ELSEVIER

Seminars in Cutaneous Medicine and Surgery

Photodynamic Therapy in Dermatology: An Update on Applications and Outcomes

Mollie A. MacCormack, MD*,†

Photodynamic therapy is a relatively new and rapidly evolving therapeutic option in dermatology. Initially used for the treatment of actinic damage and nonmelanotic skin cancer, more recent work indicates efficacy in the treatment of a wide range of conditions, such as acne, infectious processes, cutaneous T-cell lymphoma, and photorejuvenation, among others. This article provides a comprehensive review of applications and outcomes that use topical photodynamic therapy in the treatment of dermatologic disease.
Semin Cutan Med Surg 27:52-62 © 2008 Elsevier Inc. All rights reserved.

KEYWORDS photodynamic therapy, aminolevulinic acid, methyl aminolevulinate, actinic keratoses, basal cell carcinoma, squamous cell carcinoma in situ

Photodynamic therapy (PDT) harnesses the power of light and oxygen to enact biologic change. In its infancy, the use of PDT in the treatment of dermatologic disease was limited due to the prolonged and pronounced photosensitivity resulting from systemic photosensitizing agents. However, in the early 1990s Kennedy and Pottier described the use of topical 5-aminolevulinic acid (ALA) to create endogenous protoporphyrin IX (PpIX) from which came a limited, localized, photodynamic response.[1] With this development, many of the early limitations of PDT were alleviated, and the treatment became much more convenient. Early application focused primarily on the treatment of dysplastic and neoplastic disease; however, during the past few years, the versatility of PDT has been more fully realized, and it is now also being used to treat a wide variety of inflammatory and infectious processes. As the history of PDT has previously been extensively reviewed,[2-5] this article will focus on current uses with an emphasis on the most commonly used photosensitizing agents and recent developments in practical application.

Mechanism of Action

The basic premise of PDT is quite simple. In the presence of oxygen a photosensitizing agent, either endogenous or exogenous, is exposed to light resulting in the creation of activated intermediates, primarily singlet oxygen. Singlet oxygen is a very reactive molecule that can damage many components of the target cell, including mitochondria resulting in cell death.[6,7] Supplementing this direct assault are indirect pathways of cellular destruction such as the recruitment of inflammatory cells, increased immune response and vascular compromise.[8] Singlet oxygen can also destroy the photosensitizing agent itself preventing further action, a process referred to as photobleaching.

The effectiveness of PDT depends on (1) the photosensitizer used, its ability to selectively penetrate diseased tissue, and the duration of application; (2) the activating light source, its ability to penetrate to the desired target, and its duration of exposure; and (3) the type of target cells and their oxygenation status. To be effective, the damage resulting from PDT must surpass cellular repair mechanisms, a feature referred to as the minimum photodynamic dose.

Aminolevulinic Acid (ALA)

Currently Food and Drug Administration (FDA) approved for the treatment of actinic keratoses, ALA (Levulan®: DUSA Pharmarceuticals, Wilmington, MA) is the only topical photosensitizing agent available for dermatologic use in the United States. ALA is a hydrophilic, low molecular weight molecule that is absorbed readily through abnormal but not through normal keratin.[9] Once absorbed by epidermal or appendageal cells ALA is converted to PpIX, a potent photosensitizer. Due to of limited supplies of iron, a necessary catalyst for ferrochelatase, recipient cells are unable to complete the final stage of conversion of PpIX to heme leading to PpIX accumulation. With short application times (<4

*Harvard Medical School, Boston, MA.
†Director of Dermatologic Surgery, Lahey Clinic, Burlington, MA.
Address reprint requests to Mollie Maccormack, MD, Lahey Clinic, Department of Dermatology, 41 Mall Road, Burlington, MA 01805. E-mail: Mollie.maccormack@lahey.org

1085-5629/08/$-see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.sder.2007.12.001

hours), PpIX production is largely limited to the target site; however, with longer application periods, a larger area of reaction may develop.[10] Photosensitization typically resolves within 24 hours after application is completed. Maximal light absorption is seen at 409 nm, and smaller peaks occur at 509 nm, 544 nm, 584 nm, and 635 nm. Existing FDA approval is based on a 14- to 18-hour application period; however, studies have demonstrated efficacy with shorter incubation periods (1 hour) that are more convenient for both patient and practitioner.[11,12]

Methyl Aminolevulinate (MAL)

Methyl aminolevulinate (MAL) (Metvix®; Photocure ASA, Oslo, Norway) is the methyl ester of ALA. Although approved by the FDA in 2004 for the treatment of actinic keratoses, it is not currently available in the United States. Unlike ALA, MAL is provided as a 160 mg/g cream designed to be applied under occlusion for 3 hours followed by red light activation (570-670 nm for a total dose of 75J/cm^2), at which point complete photobleaching should have occurred. More lipophillic than ALA, MAL is felt to exhibit increased tumor/diseased skin specificity when compared with ALA.[13] Initially MAL also was expected to exhibit improved tissue penetration and thus greater efficacy when compared with ALA; however, recent studies suggest similar levels of effect or perhaps even increased activity of ALA.[14-16]

Light Sources

Both ALA and MAL lead to the production of PpIX which, as previously noted, displays a large peak in absorption spectra at 409 nm, with much smaller peaks at 509 nm, 544 nm, 584 nm and 635 nm. While blue light such as that emitted by the Blu-U® (DUSA Pharmaceuticals, Wilmington, MA) or Omnilux Blue™ (Photo Therapeautics Inc., Carlsbad, CA) takes advantage of the largest absorption spike at 417 nm, it is limited by depth of penetration to about 1.5 to 2 mm. Red light (>600 nm) requires higher energy levels to achieve the same effect (because of the lower PpIX light absorption at longer wavelengths), but has the advantage of being able to penetrate deeper (approximately 8-10 mm). However, this deeper penetration can be limited be melanin.[17] Filtered red or green noncoherent light sources are commonly used in Europe, whereas in the United States longer wavelength light sources include diode and pulsed dye lasers as well as intense pulsed light (IPL).

Dermatologic Clinical Applications

Actinic Keratoses

ALA and Actinic Keratoses

First described by Kennedy and coworkers,[9] the use of ALA–PDT to treat actinic keratoses has become the most frequent and well studied dermatologic application of PDT in the United States (Table 1).[18-41] Although the earliest studies used an oil in water formulation of ALA that required occlusion for penetration,[18,23] in 1999, FDA approval was granted for a treatment protocol that involves application of 20% ALA solution to individual actinic keratoses for a period of 14 to 18 hours followed by a 16-minute, 40-second exposure to blue light (417 ± 5 nm) for a total dose of 10 J/cm^2. A second treatment, if needed, is performed at week 8. Complete response of nonhyperkeratotic actinic keratoses after one treatment is approximately 65%, increasing to 85% after the second treatment.[10,35] A subsequent phase IV clinical trial found recurrence rates of 19% at 12 months.[40] Practical considerations led to a number of modifications to the aforementioned treatment protocol such as much abbreviated incubation periods (1 hour)[11] and broad application in lieu of spot treatment.[29] Broad application, short contact (1 hour), ALA–PDT activated by blue light has been found to be both more effective and more easily tolerated than 0.5% fluorouracil cream applied 1 to 2 times daily for 4 weeks.[12] The safety of broad area application is supported by an animal study published by Bissonette and coworkers in which hairless mice were treated weekly with either ALA, blue light alone or ALA–PDT. No carcinogenic potential was seen in any group.[42] ALA–PDT for the treatment of actinic keratoses has also been described utilizing IPL with 42-68% improvement after one treatment, however, these studies tend to be small and not well controlled.[36,37]

