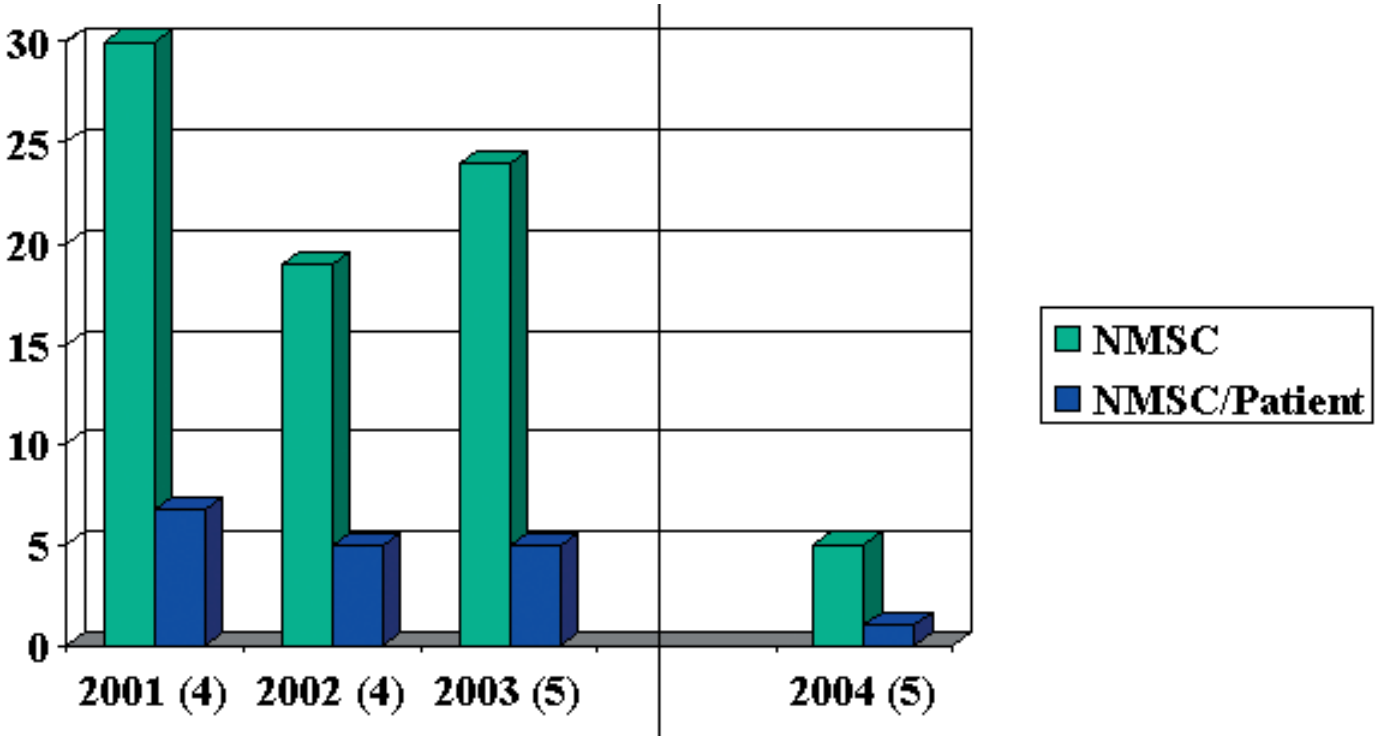
• Since number of treatments and timing depend upon indication, give 2 to 5 treatments, 2 to 4 weeks apart as a general rule.

• 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

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.



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 microdermabreasion 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 colleagues[53] 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 light[121,122] and ALA[123] in carcinogenesis led Bissonette and colleagues[54] 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]

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

This statement was drafted, reviewed, and revised by the ASPDT chair and has been carefully reviewed by the participants as well as the governing board of directors of the American Society of Photodynamic Therapy (ASPDT). Funding to ASPDT was provided by an unrestricted educational grant from DUSA Pharmaceuticals, Inc.

