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.

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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. 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, 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. Supplementing this direct assault are indirect pathways of cellular destruction such as the recruitment of inflammatory cells, increased immune response and vascular compromise. 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 Pharmaceuticals, 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 normal but not through normal keratin. 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
hours), PpIX production is largely limited to the target site; however, with longer application periods, a larger area of reaction may develop. 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.

**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 75 J/cm²), at which point complete photobleaching should have occurred. More lipophilic than ALA, MAL is felt to exhibit increased tumor/diseased skin specificity when compared with ALA. 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.

**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 Therapeutics 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 by melanin. 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, 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). Although the earliest studies used an oil in water formulation of ALA that required occlusion for penetration, 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/cm². 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. A subsequent phase IV clinical trial found recurrence rates of 19% at 12 months. Practical considerations led to a number of modifications to the aforementioned treatment protocol such as much abbreviated incubation periods (1 hour) and broad application in lieu of spot treatment. 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. 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. 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.

**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/cm²), with repeat treatment at 1 week. Complete response ranges from 69% to 91%; with only a single treatment this decreases to 70%. These numbers are similar to those seen with cryotherapy (complete response 68-75%); however, many feel that MAL–PDT is superior in terms of cosmetic outcome and patient satisfaction. Superior outcomes have also been described in comparison to 5-fluorouracil cream applied twice daily for 3 weeks. 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.

**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. 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. As expected, superficial basal cell carcinoma (sBCC) seems to respond best, with reported complete response rates ranging from 50 to 100%. 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

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

ALAs: 20% 5-aminolevulinic acid oil in water emulsion; MAL: methyl aminolevulinate 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). Pigmented lesions in particular tend to respond poorly because of interference by melanin. Recurrence is an issue for all tumor types, reaching as high as 44% at 19 months for sBCC and 57% at 3 months for nBCC treated with ALA and 18% at 12 to 24 months for lesions treated with MAL. Vinculillo 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%.

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. Various attempts have been made to ameliorate this phenomenon, including pretreatment debulking, multiple treatments, the use of fractionated light delivery to limit photobleaching, interstitial light delivery, intralesional injection of ALA, and the use of PDT as an adjunct to Mohs surgery. A recent pilot study by Berroeta and coworkers was designed to compare laser activation with surgical excision for primary, recurrent BCC, or intralesional injection of ALA, and the use of PDT to treat tumors using 20% ALA applied for 4 hours with 630 nm argon laser activation. Seven of 10 patients cleared in 1 treatment, 3 cleared after 2. Side effects included transient erythema and edema.