MAL and Actinic Keratoses

A number of prospective randomized studies have been published evaluating the use of MAL–PDT for the treatment of actinic keratoses (Table 1). The most commonly used protocol involves light curettage of lesions, application of a thick layer of MAL cream left under occlusion for at least 3 hours, followed by exposure to noncoherent red light (570-670 nm, 75 J/cm^2), with repeat treatment at 1 week. Complete response ranges from 69% to 91%[31]; with only a single treatment this decreases to 70%.[38] These numbers are similar to those seen with cryotherapy (complete reponse 68-75%); however, many feel that MAL–PDT is superior in terms of cosmetic outcome and patient satisfaction.[21,30,39] Superior outcomes have also been described in comparison to 5-fluorouracil cream applied twice daily for 3 weeks.[41] When compared with PDT using 20% ALA cream, similar efficacy was seen in both groups; however, ALA–PDT was noted to be more uncomfortable for patients then MAL–PDT.[43]

Nonmelanotic Skin Cancer

Basal Cell Carcinoma

Although not currently approved by the FDA, numerous studies have documented the efficacy of PDT in the treatment of basal cell carcinoma.[1,20,44,45] Most early studies used 20% ALA in an oil and water emulsion with red light activation; however, more recent work has focused on 20% ALA solution and MAL.[46,47] As expected, superficial basal cell carcinoma (sBCC) seems to respond best, with reported complete response rates ranging from 50 to 100%[46-48] whereas complete response of nodular tumors ranges from 10% to 100%

Table 1 Studies on the Use of Topical ALA/MAL PDT for the Treatment of Actinic Keratoses

Reference	Lesions Treated	Photosensitizer, Time (hours)	Light Source (nm)	Results	Follow-Up (mos)
Kennedy 1990[9]	10	ALA, 3 to 6	Tungsten > 600	90% CR, 10% NR	18
Wolf 1993[18]	9	ALA, 4 to 8	Tungsten unfiltered	100% CR	3 to 12
Calzavara-Pinton 1995[19]	50	ALA, 6 to 8	ArDL 630	100% CR (multiple treatments)	24 to 36
Fijan 1995[20]	43	ALA, 3% DFO, 20	Halogen 570 to 690	81% CR	3 to 20
Szeimies 1996[21]	36	ALA, 6	Red 580 to 740	71% CR (lesser response seen on hands)	3
Fink-Puches 1997[22]	251	ALA, 4	UVA +/or FSVL +/or FL >515, >530, 570, >610	Face, scalp, and Neck: 91 to 100% CR* Forearms and Hands: 33% to 51% CR†	36
Jeffes 1997[23]	240	0, 10, 20, 30% ALA, 3	ArDL 630	91% CR-face and scalp 45% CR-trunk and extremities	2
Kurwa 1999[24]	–	ALA, 4	Red 580 to 740	73% reduction in lesional area – hands	6
Dijkstra 2001[25]	4	ALA, 8	Violet 400 to 450	25% CR, 75% PR	3 to 12
Varma 2001[26]	111	ALA, 4 to 6	Red 600 to 730	1 rx - 77% CR, 3 rx - 100% CR	13‡
Jeffes 2001[10]	70	ALA, 14 to 18	Blue 417 ± 5	1 rx - 66% CR, 17% PR 17% NR 2 rx - 85% CR, 6% PR 9% NR	4
Ruiz-Rodriguez 2002[27]	38	ALA, 4	IPL 590 to 1200 w/cutoff filter 615	1 rx - 76% CR 2 rx - 91% CR	3
Szeimies 2002[28]	54	MAL, 3	Red 570 to 670	71% CR Face, 61% CR Scalp, 75% CR other	3
Goldman 2003[29]	35	ALAs, 15 to 20	Blue 417 ± 5	94% CR, 6% PR	1
Freeman 2003[30]	360	MAL, 3, 2 rx	Red 570 to 670	91% CR	3
Pariser 2003[31]	260	MAL, 3, 2 rx	Red 570 to 670	82% CR	3
Smith 2003[12]	148	ALAs, 1	Blue 417 ± 5 or PDL 595	Blue light: 50% CR, 25% PR PDL: 8% CR, 33% PR	1
Alexiades 2003[32]	3622	ALAs 3 w/occlusion 14 to 18 w/o	PDL 595	10 days Head – 99.8% CR, Exts – 75.2% CR Trunk – 77% CR 8 months Head – 87.7% CR, Exts – 100% CR Trunk – NR	8
Dragieva 2004[33]	44 (OT)	ALA, 5	Red 570 to 650	Face – 96% CR, 86% CR at 3 month	3
Dragieva 2004[34]	62 (OT)	MAL, 3, 2rx	Red 600 to 730	90% CR	4
Piacquadio 2004[35]	1403	ALAs, 14 to 18	Blue 417 ± 5	1 rx - 91% CR, 2 rx - 83% CR	3
Avram 2004[36]	–	ALAs, 1	IPL w/560 filter	68% CR	3
Touma 2004[11]	>72	ALAs, 1, 2, or 3	Blue 417 ± 5	CR: 1 month - 85% to 96%, 5 months: 87% to 94%	5
Kim 2005[37]	12	ALA, 4	IPL 555 to 950	50% CR	3
Tarstedt 2005[38]	413	MAL, 3, 1-2rx	Red 634 ± 3	Thin Lesion, 93% CR 1 rx, 89% CR 2 rx Thick Lesion, 70% CR 1 rx, 88% CR 2 rx	3
Morton 2006[39]	758	MAL, 3, 1-2 rx	Red Light	88% CR Face, 83% CR Scalp	6
Tschen 2006[40]	968	ALAs, 14 to 18	Blue 417 ± 5	1 rx: 76% CR at 1 month, 72% CR at 2 month 2 rx: 86% CR at 4 month, 78% CR at 12 month	12
Perrett 2007[41]	9 (OT)	MAL, 3, 2 rx	Red 570 to 670	89% CR	6

ALA, 20% 5-aminolevulinic acid oil in water emulsion; MAL, methyl aminolevulate 160 mg/g; ALAs, 20% 5 aminolevulinic acid solution; CR, complete response; NR, no response; PR, partial response; rx, treatment; ArDL, Argon pumped tunable dye laser; DFO, desferrioxamine; UVA, ultraviolet A; FSVL, full spectrum visible light; FL, filtered light; IPL, intense pulsed light device; PDL, pulsed dye laser; OT, organ transplant patients.

*Best results seen with UVA + FSVL.

†Best results seen with FSVL + FL.

‡28% recurrence rate.