The following disclosures refer to relationships with Dusa Pharmaceuticals, Inc. Dr. Nestor has received research support and is a funded speaker, consultant, and physician advisory board member. Drs. Gold, Goldman, and Taub have received research support and are funded speakers, consultants, physician advisory board members, and shareholders. Drs. Geronemus and Pariser have received research support. Dr. Gilbert is a funded speaker and shareholder. Dr. Alster is a member of the physician advisor board. Dr. Hanke is a member of the physician advisor board, has received research support, and owns stock. Dr. Zelickson is a shareholder and has active research grants. Dr. Robins is a consultant. Dr. Ritvo is a funded speaker. Drs. Anderson, Bank, A. Carruthers, J. Carruthers, Lowe, Richey, Spencer, Kauvar, and Goldberg have no financial relationships.

References

1. Taub A. Photodynamic therapy in dermatology: history and horizons. *J Drugs Dermatol.* 2004;3(Suppl):S8-S25.
2. Gold MH, Goldman MP. 5-aminolevulinic acid photodynamic therapy: where we have been and where we are going. *Dermatol Surg.* 2004;30:1077-1083
3. Daniell MD, Hill JS. A history of photodynamic therapy. *Aust N Z J Surg.* 1991;61:340-348.
4. Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. *J Photochem Photobiol B.* 1990;6:143-148.
5. Wilson BC, Patterson MS. The physics of photodynamic therapy. *Phys Med Biol.* 1986;31:327-360.
6. Dougherty TJ, Kaufman JE, Goldfarb A, et al. Photoradiation therapy for the treatment of malignant tumors. *Cancer Res.* 1978;38:2628-2635.
7. Pass HI. Photodynamic therapy in oncology: mechanisms and clinical use. *J Natl Cancer Inst.* 1993;85:443-456.
8. Kalka K, Merk H, Mukhtar H. Photodynamic therapy in dermatology. *J Am Acad Dermatol.* 2000;42:389-413.
9. Hongcharu W, Taylor C, Chang Y, et al. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. *J Invest Dermatol.* 2000;115:183-192.
10. Kennedy JC, Marcus SL, Pottier RH. Photodynamic therapy (PDT) and photodiagnosis (PD) using endogenous photosensitization induced by 5-aminolevulinic acid (ALA): mechanisms and clinical results. *J Clin Laser Med Surg.* 1996;14:289-304.
11. Kennedy J, Pottier R. Endogenous protoporphyrin IX, a clinically useful photosensitizer for photodynamic therapy. *J Photochem Photobiol B: Biol.* 1992;14:275-292.
12. Goldman MP, Atkin D, Kincad S. PDT/ALA in the treatment of actinic damage: real world experience. *J Lasers Med Surg.* 2002;14(Suppl):24.
13. Touma D, Yaar M, Whitehead S, et al. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *Arch Dermatol.* 2004;140:33-40.
14. Marcus S, McIntyre W. Photodynamic therapy systems and applications. *Expert Opin Emerging Drugs.* 2002;7:321-334.
15. Kloek J, Beijersbergen van Henegouwen GMJ. Prodrugs of 5-aminolevulinic acid for photodynamic therapy. *Photochem Photobiol.* 1996;64:994-1000.
16. Uehlinger P, Zellweger M, Wagnieres G, et al. 5-Aminolevulinic acid and its derivatives: physical chemical properties and protoporphyrin IX formation in cultured cells. *J Photochem Photobiol B.* 2000;54:72-80.
17. Fritsch C, Homey B, Stahl W, et al. Preferential relative porphyrin enrichment in solar keratoses upon topical application of delta-aminolevulinic acid methylester. *Photochem Photobiol.* 1998;68:218-221.
18. Szeimies RM, Karrer S, Radakovic-Fijan S, et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: A prospective, randomized study. *J Am Acad Dermatol.* 2002;47:258-262.
19. Pariser DM, Lowe NJ, Stewart DM, et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. *J Am Acad Dermatol.* 2003;48:227-232.
20. Freeman M, Vinciullo C, Francis D, et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. *J Dermatolog Treat.* 2003;14:99-106.
21. Rhodes LE, de Rie M, Enstrom Y, et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. *Arch Dermatol.* 2004;140:17-23.
22. Hauschild A, Lischner S, Lange-Asschenfeldt B, et al. Treatment of actinic cheilitis using photodynamic therapy with methylaminolevulinate: report of three cases. *Dermatol Surg.* 2005;31:1344-1347.

