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

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 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

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.

(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 tial 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 ses-

2 Studies on the Use of Photodynamic Therapy for Acne

Reference	Patient No.	Photosensitizer	Light Source (nm)	Results
ert 1990[73]		None	Blue 400 to 420 10 min x 10 exposures (cumulative dose –325J/cm^2)	Improvement in acne and oil production
georgiou 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
charu 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
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
man 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
ck 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
g 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
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
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
on 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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.