(multiple treatments were necessary to achieve the higher figure).[18,45,47,49] Pigmented lesions in particular tend to respond poorly because of interference by melanin.[19] Recurrence is an issue for all tumor types, reaching as high as 44% at 19 months for sBCC[50] and 57% at 3 months for nBCC[20] treated with ALA and 18% at 12 to 24 months for lesions treated with MAL.[26,45] Vinciullo and coworkers treated 148 "difficult-to-treat" BCCs, which they defined as large lesions, lesions in the H-zone, or BCC in patients with high risk of surgical complications, with MAL-PDT. Initial complete response was 89% at 3 months; however, by 24 months it had decreased to 78%.[51]

One of the limitations of PDT is that both the photosensitizing agent and the light source may have difficulty reaching deeper areas of disease. This limitation is evidenced by a 2003 study in which the probability of 1-year control was 85% for BCC less than 1.5 mm deep but decreased to 75% when lesions 3 mm thick were included.[52] Various attempts have been made to ameliorate this phenomenon, including pretreatment debulking,[44,53] multiple treatments,[19] the use of fractionated light delivery to limit photobleaching,[54] interstitial light delivery,[55] intralesional injection of ALA,[56] and the use of PDT as an adjunct to Mohs surgery.[57] A recent pilot study by Berroeta and coworkers was designed to compare minimal curettage followed by ALA–PDT (20% ALA cream applied under occlusion for 6 hours followed by 620-nm laser activation 125 J/cm^2) with surgical excision for primary, <2 cm, well-defined, nodular, BCCs in low risk anatomic areas. Altough cosmesis was equivalent between the two groups, 17% more tumors cleared with surgical excision and PDT was deemed to be the more painful intervention. Based on these results the authors concluded that for now, surgery remains the first treatment option for nodular BCCs.[58] A number of studies have evaluated the use of PDT in the treatment of nevoid BCC syndrome. Treatment parameters vary, but reported efficacy ranges from 67 to 100% for sBCC and 31 to 98% for nevoid BCC.[25,59-61]

Squamous Cell Carcinoma and Squamous Cell Carcinoma In-Situ

Because of limitations in the ability to treat deep-set disease, PDT is not currently recommended as a treatment modality for invasive SCC.[62] Many studies, however, have shown good effect with the use of PDT to treat in situ disease. Initial cure rates typically range from 60% to 100% with the largest multicenter trial (225 patients) revealing a 93% cure rate at 3 months, decreasing to 80% at 12 months using MAL–PDT.[63] In comparison, the same study found complete response rates of 86% and 67% with cryotherapy and 83% and 69% with 5-fluorouracil at 3 and 12 months respectively. Case reports have also described effective treatment of subungual Bowen's disease with ALA PDT,[64,65] in situ disease in patients with epidermolysis bulosa,[66] and an ambulatory system designed to facilitate treatment.[67]

Numerous articles have described the use of PDT for the treatment of erythroplasia of Queyrat.[68-70] Unfortunately, results have been somewhat disappointing with fairly low initial response rates, high recurrence, and (in 1 case) progression to invasive disease.[69]

Acne

In the era of increasing antibiotic resistance and increasing bureaucratic regulation of systemic retinoid use, an alternative and effective acne treatment is desirable. The initial theory behind the use PDT for acne centered on the endogenous production of porphyrins by bacteria, such as Propionibacterium acnes, as a byproduct of their metabolism. By exposing the skin to the appropriate wavelength of light, these porphyrins can be activated leading to bacterial elimination.[71,72] Many investigators have attempted to capitalize on this phenomenon with varying levels of success (Table 2).[73-89] Blue light alone has been demonstrated to improve both inflammatory and comedonal lesions.[73,74,77,79,82] Because ALA accumulates not only in malignant cells but also in sebaceous glands, it was hypothesized that an even-greater effect could be obtained by applying either ALA or MAL to the skin before light exposure. The earliest studies involved application of ALA for 3 or 4 hours followed by exposure to red/visible light.[75,76] Although clearly effective, side effects such as an acneiform flare at day 3 to 4, erythema, hyperpigmentation, and exfoliation were pronounced. Modifications followed, including decreased time of photosensitizer application,[77,85] and use of blue light or IPL as a light source.[80,84] As seen in Table 2, although many different regimens have been tried, no one single protocol has proven to be the best. Of note, Wiegel and Wolff did compare ALA and MAL applied for 3 hours under occlusion followed by red light activation. Although no significant difference was noted in terms of efficacy (both led to a 59% in inflammatory lesions at week 12), ALA was noted to cause more side effects such as edema, erythema, and scale.[15]

Sebaceous Hyperplasia

Accumulation of ALA in sebaceous glands led not only to its use in the treatment of acne but also prompted investigation of its use for the treatment of sebaceous hyperplasia. Various light sources have been used ranging from halogen >620 nm,[90] to blue light,[91] to pulsed dye laser (595 nm) (PDL) to IPL.[92] Application time of ALA ranges from 1 to 4 hours, and number of treatments ranges from 1 to 6. The most effective results seem to be those described in studies by both Alster[93] and Richey.[89] Alster applied ALA for 1 hour followed by PDL activation. Seven of 10 patients cleared in 1 treatment, 3 cleared after 2. Side effects included transient erythema and crusting. Richey treated patients with 45 minute-1 hour of ALA, followed by blue light for 3 to 6 treatments. Clearance was 70% after 6 months; however, 10-20% recurrence was noted 3 to 4 months after the last treatment. Side effects were similar to those previously noted. Clearance of a nevus sebaceous was obtained by Dierickx and colleagues after 13 sessions using 20% ALA applied for 4 hours with 630 nm argon laser activation.[94]

Table 2 Studies on the Use of Photodynamic Therapy for Acne

Reference	Patient No.	Photosensitizer	Light Source (nm)	Results
Meffert 1990[73]		None	Blue 400 to 420 10 min x 10 exposures (cumulative dose –325J/cm^2)	Improvement in acne and oil production
Papageorgiou 2000[74]	107	None	Blue 415 + 20/-15, or Blue and Red 415 & 660 ± 10, 15 min qd x 12 weeks (cumulative dose 320 J/cm^2 blue, 202 J/cm^2 red)	Blue: 45% improvement comedones, 63% improvement inflammatory lesions. Blue and Red: 58% improvement comedones, 76% improvement inflammatory lesions
Hongcharu 2000[75]	22 (Truncal Acne)	ALA 20% occluded x 3 hours	Red 550 to 700 (150 J/cm^2) ½ had single rx, ½ had rx 1x/wk x 4 weeks	Flare noted 3 to 4d after rx. Significant improvement noted. Improvement persisted >10 weeks after single rx and >20 weeks after 4 rx. Side effects included erythema, hyperpigmentation, exfoliation
Itoh 2001[76]	13	ALA 20% occluded x 4 hours	Visible 600 to 700 (13 J/cm^2) Single rx	Reduction in new acne lesions noted for 6 months. Side effects included erythema, hyperpigmentation, exfoliation
Goldman 2003[77]	22	None or ALA 20% soln x 15 min	Blue 417 x 6 min 1x/wk x 2 weeks	Blue light alone: 25% improvement acne severity 40% decrease papules 65% decrease pustules 62% decrease comedones ALA + Blue light: 32% improvement in acne severity 68% decrease papules 61% decrease pustules 62% decrease comedones
Pollock 2004[78]	10 (Truncal Acne)	ALA 20% occluded x 3 hours	Red Diode Laser 635, (15 J/cm^2) 1x/wk x 3 weeks	31% decrease in inflammatory lesions seen after 2nd rx and at 3 week f/u
Tzung 2004[79]	31 (1/2 face study w/self control)	None	Blue 420 ± 20 2x/wk x 4 weeks (40 J/cm^2/rx cumulative dose 320 J/cm^2)	52% mean improvement with greatest benefit seen in comedonal and papulopustular lesions, nodulocystic acne worsened
Taub 2004[80]	18	ALA 20% soln X 15 to 30 min	Blue 417 to 420 × 3 to 7 min, then 1 pass combined bi-polar radiofrequency/IPL (18 to 25 J/cm^2, 18 to 20 J/cm^2 RF) 2 to 4 rx 2 weeks apart or 2 cycles of salicylic acid peel at week 1 w/PDT at week 2	66%% of patients had at least 50% improvement, no significant difference noted between groups, side effects included erythema and peeling
Gold 2005[81]	25	None	Blue 417 16 min, 40 s 2x/wk x 4 weeks	21% improvement in comedones at week 4 and 8, 36% improvement inflammatory lesions at week 4 and 8. Control arm using 1% clindamycin bid had 14% improvement in both comedonal and inflammatory lesions
Morton 2005[82]	30	None	Blue 409 to 419, (40 mW/cm^2) 10- to 20-min exposures 2x/wk x 4 weeks	Statistically significant decrease inflammatory lesions seen at week 8, persisted to week 12, no change comedonal lesions