23. Lee MR, Ryman W. Erythroplasia of Queyrat treated with topical methyl aminolevulinate photodynamic therapy. Australas *J Dermatol.* 2005;46:196-198.

24. Vinciullo C, Elliott T, Francis D, et al. Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. *Br J Dermatol.* 2005;152:765-772.

25. Dragieva G, Prinz BM, Hafner J, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. *Br J Dermatol.* 2004;151:196-200.

26. Morton CA. Methyl aminolevulinate (Metvix) photodynamic therapy—practical pearls. *J Dermatolog Treat*. 2003;14 (Suppl 3):23-26.

27. Foley P. Clinical efficacy of methyl aminolevulinate (Metvix) photodynamic therapy. *J Dermatolog Treat*. 2003;14(Suppl 3): 15-22.

28. Gniazdowska B, Rueff F, Hillemanns P, et al. Allergic contact dermatitis from delta-aminolevulinic acid used for photodynamic therapy. *Contact Dermatitis*. 1998;38:348-349.

29. Wulf HC, Philipsen P. Allergic contact dermatitis to 5-aminolaevulinic acid methylester but not to 5-aminolaevulinic acid after photodynamic therapy. *Br J Dermatol.* 2004;150:143-145.

30. Svaasand LO, Tromberg BJ, Wyss P, et al. Light and drug distribution with topically administered photosensitizers. *Lasers Med Sci.* 1996;11:261-265.

31. Henderson BW. Photodynamic therapy—coming of age. *Photodermatol.* 1989;6:200-211.

32. Weishaupt KR, Gomer CJ, Dougherty TJ. Identification of singlet oxygen as the cytotoxic agent in photoinactivation of a murine tumor. *Cancer Res*. 1976;36(7 pt 1):2326-2329.

33. Niedre MJ, Yu CS, Patterson MS, et al. Singlet oxygen luminescence as an in vivo photodynamic therapy dose metric: validation in normal mouse skin with topical amino-levulinic acid. *Br J Cancer.* 2005;92:298-304.

34. Svaasand LO, Wyss P, Wyss MT, et al. Dosimetry model for photodynamic therapy with topically administered photosensitizers. *Lasers Surg Med.* 1996;18:139-149.

35. Nakaseko H, Kobayashi M, Akita Y, et al. Histological changes and involvement of apoptosis after photodynamic therapy for actinic keratoses. *Br J Dermatol.* 2003;148:122-127.

36. Cockerell CJ, Wharton JR. New histopathological classification of actinic keratosis (incipient intraepidermal squamous cell carcinoma). *J Drugs Dermatol.* 2005;4:462-467.

37. Gold MH. The evolving role of aminolevulinic acid hydrochloride with photodynamic therapy in photoaging. *Cutis*. 2002;69(6 Suppl):S8-S13.

38. Varma S, Wilson H, Kurwa HA, et al. Bowen's disease, solar keratoses and superficial basal cell carcinomas treated by photodynamic therapy using a large-field incoherent light source. *Br J Dermatol.* 2001;144:567-574.

39. Alexiades-Armenakas MR, Geronemus RG. Laser-mediated photodynamic therapy of actinic keratoses. *Arch Dermatol.* 2003;139:1313-1320.

40. Jeffes EW, McCullough JL, Weinstein GD, et al. Photodynamic therapy of actinic keratosis with topical 5-aminolevulinic acid. A pilot dose-ranging study. *Arch Dermatol.* 1997; 133:727-732.

41. Jeffes EW, McCullough JL, Weinstein GD, et al. Photodynamic therapy of actinic keratoses with topical aminolevulinic acid hydrochloride and fluorescent blue light. *J Am Acad Dermatol.* 2001;45:96-104.

42. Piacquadio DJ, Chen DM, Farber HF, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. *Arch Dermatol.* 2004;140:41-46.

43. Data on file, Levulan® Kerastick® (aminolevulinic acid HCl) for topical solution, 20%, Dusa Pharmaceuticals, Inc., Wilmington, Mass.