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, to blue light, to pulsed dye laser (595 nm) (PDL) to IPL. 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 and Riech. 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. Riech 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 sebaeous was obtained by Dierickx and colleagues after 13 sessions using 20% ALA applied for 4 hours with 630 nm argon laser activation.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient No.</th>
<th>Photosensitizer</th>
<th>Light Source (nm)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meffert 1990</td>
<td>None</td>
<td>None</td>
<td>Blue 400 to 420 10 min x 10 exposures (cumulative dose ~325J/cm²)</td>
<td>Improvement in acne and oil production</td>
</tr>
<tr>
<td>Papageorgiou 2000</td>
<td>107</td>
<td>None</td>
<td>Blue 415 ± 20/-15, or Blue and Red 415 &amp; 660 ± 10, 15 min qd x 12 weeks (cumulative dose 320 J/cm² blue, 202 J/cm² red)</td>
<td>Blue: 45% improvement comedones, 63% improvement inflammatory lesions. Blue and Red: 58% improvement comedones, 76% improvement inflammatory lesions</td>
</tr>
<tr>
<td>Hongcharu 2000</td>
<td>22 (Truncal Acne)</td>
<td>ALA 20% occluded</td>
<td>Red 550 to 700 (150 J/cm²) ½ had single rx, ½ had rx 1x/wk x 4 weeks</td>
<td>Flare noted 3 to 4d after rx. Significant improvement noted. Improvement persisted &gt;10 weeks after single rx and &gt;20 weeks after 4 rx. Side effects included erythema, hyperpigmentation, exfoliation</td>
</tr>
<tr>
<td>Itoh 2001</td>
<td>13</td>
<td>ALA 20% occluded</td>
<td>Visible 600 to 700 (13 J/cm²) Single rx</td>
<td>Reduction in new acne lesions noted for 6 months. Side effects included erythema, hyperpigmentation, exfoliation</td>
</tr>
<tr>
<td>Goldman 2003</td>
<td>22</td>
<td>None or ALA 20%</td>
<td>Blue 417 x 6 min 1x/wk x 2 weeks</td>
<td>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</td>
</tr>
<tr>
<td>Pollock 2004</td>
<td>10 (Truncal Acne)</td>
<td>ALA 20% occluded</td>
<td>Red Diode Laser 635, (15 J/cm²) 1x/wk x 3 weeks</td>
<td>31% decrease in inflammatory lesions seen after 2nd rx and at 3 week f/u</td>
</tr>
<tr>
<td>Tzung 2004</td>
<td>31 (1/2 face study w/self control)</td>
<td>None</td>
<td>Blue 420 ± 20 2x/wk x 4 weeks (40 J/cm²/x cumulative dose 320 J/cm²)</td>
<td>52% mean improvement with greatest benefit seen in comedonal and papulopustular lesions, nodulocystic acne worsened</td>
</tr>
<tr>
<td>Taub 2004</td>
<td>18</td>
<td>ALA 20% soln X</td>
<td>Blue 417 to 420 x 3 to 7 min, then 1 pass combined bi-polar radiofrequency/IPL (18 to 25 J/cm², 18 to 20 J/cm² RF) 2 to 4 rx 2 weeks apart or 2 cycles of salicylic acid peel at week 1 w/PDT at week 2</td>
<td>66% of patients had at least 50% improvement, no significant difference noted between groups, side effects included erythema and peeling</td>
</tr>
<tr>
<td>Gold 2005</td>
<td>25</td>
<td>None</td>
<td>Blue 417 16 min, 40 s 2x/wk x 4 weeks</td>
<td>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</td>
</tr>
<tr>
<td>Morton 2005</td>
<td>30</td>
<td>None</td>
<td>Blue 409 to 419, (40 mW/cm²) 10- to 20-min exposures 2x/wk x 4 weeks</td>
<td>Statistically significant decrease inflammatory lesions seen at week 8, persisted to week 12, no change comedonal lesions</td>
</tr>
<tr>
<td>Reference</td>
<td>Patient No.</td>
<td>Photosensitizer</td>
<td>Light Source (nm)</td>
<td>Results</td>
</tr>
<tr>
<td>--------------------</td>
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<td>-------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hong 200583</td>
<td>8 (½ face study w/self control)</td>
<td>ALA occluded x 4 hours</td>
<td>Red $630 \pm 30$, (18 J/cm$^2$) Single rx</td>
<td>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</td>
</tr>
<tr>
<td>Santos 200584</td>
<td>13</td>
<td>ALAs to ½ face x 3 hours, light rx to both sides</td>
<td>IPL w/560 nm cutoff filter, (26 J/cm$^2$) 2 rx spaced 2 weeks apart</td>
<td>Global improvement seen by week 2, by week 4 greater improvement noted w/ALA lasting up to week 8</td>
</tr>
<tr>
<td>Rojanamatin 200685</td>
<td>14</td>
<td>ALA under occlusion x 30 min to ½ face</td>
<td>IPL with 560 to 590 cutoff filter, (25 to 30 J/cm$^2$), 3 rx at 3- to 4-week intervals</td>
<td>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</td>
</tr>
<tr>
<td>Wiegell 200686</td>
<td>21</td>
<td>MAL under occlusion x 3 hour</td>
<td>Red, 9 min (37 J/cm$^2$) 2 rx, 2 weeks apart</td>
<td>29% increase in comedonal lesions, 68% decrease in inflammatory lesions at week 12</td>
</tr>
<tr>
<td>Wiegell 200615</td>
<td>15</td>
<td>ALA or MAL under occlusion x 3 hrs</td>
<td>Red, (37 J/cm$^2$) single rx</td>
<td>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</td>
</tr>
<tr>
<td>Horfelt 200687</td>
<td>30</td>
<td>MAL under occlusion x 3 hours, split face study</td>
<td>Red light 635, (37 J/cm$^2$) 2 rx, 2 weeks apart</td>
<td>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</td>
</tr>
<tr>
<td>Gold 200788</td>
<td>19</td>
<td>ALAs x 15 to 30 min</td>
<td>AFT pulsed light 420 to 950 4 rx, 2 weeks apart</td>
<td>54.5% decrease inflammatory lesions, 37.5% decrease comedonal lesions</td>
</tr>
<tr>
<td>Yeung 200789</td>
<td>30</td>
<td>MAL 16% x 30 min</td>
<td>IPL 530 to 750 4 rx, 3 weeks apart</td>
<td>No difference in inflammatory lesions between PDT, IPL or control at 4 &amp; 12 weeks, 38% (PDT) and 43% (IPL) improvement in comedonal lesions at 12 weeks, 25% of PDT subjects withdrew due to side effects</td>
</tr>
</tbody>
</table>

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

Leishmaniasis
A number of reports have described efficacy in the treatment of cutaneous leishmaniasis by PDT. 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, 100 J/cm²), twice daily topical paromomycin or placebo. Patients were followed for 2 months. 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.

Dermatophytes
On the basis of successful in vitro data, 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 (75 J/cm²). Treatments were repeated weekly until lesions resolved for up to 4 weeks. Overall response was 66%, however, 4 patients recurred after 4 weeks.

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. Later studies incorporated simple interventions such as paring hyperkeratotic skin and use of keratolytics, efficacy subsequently improved. 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%. 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/cm²). 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. Positive response utilizing 20% ALA solution applied for 14 to 24 hours followed by illumination with blue light (417 nm, 10 J/cm²) with up to 5 treatments performed at 2-week intervals has also been described in the treatment molluscum contagiosum.

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. 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). Good results have also been described using MAL and in the treatment of Woringer-Kolopp. 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. Efficacy in the treatment of extra-mammary Paget’s disease ranges from 50% to 100% initial response. Recurrence tends to be high (38-50%) but despite this is comparable with that observed with surgical treatment (31-61%).

Psoriasis
Although PDT has been shown to induce T-cell apoptosis in psoriatic plaques, 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, high rates of relapse (100% within 2 weeks), and numerous side effects such as pain and koebnerization. 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 or 20% ALA followed by 632 nm diode laser activation. These findings were echoed by a slightly larger case series in 2007 in which 3 cases of refractory PPP were treated with 20% ALA with red light activation (15 J/cm²). Mild-to-moderate improvement was appreciated in all subjects.

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. 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. 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. 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. 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. Improved response to ALA-IPL versus IPL was further corroborated by Gold and coworkers. Guidelines regarding settings for IPL devices used in conjunction with ALA can be found in a 2007 review article by Nootheti and Goldman.
Miscellaneous Case Reports

A number of individual case reports describe success using PDT to treat nephrogenic fibrosing dermopathy, granuloma annulare, disseminated superficial actinic porokeratosis, necrobiosis lipoidica diabetorum, lymphadenosis benigna cutis, mycobacterium marinum, both success and failure in the treatment of Darier’s disease and both success and failure in the treatment of hidradenitis suppurativa.

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

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-
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)