Table 2 Continued

Reference	Patient No.	Photosensitizer	Light Source (nm)	Results
Hong 2005[83]	8 (½ face study w/self control)	ALA occluded x 4 hours	Red 630 ± 30, (18 J/cm^2) Single rx	27.6%, 37.9%, and 41.9% reduction in inflammatory lesions at 1, 3 and 6 months. 8.0%, 14.7% and 15.4% reduction seen in control
Santos 2005[84]	13	ALAs to ½ face x 3 hours, light rx to both sides	IPL w/560 nm cutoff filter, (26 J/cm^2) 2 rx spaced 2 weeks apart	Global improvement seen by week 2, by week 4 greater improvement noted w/ALA lasting up to week 8
Rojanamatin 2006[85]	14	ALA under occlusion x 30 min to ½ face	IPL with 560 to 590 cutoff filter, (25 to 30 J/cm^2), 3 rx at 3- to 4-week intervals	87.7% decrease in lesions w/ALA at 12 weeks, 66.8% decrease w/IPL alone at 12 weeks, side effects included mild edema and crusting
Wiegell 2006[86]	21	MAL under occlusion x 3 hour	Red, 9 min (37 J/cm^2) 2 rx, 2 weeks apart	29% increase in comedonal lesions, 68% decrease in inflammatory lesions at week 12
Wiegell 2006[15]	15	ALA or MAL under occlusion x 3 hrs	Red, (37 J/cm^2) single rx	59% decrease in inflammatory lesions at week 12, no difference between groups, side effects were greater w/ALA and included erythema, acne flare, and peeling
Horfelt 2006[87]	30	MAL under occlusion x 3 hours, split face study	Red light 635, (37 J/cm^2) 2 rx, 2 weeks apart	63% vs 28% reduction in inflammatory lesions of treatment group vs control at 6 weeks, 54 vs 20% at week 12, no difference between groups w/comedonal lesions, side effects included pain, redness and swelling
Gold 2007[88]	19	ALAs x 15 to 30 min	AFT pulsed light 420 to 950 4 rx, 2 weeks apart	54.5% decrease inflammatory lesions, 37.5% decrease comedonal lesions
Yeung 2007[89]	30	MAL 16% × 30 min	IPL 530 to 750 4 rx, 3 weeks apart	No difference in inflammatory lesions between PDT, IPL or control at 4 & 12 weeks, 38% (PDT) and 43% (IPL) improvement in comedonal lesions at 12 weeks, 25% of PDT subjects withdrew due to side effects

ALA, 20% 5-aminolevulinic acid oil in water emulsion; ALAs, 20% 5-aminlevulinic acid solution: IPL, Intense pulsed light; MAL, methyl aminolevulinate 160 mg/g; rx, treatment, ELOS.

Infectious Disease

Leishmania

A number of reports have described efficacy in the treatment of cutaneous leishmaniasis by PDT.[95-97] The largest of these involved 60 patients with Old-World cutaneous leishmaniasis who were treated for 4 weeks with either weekly PDT (10% ALA applied under occlusion for 4 hours followed by red light irradiation 633 nm, 100J/cm2), twice daily topical paromomycin or placebo. Patients were followed for 2 months.[95] Resolution of lesions was 93.5% PDT, 41.2% paromomycin, and 13.3% placebo. Interestingly, Leishmania are deficient in seven of the eight enzymes required for heme synthesis and are unable to convert ALA to PpIX. Thus, the parasiticidal effect noted is attributed to host factors such as vascular damage and effects on macrophages.[98]

Dermatophytes

On the basis of successful in vitro data,[99] Calzavara-Pinton and coworkers treated 9 patients with interdigital mycosis using 20% ALA in Eucerin cream applied to one foot for 4 hours followed by red light (75J/cm2). Treatments were repeated weekly until lesions resolved for up to 4 weeks. Overall response was 66%, however, 4 patients recurred after 4 weeks.[100]

Warts/Molluscum Contagiosum

Early studies evaluating the use of PDT for the treatment of warts were disappointing, likely due to poor penetration of both the photosensitizing agent and light source.[9,101] Later studies incorporated simple interventions such as paring hyperkeratotic skin and use of keratolytics, efficacy subsequently improved.[102,103] Schroeter and coworkers treated 48 plantar warts pared to the papillary dermis with 20% ALA cream applied for 4 to 8 hours followed by blue light activation. Treatments were performed every 2 to 4 weeks with an average of 2.3 treatments. Complete response was seen in 88%.[104] Stender and coworkers studied 232 foot and hand warts that were pared and treated with a keratolytic and then assigned to placebo or 20% ALA followed by red light (70 J/cm^2). Complete response was 16% versus 17%, 50% versus 35%, and 56 versus 42% at weeks 7, 14, and 18 for ALA-PDT and placebo respectively.[102] Positive response utilizing 20% ALA solution applied for 14 to 24 hours followed by illumination with blue light (417 nm, 10 J/cm^2) with up to 5 treatments performed at 2-week intervals has also been described in the treatment molluscum contagiosum.[105,106]

Cutaneous T-Cell Lymphoma/ Extramammary Paget's Disease

Nonmelanotic skin cancer is not the only form of malignancy that responds to PDT. Numerous reports highlight the efficacy of PDT in the treatment of cutaneous T-cell lymphoma.[107-109] Complete remission with no recurrence over 14 to 18 months was obtained in 4 patients with therapy-resistant stage IA-IIB lesions with 2 to 7 cycles of 20% ALA cream applied for 6 hours followed by activation with visible light (580-740 nm).[107] Good results have also been described using MAL[110] and in the treatment of Woringer-Kolopp.[111] As would be expected due to limited penetration of both photosensitizing agent and activating light source, tumor stage cutaneous T-cell lymphoma appears to be somewhat more resistant to treatment.[112] Efficacy in the treatment of extra-mammary Paget's disease ranges from 50% to 100% initial response.[113-116] Recurrence tends to be high (38-50%) but despite this is comparable with that observed with surgical treatment (31-61%).[113]