44. Fowler JF Jr, Zax RH. Aminolevulinic acid hydrochloride with photodynamic therapy: efficacy outcomes and recurrence 4 years after treatment. *Cutis*. 2002;69(6 Suppl):2-7.

45. Gold MH. Intense pulsed light therapy for photorejuvenation enhanced with 20% aminolevulinic acid photodynamic therapy. *J Lasers Med Surg.* 2003;15(Suppl):47.

46. Smith S, Piacquadio D, Morhenn V, et al. Short incubation PDT versus 5-FU in treating actinic keratoses. *J Drugs Dermatol.* 2003;2:629-635.

47. Avram DK, Goldman MP. Effectiveness and safety of ALA-IPL in treating actinic keratoses and photodamage. *J Drugs Dermatol.* 2004;3(1 Suppl):S36-S39.

48. Markham T, Collins P. Topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratoses. *Br J Dermatol.* 2001;145:502-504.

49. Weinstein GD, Taylor JR, Glazer SD, et al. A dose-ranging study of photodynamic therapy with topical 5-aminolevulinic acid for treatment of actinic keratoses. Poster presented at: 61st Annual Meeting of the American Academy of Dermatology, San Francisco, 2003.

50. Gold MH. A single-center, open-label investigatory study of photodynamic therapy in the treatment of photoaging with aminolevulinic acid topical solution 20% and intense pulsed light. Poster presented at: 61st Annual Meeting of the American Academy of Dermatology, San Francisco, 2003.

51. Gold MH. A single-center, open-label investigatory study of photodynamic therapy in the treatment of moderate to severe acne vulgaris with aminolevulinic acid topical solution 20% and visible blue light. Poster presented at: 61st Annual Meeting of the American Academy of Dermatology, San Francisco, 2003.

52. Goldman MP, Boyce SM. A Single Center Study of 5-Aminolevulinic Acid and 417 nm Photodynamic Therapy in the Treatment of Moderate to Severe Acne Vulgaris. *J Drugs Dermatol.* 2003;2:393-396.

53. Stender IM, Bech-Thomsen N, Poulsen T, et al. Photodynamic therapy with topical delta-aminolevulinic acid delays UV photocarcinogenesis in hairless mice. *Photochem Photobiol.* 1997;66:493-496.

54. Bissonette R, Bergeron A, Liu Y. Large surface photodynamic therapy with aminolevulinic acid: treatment of actinic keratoses and beyond. *J Drugs Dermatol.* 2004;3(1 Suppl):S26-S31.

55. Liu Y, Viau G, Bissonnette R. Multiple large-surface photodynamic therapy sessions with topical or systemic aminolevulinic acid and blue light in UV-exposed hairless mice. *J Cutan Med Surg.* 2004;8:131-139.

56. Gilbert DJ. Treatment of actinic keratoses with sequential combination of 5-fluorouracil and photodynamic therapy. *J Drugs Dermatol.* 2005;4:161-163.

57. Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol.* 2002;138:1462-1470.

58. Kang S, Fisher GJ, Voorhees JJ. Photoaging: pathogenesis, prevention, and treatment. *Clin Geriatr Med.* 2001;17:643-59.

59. Nestor MS. Evolving use of 5-aminolevulinic acid (ALA) topical photodynamic therapy clinically and cosmetically: a clinician's perspective. *Cosmetic Dermatol.* 2005;18:2-8.

60. Kligman LH, Akin FJ, Kligman AM. Prevention of ultraviolet damage to the dermis of hairless mice by sunscreens. *J Invest Dermatol.* 1982;78:181-189.

61. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med.* 1993;329:1147-1151.

62. Bitter PH. Noninvasive rejuvenation of photodamaged skin using serial, full-face intense pulsed light treatments. *Dermatol Surg.* 2000;26:835-842.

63. Negishi K, Tezuka Y, Kushikata N, et al. Photorejuvenation for Asian skin by intense pulsed light. *Dermatol Surg.* 2001;27: 627-631.