Psoriasis

Although PDT has been shown to induce T-cell apoptosis in psoriatic plaques,[117] clinically efficacy leaves much to be desired in the treatment of plaque psoriasis. Despite the use of multiple different treatment protocols, almost all investigators have seen low response rates,[118] high rates of relapse (100% within 2 weeks),[119] and numerous side effects such as pain[120] and koebnerization.[121] One potential exception appears to be palmoplantar psoriasis (PPP). Two separate case reports describe success in the treat of PPP using either topically applied hematoporphyrin derivative and visible light[122] or 20% ALA followed by 632 nm diode laser activation.[123] These findings were echoed by a slighter larger case series in 2007 in which 3 cases of refractory PPP were treated with 20% ALA with red light activation (15 J/cm^2). Mild-to-moderate improvement was appreciated in all subjects.[124]

Photorejuvenation/Cosmesis

While using ALA-PDT in the treatment of patients with actinic damage and skin cancer, many investigators noted an incidental improvement in overall cosmesis.[59] Goldman and coworkers treated 32 patients with 20% ALA solution applied for 15 to 20 hours followed by blue light and found that 72% experienced an improvement in skin texture.[125] Other investigators describe decreased sallowness, decreased fine skin wrinkling, and improvement in mottled hyperpigmentation after short contact (1-3 hours) ALA with blue light exposure.[11] Most of the work focused on cosmesis, however, has used IPL as the activating light source. A split face study by Alster and coworkers compared 2 treatments 1 month apart of either IPL alone or IPL + ALA. Greater improvement was noted in the IPL + ALA cohort; however, these patients also had greater side effects, such as mild edema, erythema, and peeling.[126] A similar study by Dover and coworkers treated 20 patients with 3 treatments 3 weeks apart. Combined ALA-IPL had better results than IPL alone with regards to improvement in photoaging (80% versus 50%), mottled pigmentation (95% versus 65%), and fine lines (55% versus 20%). Side effects were equal in both groups.[127] Improved response to ALA-IPL versus. IPL was further corroborated by Gold and coworkers.[128] Guidelines regarding settings for IPL devices used in conjunction with ALA can be found in a 2007 review article by Nootheti and Goldman.[129]

Miscellaneous Case Reports

A number of individual case reports describe success using PDT to treat nephrogenic fibrosing dermopathy,[130] granuloma annulare,[131] disseminated superficial actinic porokeratosis,[132] necrobiosis lipoidica diabeticorum,[133] lymphadenosis benigna cuitis,[134] mycobacterium marinum,[135] both success,[136] and failure[137] in the treatment of Darier's disease and both success[138] and failure in the treatment of hidradenitis suppurativa.[139]

Summary

Photodynamic therapy is a safe, noninvasive therapeutic modality that allows for the treatment of broad areas with generally excellent cosmesis. Current use centers primarily on the treatment of actinic damage and early nonmelanotic skin cancers, yet recent work supports its use in the treatment numerous other conditions ranging from cosmetic interventions to infectious processes. As further advances overcome current limitations, such as inadequate penetration of both light source and photosensitizing agent, the use of PDT in dermatology will likely increase.

References

1. Kennedy JC, Pottier RH: Endogenous protoporphyrin IX, a clinically useful photosensitizer for photodynamic therapy. J Photochem Photobiol B 14:275-292, 1992
2. Ackroyd R, Kelty C, Brown N, et al: The history of photodetection and photodynamic therapy. Photochem Photobiol 74:656-669, 2001
3. Daniell MD, Hill JS: A history of photodynamic therapy. Aust N Z J Surg 61:340-348, 1991
4. Kato H: [History of photodynamic therapy—past, present and future]. Gan To Kagaku Ryoho 23:8-15, 1996
5. Taub AF: Photodynamic therapy in dermatology: History and horizons. J Drugs Dermatol 3:S8-25, 2004 (suppl 1)
6. Hilf R: Mitochondria are targets of photodynamic therapy. J Bioenerg Biomembr 39:85-89, 2007
7. Lam M, Oleinick NL, Nieminen AL: Photodynamic therapy-induced apoptosis in epidermoid carcinoma cells. Reactive oxygen species and mitochondrial inner membrane permeabilization. J Biol Chem 276: 47379-47386, 2001
8. Korbelik M: PDT-associated host response and its role in the therapy outcome. Lasers Surg Med 38:500-508, 2006
9. Kennedy JC, Pottier RH, Pross DC: Photodynamic therapy with endogenous protoporphyrin IX: Basic principles and present clinical experience. J Photochem Photobiol B 6:143-148, 1990
10. 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 45:96-104, 2001
11. 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 140:33-40, 2004
12. Smith S, Piacquadio D, Morhenn V, et al: Short incubation PDT versus 5-FU in treating actinic keratoses. J Drugs Dermatol 2:629-635, 2003
13. 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 68:218-221, 1998
14. Kuijpers DI, Thissen MR, Thissen CA, et al: Similar effectiveness of methyl aminolevulinate and 5-aminolevulinate in topical photodynamic therapy for nodular basal cell carcinoma. J Drugs Dermatol 5:642-645, 2006
15. Wiegell SR, Wulf HC: Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. J Am Acad Dermatol 54:647-651, 2006
16. Juzeniene A, Juzenas P, Ma LW, et al: Topical application of 5-aminolaevulinic acid, methyl 5-aminolaevulinate and hexyl 5-aminolaevulinate on normal human skin. Br J Dermatol 155:791-799, 2006
17. Ceburkov O, Gollnick H: Photodynamic therapy in dermatology. Eur J Dermatol 10:568-575, 2000; discussion 576
18. Wolf P, Rieger E, Kerl H: Topical photodynamic therapy with endogenous porphyrins after application of 5-aminolevulinic acid. An alternative treatment modality for solar keratoses, superficial squamous cell carcinomas, and basal cell carcinomas? J Am Acad Dermatol 28: 17-21, 1993
19. Calzavara-Pinton PG: Repetitive photodynamic therapy with topical delta-aminolaevulinic acid as an appropriate approach to the routine treatment of superficial non-melanoma skin tumours. J Photochem Photobiol B 29:53-57, 1995
20. Fijan S, Honigsmann H, Ortel B: Photodynamic therapy of epithelial skin tumours using delta-aminolaevulinic acid and desferrioxamine. Br J Dermatol 133:282-288, 1995
21. Szeimies RM, Karrer S, Sauerwald A, et al: Photodynamic therapy with topical application of 5-aminolevulinic acid in the treatment of actinic keratoses: An initial clinical study. Dermatology 192:246-251, 1996
22. Fink-Puches R, Hofer A, Smolle J, et al: Primary clinical response and long-term follow-up of solar keratoses treated with topically applied 5-aminolevulinic acid and irradiation by different wave bands of light. J Photochem Photobiol B 41:145-151, 1997
23. 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 133:727-732, 1997
24. Kurwa HA, Yong-Gee SA, Seed PT, et al: A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. J Am Acad Dermatol 41:414-418, 1999
25. Dijkstra AT, Majoie IM, van Dongen JW, et al: Photodynamic therapy with violet light and topical 6-aminolaevulinic acid in the treatment of actinic keratosis. Bowen's disease and basal cell carcinoma. J Eur Acad Dermatol Venereol 15:550-554, 2001
26. 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 144:567-574, 2001
27. Ruiz-Rodriguez R, Sanz-Sanchez T, Cordoba S: Photodynamic photorejuvenation. Dermatol Surg 28:742-744, 2002; discussion 744
28. 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 47:258-262, 2002
29. Goldman M, Atkin D: ALA/PDT in the treatment of actinic keratosis: Spot versus confluent therapy. J Cosmet Laser Ther 5:107-110, 2003
30. 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 Dermatol Treat 14:99-106, 2003
31. 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 48:227-232, 2003
32. Alexiades-Armenakas MR, Geronemus RG: Laser-mediated photodynamic therapy of actinic keratoses. Arch Dermatol 139:1313-1320, 2003
33. Dragieva G, Hafner J, Dummer R, et al: Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. Transplantation 77:115-121, 2004
34. 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 151:196-200, 2004
35. 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: Investi-

gator-blinded, phase 3, multicenter trials. Arch Dermatol 140:41-46, 2004
36. Avram DK, Goldman MP: Effectiveness and safety of ALA-IPL in treating actinic keratoses and photodamage. J Drugs Dermatol 3:S36-S39, 2004 (suppl 1)
37. Kim HS, Yoo JY, Cho KH, et al: Topical photodynamic therapy using intense pulsed light for treatment of actinic keratosis: Clinical and histopathologic evaluation. Dermatol Surg 31:33-36, 2005; discussion 36-37
38. Tarstedt M, Rosdahl I, Berne B, et al: A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp. Acta Dermatol Venereol 85:424-428, 2005
39. Morton C, Campbell S, Gupta G, et al: Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: A multicentre, randomized controlled study. Br J Dermatol 155:1029-1036, 2006
40. Tschen EH, Wong DS, Pariser DM, et al: Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: Phase IV multicentre clinical trial with 12-month follow up. Br J Dermatol 155:1262-1269, 2006
41. Perrett CM, McGregor JM, Warwick J, et al: Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. Br J Dermatol 156:320-328, 2007
42. Bissonette R, Bergeron A, Liu Y: Large surface photodynamic therapy with aminolevulinic acid: Treatment of actinic keratoses and beyond. J Drugs Dermatol 3:S26-S31, 2004 (suppl 1)
43. Moloney FJ, Collins P: Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis. Br J Dermatol 157:87-91, 2007
44. Soler AM, Warloe T, Tausjo J, et al: Photodynamic therapy by topical aminolevulinic acid, dimethylsulphoxide and curettage in nodular basal cell carcinoma: A one-year follow-up study. Acta Derm Venereol 79:204-206, 1999
45. Horn M, Wolf P, Wulf HC, et al: Topical methyl aminolaevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional treatment. Br J Dermatol 149:1242-1249, 2003
46. Cairnduff F, Stringer MR, Hudson EJ, et al: Superficial photodynamic therapy with topical 5-aminolaevulinic acid for superficial primary and secondary skin cancer. Br J Cancer 69:605-608, 1994
47. Svanberg K, Andersson T, Killander D, et al: Photodynamic therapy of non-melanoma malignant tumours of the skin using topical delta-amino levulinic acid sensitization and laser irradiation. Br J Dermatol 130:743-751, 1994
48. Lui H, Salasche S, Kollias N, et al: Photodynamic therapy of nonmelanoma skin cancer with topical aminolevulinic acid: a clinical and histologic study. Arch Dermatol 131:737-738, 1995
49. Soler AM, Warloe T, Berner A, et al: A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl 5-aminolaevulinate-based photodynamic therapy alone and with prior curettage. Br J Dermatol 145: 467-471, 2001
50. Fink-Puches R, Wolf P, Kerl H: Photodynamic therapy of superficial basal cell carcinoma by instillation of aminolevulinic acid and irradiation with visible light. Arch Dermatol 133:1494-1495, 1997
51. Vinciullo C, Elliott T, Francis D, et al: Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. Br J Dermatol 152:765-772, 2005
52. Moore JV, Allan E: Pulsed ultrasound measurements of depth and regression of basal cell carcinomas after photodynamic therapy: Relationship to probability of 1-year local control. Br J Dermatol 149: 1035-1040, 2003
53. Thissen MR, Schroeter CA, Neumann HA: Photodynamic therapy with delta-aminolaevulinic acid for nodular basal cell carcinomas using a prior debulking technique. Br J Dermatol 142:338-339, 2000
54. de Haas ER, Kruijt B, Sterenborg HJ, et al: Fractionated illumination significantly improves the response of superficial basal cell carcinoma to aminolevulinic acid photodynamic therapy. J Invest Dermatol 126:2679-2586, 2006
55. Thompson MS, Andersson-Engels S, Svanberg S, et al: Photodynamic therapy of nodular basal cell carcinoma with multifiber contact light delivery. J Environ Pathol Toxicol Oncol 25:411-424, 2006
56. Cappugi P, Mavilia L, Campolmi P, et al: New proposal for the treatment of nodular basal cell carcinoma with intralesional 5-aminolevulinic acid. J Chemother 16:491-493, 2004
57. Kuijpers DI, Smeets NW, Krekels GA, et al: Photodynamic therapy as adjuvant treatment of extensive basal cell carcinoma treated with Mohs micrographic surgery. Dermatol Surg 30:794-798, 2004
58. Berroeta L, Clark C, Dawe RS, et al: A randomized study of minimal curettage followed by topical photodynamic therapy compared with surgical excision for low-risk nodular basal cell carcinoma. Br J Dermatol 157:401-403, 2007
59. Itkin A, Gilchrest BA: delta-Aminolevulinic acid and blue light photodynamic therapy for treatment of multiple basal cell carcinomas in two patients with nevoid basal cell carcinoma syndrome. Dermatol Surg 30:1054-1061, 2004
60. Chapas AM, Gilchrest BA: Broad aread photodynamic therapy for treatment of multiple basal cell carcinomas in a patient with nevoid basal cell carcinoma syndrome. J Drugs Dermatol 5:3-5, 2006 (suppl 2)
61. Oseroff AR, Shieh S, Frawley NP, et al: Treatment of diffuse basal cell carcinomas and basaloid follicular hamartomas in nevoid basal cell carcinoma syndrome by wide-area 5-aminolevulinic acid photodynamic therapy. Arch Dermatol 141:60-67, 2005
62. Braathen LR, Szeimies RM, Basset-Seguin N, et al: Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. J Am Acad Dermatol 56:125-143, 2007
63. Morton C, Horn M, Leman J, et al: Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: Results of a multicenter randomized trial. Arch Dermatol 142:729-735, 2006
64. Tan B, Sinclair R, Foley P: Photodynamic therapy for subungual Bowen's disease. Australas J Dermatol 45:172-174, 2004
65. Usmani N, Stables GI, Telfer NR, et al: Subungual Bowen's disease treated by topical aminolevulinic acid-photodynamic therapy. J Am Acad Dermatol 53:S273-S276, 2005 (suppl 1)
66. Souza CS, Felicio LB, Bentley MV, et al: Topical photodynamic therapy for Bowen's disease of the digit in epidermolysis bullosa. Br J Dermatol 153(3):672-674, 2005
67. Moseley H, Allen JW, Ibbotson S, et al: Ambulatory photodynamic therapy: A new concept in delivering photodynamic therapy. Br J Dermatol 154:747-750, 2006
68. Stables GI, Stringer MR, Robinson DJ, et al: Erythroplasia of Queyrat treated by topical aminolaevulinic acid photodynamic therapy. Br J Dermatol 140:514-517, 1999
69. Varma S, Holt PJ, Anstey AV: Erythroplasia of queyrat treated by topical aminolaevulinic acid photodynamic therapy: A cautionary tale. Br J Dermatol 142:825-826, 2000
70. Paoli J, Ternesten Bratel A, Lowhagen GB, et al: Penile intraepithelial neoplasia: Results of photodynamic therapy. Acta Derm Venereol 86: 418-421, 2006
71. Ashkenazi H, Malik Z, Harth Y, et al: Eradication of Propionibacterium acnes by its endogenic porphyrins after illumination with high intensity blue light. FEMS Immunol Med Microbiol 35:17-24, 2003
72. Kjeldstad B: Photoinactivation of *Propribacterium acnes* by near-ultraviolet light. Z Naturforsch [C] 39:300-302, 1984
73. Meffert H, Gaunitz K, Gutewort T, et al: [Therapy of acne with visible light. Decreased irradiation time by using a blue-light high-energy lamp]. Dermatol Monatsschr 176:597-603, 1990
74. Papageorgiou P, Katsambas A, Chu A: Phototherapy with blue (415nm) and red (660nm) light in the treament of acne vulgaris. Br J Dermatol 142:973, 2000
75. Hongcharu W, Taylor CR, Chang Y, et al: Topical ALA-photodynamic therapy for the treatment of acne vulgaris. J Invest Dermatol 115:183-192, 2000