64. Ruiz-Rodriguez R, Sanz-Sanchez T, Cordoba S. Photodynamic rejuvenation. *Dermatol Surg.* 2002;28:742-744.

65. Nestor MS, Goldbert DJ, Goldman MP, et al. New Perspectives on Photorejuvenation. *Skin & Aging.* 2003;11:68-74.

66. Bhatia AC, Dover JS, et al. Adjunctive use of topical aminolevulinic acid with intense pulsed light in the treatment of photoaging. Paper presented at: Controversies and Conversations in Cutaneous Laser Surgery, Mt. Tremblant, Canada, August 2004.

67. Gold MH, Bradshaw VL, Boring MM, et al. A split-face comparison study of ALA-PDT with intense pulsed light versus intense pulse light alone for photodamage/photorejuvenation. *Dermatol Surg.* In press.

68. Dover JS, Bhatia AC, Stewart B, et al. Topical 5-aminolevulinic acid combined with intense pulsed light in the treatment of photoaging. *Arch Dermatol.* 2005;141:1247-1252.

69. Lowe NJ, Lowe PL. A pilot study to determine the efficacy of ALA-PDT photorejuvenation for the treatment of facial aging. *J Cos Laser Ther.* Dec. 2005.

70. Hall J, Keller P, Keller G. Dose response of combination photorejuvenation using intense pulsed light-Activated photodynamic therapy and radiofrequency energy. *Arch Facial Plast Surg.* 2004;6:374-378.

71. Alster TS, Tanzi EL, Welsh EC. Photorejuvenation of facial skin with topical 20% 5-aminolevulinic acid and intense pulsed light treatment: A split-face comparison study. *J Drugs Dermatol.* 2005; 4:35-38.

72. Leyden JJ. Therapy for acne vulgaris. *N Engl J Med.* 1997;336:1156-1162.

73. Gollnick HP, Krautheim A. Topical treatment in acne: current status and future aspects. *Dermatology.* 2003;206:29-36.

74. Zouboulis CC, Piquero-Martin J. Update and future of systemic acne treatment. *Dermatology.* 2003;206:37-53.

75. Thiboutot D, Chen W. Update and future of hormonal therapy in acne. *Dermatology.* 2003;206:57-67.

76. Elman M, Lebzelter J. Light therapy in the treatment of acne vulgaris. *Dermatol Surg.* 2004;30(2 Pt 1):139-146.

77. Ruiz-Esparza J, Gomez JB. Nonablative radiofrequency for active acne vulgaris: the use of deep dermal heat in the treatment of moderate to severe active acne vulgaris (thermotherapy): a report of 22 patients. *Dermatol Surg.* 2003;29:333-339.

78. Omi T, Bjerring P, Sato S, et al. 420 nm intense continuous light therapy for acne. *J Cosmet Laser Ther.* 2004;6:156-162.

79. Gollnick H, Cunliffe W, Berson D, et al. Global Alliance to Improve Outcomes in Acne. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003;49(1 Suppl):S1-S37.

80. Itoh Y, Ninomiya Y, Tajima S, et al. Photodynamic Therapy for Acne Vulgaris With Topical 5-Aminolevunic Acid. *Arch Dermatol.* 2000:136;1093-1095.

81. Itoh Y, Ninomiya Y, Tajima S, et al. Photodynamic therapy of acne vulgaris with topical delta-aminolevulinic acid and incoherent light in Japanese patients. *Br J Dermatol.* 2001;144:575-579.

82. Alexiades-Armenakas M. Long-Pulsed Dye Laser-Mediated Photodynamic Therapy Combinded with Topical Therapy for Mild to Severe Comedonal, Inflammatory, or Cystic Acne. *J Drugs Dermatol.* 2006;5(1):45.

83. Divaris DX, Kennedy JC, Pottier RH. Phototoxic damage to sebaceous glands and hair follicles of mice after systemic administration of 5-aminolevulinic acid correlates with localized protoporphyrin IX fluorescence. *Am J Pathol.* 1990;136:891-897.

84. Cunliffe WJ, Goulden V. Phototherapy and acne vulgaris. *Br J Dermatol.* 2000;142:855-856.

85. Arakane K, Ryu A, Hayashi C, et al. Singlet oxygen (1 delta g) generation from coproporphyrin in Propionibacterium acnes on irradiation. *Biochem Biophys Res Commun.* 1996;223:578-582.