76. Itoh Y, Ninomiya Y, Tajima S, et al: Photodynamic therapy of acne vulgaris with topical delta-aminolaevulinic acid and incoherent light in Japanese patients. Br J Dermatol 144:575-579, 2001
77. Goldman MP, Boyce SM: A single-center study of aminolevulinic acid and 417 NM photodynamic therapy in the treatment of moderate to severe acne vulgaris. J Drugs Dermatol 2:393-396, 2003
78. Pollock B, Turner D, Stringer MR, et al: Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: A study of clinical efficacy and mechanism of action. Br J Dermatol 151:616-622, 2004
79. Tzung T, Wu K, Huang M: Blue light phototherapy in the treatment of acne. Photodermatol Photoimmunol Photomed 20:266-269, 2004
80. Taub AF: Photodynamic therapy for the treatment of acne: A pilot study. J Drugs Dermatol 3:S10-S14, 2004 (suppl 6)
81. Gold MH, Rao J, Goldman MP, et al: A multicenter clinical evaluation of the treatment of mild to moderate inflammatory acne vulgaris of the face with visible blue light in comparison to topical 1% clindamycin antibiotic solution. J Drugs Dermatol 4:64-70, 2005
82. Morton CA, Scholefield RD, Whitehurst C, et al: An open study to determine the efficacy of blue light in the treatment of mild to moderate acne. J Dermatolog Treat 16:219-223, 2005
83. Hong SB, Lee MH: Topical aminolevulinic acid-photodynamic therapy for the treatment of acne vulgaris. Photodermatol Photoimmunol Photomed 21:322-325, 2005
84. Santos MA, Belo VG, Santos G: Effectiveness of photodynamic therapy with topical 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone in the treatment of acne vulgaris: Comparative study. Dermatol Surg 31:910-915, 2005
85. Rojanamatin J, Choawawanich P: Treatment of inflammatory facial acne vulgaris with intense pulsed light and short contact of topical 5-aminolevulinic acid: a pilot study. Dermatol Surg 32:991-996, 2006; discussion 996-997
86. Wiegell SR, Wulf HC: Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. Br J Dermatol 154:969-976, 2006
87. Horfelt C, Funk J, Frohm-Nilsson M, et al: Topical methyl aminolaevulinate photodynamic therapy for treatment of facial acne vulgaris: Results of a randomized, controlled study. Br J Dermatol 155:608-613, 2006
88. Gold MH, Biron JA, Boring M, et al: Treatment of moderate to severe inflammatory acne vulgaris: photodynamic therapy with 5-aminolevulinic acid and a novel advanced fluorescence technology pulsed light source. J Drugs Dermatol 6:319-322, 2007
89. Yeung CK, Shek SY, Bjerring P, et al: A comparative study of intense pulsed light alone and its combination with photodynamic therapy for the treatment of facial acne in Asian skin. Lasers Surg Med 39:1-6, 2007
90. 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 148:1274-1276, 2003
91. Richey DF: Aminolevulinic acid photodynamic therapy for sebaceous gland hyperplasia. Dermatol Clin 25:59-65, 2007
92. 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 3:S6-S9, 2004 (suppl 6)
93. Alster TS, Tanzi EL: Photodynamic therapy with topical aminolevulinic acid and pulsed dye laser irradiation for sebaceous hyperplasia. J Drugs Dermatol 2:501-504, 2003
94. Dierickx CC, Goldenhersh M, Dwyer P, et al: Photodynamic therapy for nevus sebaceus with topical delta-aminolevulinic acid. Arch Dermatol 135:637-640, 1999
95. Asilian A, Davami M: Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: A placebo-controlled, randomized clinical trial. Clin Exp Dermatol 31:634-637, 2006
96. Sohl S, Kauer F, Paasch U, et al: Photodynamic treatment of cutaneous leishmaniasis. J Dtsch Dermatol Ges 5:128-130, 2007
97. Ghaffarifar F, Jorjani O, Mirshams M, et al: Photodynamic therapy as a new treatment of cutaneous leishmaniasis. East Mediterr Health J 12:902-908, 2006
98. Kosaka S, Akilov OE, O'Riordan K, et al: A mechanistic study of delta-aminolevulinic acid-based photodynamic therapy for cutaneous leishmaniasis. J Invest Dermatol 127:1546-1549, 2007
99. Smijs TG, Schuitmaker HJ: Photodynamic inactivation of the dermatophyte *Trichophyton rubrum*. Photochem Photobiol 77:556-560, 2003
100. Calzavara-Pinton PG, Venturini M, Sala R: A comprehensive overview of photodynamic therapy in the treatment of superficial fungal infections of the skin. J Photochem Photobiol B 78:1-6, 2005
101. Ammann R, Hunziker T, Braathen LR: Topical photodynamic therapy in verrucae. A pilot study. Dermatology 191:346-347, 1995
102. Stender IM, Na R, Fogh H, et al: Photodynamic therapy with 5-aminolaevulinic acid or placebo for recalcitrant foot and hand warts: Randomised double-blind trial. Lancet 355:963-966, 2000
103. Fabbrocini G, Di Costanzo MP, Riccardo AM, et al: Photodynamic therapy with topical delta-aminolaevulinic acid for the treatment of plantar warts. J Photochem Photobiol B 61:30-34, 2001
104. Schroeter CA, Pleunis J, van Nispen tot Pannerden C, et al: Photodynamic therapy: New treatment for therapy-resistant plantar warts. Dermatol Surg 31:71-75, 2005
105. Moiin A: Photodynamic therapy for molluscum contagiosum infection in HIV-coinfected patients: Review of 6 patients. J Drugs Dermatol 2:637-639, 2003
106. Gold MH, Boring MM, Bridges TM, et al: The successful use of ALA-PDT in the treatment of recalcitrant molluscum contagiosum. J Drugs Dermatol 3:187-190, 2004
107. Coors EA, von den Driesch P: Topical photodynamic therapy for patients with therapy-resistant lesions of cutaneous T-cell lymphoma. J Am Acad Dermatol 50:363-367, 2004.
108. Orenstein A, Haik J, Tamir J, et al: Photodynamic therapy of cutaneous lymphoma using 5-aminolevulinic acid topical application. Dermatol Surg 26:765-769, 2000; discussion 769-770
109. Paech V, Lorenzen T, Stoehr A, et al: Remission of a cutaneous Mycosis fungoides after topical 5-ALA sensitisation and photodynamic therapy in a patient with advanced HIV-infection. Eur J Med Res 7:477-479, 2002
110. Zane C, Venturini M, Sala R, et al: Photodynamic therapy with methylaminolevulinate as a valuable treatment option for unilesional cutaneous T-cell lymphoma. Photodermatol Photoimmunol Photomed 22:254-258, 2006
111. Berroeta L, Lewis-Jones MS, Evans AT, et al: Woringer-Kolopp (localized pagetoid reticulosis) treated with topical photodynamic therapy (PDT). Clin Exp Dermatol 30:446-447, 2005
112. Edstrom DW, Porwit A, Ros AM: Photodynamic therapy with topical 5-aminolevulinic acid for mycosis fungoides: Clinical and histological response. Acta Derm Venereol 81:184-188, 2001
113. Shieh S, Dee AS, Cheney RT, et al: Photodynamic therapy for the treatment of extramammary Paget's disease. Br J Dermatol 146:1000-1005, 2002
114. 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 32:97-101, 2005
115. Zawislak AA, McCarron PA, McCluggage WG, et al: Successful photodynamic therapy of vulval Paget's disease using a novel patch-based delivery system containing 5-aminolevulinic acid. Bjog 111: 1143-1145, 2004
116. Henta T, Itoh Y, Kobayashi M, et al: Photodynamic therapy for inoperable vulval Paget's disease using delta-aminolaevulinic acid: successful management of a large skin lesion. Br J Dermatol 141:347-349, 1999
117. Bissonnette R, Tremblay JF, Juzenas P, et al: Systemic photodynamic therapy with aminolevulinic acid induces apoptosis in lesional T lymphocytes of psoriatic plaques. J Invest Dermatol 119:77-83, 2002
118. Lehmann P: Methyl aminolaevulinate-photodynamic therapy: A review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. Br J Dermatol 156:793-801, 2007
119. Collins P, Robinson DJ, Stringer MR, et al: The variable response

of plaque psoriasis after a single treatment with topical 5-aminolaevulinic acid photodynamic therapy. Br J Dermatol 137:743-749, 1997
120. Schleyer V, Radakovic-Fijan S, Karrer S, et al: Disappointing results and low tolerability of photodynamic therapy with topical 5-aminolaevulinic acid in psoriasis. A randomized, double-blind phase I/II study. J Eur Acad Dermatol Venereol 20:823-828, 2006
121. Stender IM, Wulf HC: Kobner reaction induced by photodynamic therapy using delta-aminolevulinic acid. A case report. Acta Derm Venereol 76:392-393, 1996
122. Pres H, Meffert H, Sonnichsen N: [Photodynamic therapy of psoriasis palmaris et plantaris using a topically applied hematoporphyrin derivative and visible light]. Dermatol Monatsschr 175:745-750, 1989
123. Yim YC, Lee ES, Chung PS, et al: Recalcitrant palmoplantar pustular psoriasis successfully treated with topical 5-aminolaevulinic acid photodynamic therapy. Clin Exp Dermatol 30:723-724, 2005
124. Kim JY, Kang HY, Lee ES, et al: Topical 5-aminolaevulinic acid photodynamic therapy for intractable palmoplantar psoriasis. J Dermatol 34:37-40, 2007
125. Goldman MP, Atkin D, Kincaid S: PDT/ALA in the treatment of actinic damage: Real world experience. Lasers Surg Med 14S:79, 2002
126. 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 4:35-38, 2005
127. Dover JS, Bhatia AC, Stewart B, et al: Topical 5-aminolevulinic acid combined with intense pulsed light in the treatment of photoaging. Arch Dermatol 141:1247-1252, 2005
128. Gold MH, Bradshaw VL, Boring MM, et al: JA: Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. Dermatol Surg 32:795-801, 2006; discussion 801-803
129. Nootheti PK, Goldman MP: Aminolevulinic acid-photodynamic therapy for photorejuvenation. Dermatol Clin 25:35-45, 2007
130. Schmook T, Budde K, Ulrich C, et al: Successful treatment of nephrogenic fibrosing dermopathy in a kidney transplant recipient with photodynamic therapy. Nephrol Dial Transplant 20:220-222, 2005
131. Kim YJ, Kang HY, Lee ES, et al: Successful treatment of granuloma annulare with topical 5-aminolaevulinic acid photodynamic therapy. J Dermatol 33:642-643, 2006
132. Cavicchini S, Tourlaki A: Successful treatment of disseminated superficial actinic porokeratosis with methyl aminolevulinate-photodynamic therapy. J Dermatolog Treat 17:190-191, 2006
133. Heidenheim M, Jemec GB: Successful treatment of necrobiosis lipoidica diabeticorum with photodynamic therapy. Arch Dermatol 142:1548-1550, 2006
134. Takeda H, Kaneko T, Harada K, et al: Successful treatment of lymphadenosis benigna cutis with topical photodynamic therapy with delta-aminolevulinic acid. Dermatology 211:264-266, 2005
135. Wiegell SR, Kongshoj B, Wulf HC: Mycobacterium marinum infection cured by photodynamic therapy. Arch Dermatol 142:1241-1242, 2006
136. Exadaktylou D, Kurwa HA, Calonje E, et al: Treatment of Darier's disease with photodynamic therapy. Br J Dermatol 149:606-610, 2003
137. van't Westeinde SC, Sanders CJ, van Weelden H: Photodynamic therapy in a patient with Darier's disease. J Eur Acad Dermatol Venereol 20:870-872, 2006
138. Gold M, Bridges TM, Bradshaw VL, et al: ALA-PDT and blue light therapy for hidradenitis suppurativa. J Drugs Dermatol 3:S32-S35, 2004 (suppl 1)
139. 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 152:803-804, 2005