86. Gold MH, Bradshaw VL, Boring MM, et al. Treatment of sebaceous gland hyperplasia by photodynamic therapy with 5-aminolevulinic acid and a blue light source or intense pulsed light source. *J Drugs Dermatol.* 2004;3(6 Suppl):S6-S9.

87. Gold MH. The utilization of ALA PDT and a new photoclearing device for the treatment of severe inflammatory acne vulgaris—results of an initial clinical trial. *J Lasers Surg Med.* 2003;15(Suppl);S46.

88. Taub A. Photodynamic therapy for the treatment of acne: A pilot study. *J Drugs Dermatol.* 2004;3(Suppl):S10-S14.

89. Schonermark MP, Schmidt C, Raulin C. Treatment of sebaceous gland hyperplasia with the pulsed dye laser. *Lasers Surg Med.* 1997;21:313-310.

90. Alster TS, Tanzi EL. Photodynamic therapy with topical aminolevulinic acid and pulsed dye laser irradiation for sebaceous hyperplasia. *J Drugs Dermatol.* 2003;2:501-504.

91. No D, McClaren M, Chotzen V, et al. Sebaceous hyperplasia treated with a 1450-nm diode laser. *Dermatol Surg.* 2004;30:382-384.

92. Horio T, Horio O, Miyauchi-Hashimoto H, et al. Photodynamic therapy of sebaceous hyperplasia with topical 5-aminolaevulinic acid and slide projector. *Br J Dermatol.* 2003; 148:1274-1276.

93. Richey DF, Hopson B. Treatment of sebaceous hyperplasia by photodynamic therapy. *Cosmetic Dermatol.* 2004;17:525-529.

94. Goldman MP. Using 5-aminolevulinic acid to treat acne and sebaceous hyperplasia. *Cosmetic Dermatol.* 2003;16:57-58.

95. Gold M, Bridges TM, Bradshaw VL, et al. ALA-PDT and blue light therapy for hidradenitis suppurativa. *J Drugs Dermatol.* 2004;3(1 Suppl):S32-S35.

96. Gold MH, Boring MM, Bridges TM, et al. The successful use of ALA-PDT in the treatment of recalcitrant molluscum contagiosum. *J Drugs Dermatol.* 2004;3:187-190.

97. Moiin A. Photodynamic therapy for molluscum contagiosum infection in HIV-coinfected patients: review of 6 patients. *J Drugs Dermatol.* 2003;2:637-639.

98. Coors E, von den Driesch P. Topical photodynamic therapy for patients with therapy-resistant lesions of cutaneous T-cell lymphoma. *J Am Acad Dermatol.* 2004;50:363-367.

99. Umegaki N, Moritsugu R, Katoh S, et al. Photodynamic therapy may be useful in debulking cutaneous lymphoma prior to radiotherapy. *Clin Exp Dermatol.* 2004;29:42-45.

100. Gardlo K, Horska Z, Enk CD, et al. Treatment of cutaneous leishmaniasis by photodynamic therapy. *J Am Acad Dermatol.* 2003;48:893-896.

101. Enk CD, Fritsch C, Jonas F, et al. Treatment of cutaneous leishmaniasis with photodynamic therapy. *Arch Dermatol.* 2003;139:432-434.

102. El-On J, Katz M, Weinrauch L. Treatment of cutaneous leishmaniasis by photodynamic therapy. *J Am Acad Dermatol.* 2004;50:e12; author reply e13.

103. Shieh S, Dee AS, Cheney RT, et al. Photodynamic therapy for the treatment of extramammary Paget's disease. *Br J Dermatol.* 2002;146:1000-1005.

104. Mikasa K, Watanabe D, Kondo C, et al. 5-Aminolevulinic acid-based photodynamic therapy for the treatment of two patients with extramammary Paget's disease. *J Dermatol.* 2005;32:97-101.

105. Ruiz-Rodriguez R, Alvarez JG, Jaen P, et al. Photodynamic therapy with 5-aminolevulinic acid for recalcitrant familial benign pemphigus (Hailey-Hailey disease). *J Am Acad Dermatol.* 2002;47:740-742.

106. Strauss RM, Pollock B, Stables GI, et al. Photodynamic therapy using aminolaevulinic acid does not lead to clinical improvement in hidradenitis suppurativa. *Br J Dermatol.* 2005;152:803-804.

107. Radakovic-Fijan S, Honigsmann H, Tanew A. Efficacy of topical photodynamic therapy of a giant keratoacanthoma demonstrated by partial irradiation. *Br J Dermatol.* 1999;141:936-938.

108. Clark SM, Mills CM, Lanigan SW. Treatment of keratosis pilaris atrophicans with the pulsed tunable dye laser. *J Cutan Laser Ther.* 2000;2:151-156.

109. Edstrom D, Porwit A, Ros A-M. Photodynamic therapy with topical 5-aminolevulinic acid for mycosis fungoides: Clinical and histological response. *J Eur Acad Dermatol Venereol.* 2001;81: 184-188.

110. Markham T, Sheahan K, Collins P. Topical 5-aminolevulinic acid photodynamic therapy for tumour-stage mycosis fungoides. *Br J Dermatol.* 2001;144:1262-1295.

111. Dierickx CC, Goldenhersh M, Dwyer P, et al. Photodynamic therapy for nevus sebaceus with topical delta-aminolevulinic acid. *Arch Dermatol.* 1999;135:637-640.

112. Richey DF, Hopson B. Treatment of perioral dermatitis by photodynamic therapy. *J Drugs Dermatol.* 2006;5(suppl 1).

113. Bissonnette R, Tremblay J, Juzenas P, et al. Systemic photodynamic therapy with aminolevulinic acid induces apoptosis in lesional T lymphocytes of psoriatic plaques. *J Invest Dermatol.* 2002;119:77-83.

114. Yim YC, Lee ES, Chung PS, et al. Recalcitrant palmoplantar pustular psoriasis successfully treated with topical 5-aminolaevulinic acid photodynamic therapy. *Clin Exp Dermatol.* 2005;30:723-724.

115. Radakovic-Fijan S, Blecha-Thalhammer U, Schleyer V, et al. Topical aminolaevulinic acid-based photodynamic therapy as a treatment option for psoriasis? Results of a randomized, observer-blinded study. *Br J Dermatol.* 2005;152:279-283.

116. Amari N, Ando I, Wakugawa M. Photodynamic therapy for rhinophyma. *J Dermatol.* 2004;31:771-772.

117. Karrer S, Abels C, Landthaler M, et al. Topical photodynamic therapy for localized scleroderma. *Acta Derm Venereol.* 2000;80:26-27.

118. Wang X, Wang H, Wang H, et al. Topical 5-aminolaevulinic acid-photodynamic therapy for the treatment of urethral condylomata acuminata. *Br J Dermatol.* 2004;151:880-885.

119 Smucler R, Jatsova E. Comparative study of aminolevulic acid photodynamic therapy plus pulsed dye laser versus pulsed dye laser alone in treatment of viral warts. *Photomed Laser Surg.* 2005;23:202-205.

120. Schroeter CA, Pleunis J, van Nispen tot Pannerden C, et al. Photodynamic therapy: new treatment for therapy-resistant plantar warts. *Dermatol Surg.* 2005;31:71-5.

121. Setlow RB, Grist E, Thompson K, et al. Wavelengths effective in induction of malignant melanoma. *Proc Natl Acad Sci U S A.* 1993;90:6666-6670.

122. Ohara M, Kawashima Y, Kitajima S, et al. Blue light inhibits the growth of skin tumors in the v-Ha-ras transgenic mouse. *Cancer Sci.* 2003;94:205-209.

123. Fiedler DM, Eckl PM, Krammer B. Does delta-aminolaevulinic acid induce genotoxic effects? *J Photochem Photobiol B.* 1996;33:39-44.

124. Morton CA, Brown SB, Collins S, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. *Br J Dermatol.* 2002;146:552-567.

125. Marmur ES, Phelps R, Goldberg DJ. Ultrastructural changes seen after ALA-IPL photorejuvenation: a pilot study. *J Cosmet Laser Ther.* 2005;7:21-24.

Address for Correspondence

Mark S. Nestor MD PhD
2925 Aventura Blvd, Ste. 205
Aventura, FL 33180-3108.
e-mail: nestormd@admcorp.com