Photodynamic Therapy (PDT)

- 2 Stage Process
  - Delivery of photosensitizer (PS)
  - Photoactivation

- Oxygen an absolute requirement:
  - $O_2 + PS + \text{light} \rightarrow \text{Singlet Oxygen}$
Evolution of PDT

1. Eosin red or erythrosine use with light for PR, Psoriasis, Molluscum Contagiosum, Superficial BCC in early 1900s
2. Hematoporphyrin derivative (HPD) given systemically for primary skin cancer and cutaneous metastases in 1970s resulted in prolonged photosensativity
3. Topical porphyrin precursors in 1990s

ALA PDT - Using an Endogenous Photosensitizer

- ALA (aminolevulinic acid) is taken up by cells and converted to protoporphyrin IX (PpIX), a potent photosensitizer
- Precancerous, malignant, or fast-growing cells identified by PpIX fluorescence
- Exposure to intense light of appropriate wavelength activates PpIX, leading to cell death
- Selective therapeutic benefit of ALA PDT is due to selective drug application followed by the accumulation of PpIX in target cells
Amino-levulinic acid

**Amino-levulinic acid**

Skin Surface

SucCoA and Glycine

PpIX Accumulation in ALA-PDT

Amino-levulinic acid

Therapeutic Benefit
Currently Available Porphyrin Precursors

- 1. 5-aminolevulinic acid (ALA)-solution-more rapid uptake into targeted cells, higher concentration in targeted cells, hydrophilic
- 2. methyl ester of 5-aminolevulinic acid (MAL)-cream- more selective accumulation into targeted cells, may penetrate more deeply, lipophilic
ALA and ALA Methyl Ester

- 5-aminolevulinic acid
- 5-aminolevulinic ester

Practical Application of PDT

- 1. FDA approval for non-hypertrophic/hyperkeratotic actinic keratoses
- 2. Evolving applications: superficial bcc, Bowen’s disease, thin nodular bcc, acne, photodamaged skin, verrucae, rosacea, CTCL
TYPES OF LIGHT SOURCES

1. Conventional: incandescent lamps, high pressure arc lamps, low pressure arc lamps (fluorescent), light emitting diodes, flashlamp IPL

Lasers: Diode lasers, pulse dye lasers

Commercially Available Light Sources

1. Narrow band blue fluorescent tubes for ALA-PDT

2. Narrow band red light illumination lamp for MAL-PDT

3. Other light sources such as pulse dye lasers and IPL devices have been used with success reported in various publications
ALA-PDT For Treatment Of Actinic Keratoses

- Current FDA approval for ALA-PDT involves 14—18 hour incubation with a 20% solution, for selectively treated AKs followed by activation with fluorescent blue light.
- Current trend for ALA-PDT is to treat entire field of areas of AKs with short incubation time of one hour followed by light exposure (more practical and less painful).
- Current FDA approval for MAL-PDT involves applying a 16.8 % cream under occlusive dressing for 3 hours followed by illumination with a narrow spectrum red light lamp.

Efficacy Of PDT for Treatment of Actinic Keratoses

- 50% to 71% complete clearance rates with one treatment in published studies.
- 88% to 90% clearance rates with two or more treatments.
- Face and scalp had highest clearance rates.
- More efficacious compared to cryotherapy.
- Quicker response and less erythema and scaling than with topical 5-FU or Imiquimod.
Literature review on PDT for treatment of AKS for ALA-PDT


Phase III Study Summary: Efficacy

Phase IV, 110 Patient Study:
Summary of Long-Term Safety & Efficacy in the treatment of Grade 1 & 2 AK’s


ALA-PDT before & after spot treatment

Baseline
2 minutes post-treatment
1 week post-treatment
3 weeks post-treatment

Representative patient receiving full-face application of ALA 20% for 1 hour prior to fluorescent blue light treatment.

Figure 3. A. A patient treated with 5-aminolevulinic acid/photodynamic therapy showing multiple actinic keratoses at baseline (arrows). B. The lesions have resolved within 1 month following therapy.

Representative patient receiving full-face application of ALA 20% solution for 2 hours prior to fluorescent blue light treatment.

### Comparison of ALA-PDT with MAL-PDT

<table>
<thead>
<tr>
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<th>ALA-PDT</th>
<th>MAL-PDT</th>
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<tbody>
<tr>
<td><strong>API</strong></td>
<td>Aminolevulinic acid HCl</td>
<td>Aminolevulinic acid methyl ester</td>
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<tr>
<td><strong>Formulation</strong></td>
<td>Alcohol / water solution</td>
<td>Oil in water cream</td>
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<tr>
<td><strong>Strength</strong></td>
<td>20%</td>
<td>16.8%</td>
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<tr>
<td><strong>proved Indications</strong></td>
<td>Actinic Keratosis (US)</td>
<td>Actinic Keratosis (US, EU) BCC (EU)</td>
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<tr>
<td><strong>AK Lesion Preparation</strong></td>
<td>Facial Scrub</td>
<td>Curetting</td>
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<tr>
<td><strong>Light Activation by</strong></td>
<td>Blue fluorescent light</td>
<td>Red Light (LED)</td>
</tr>
<tr>
<td><strong>Efficacy (% Lesion Clearance)</strong></td>
<td>80-90%</td>
<td>80-90%</td>
</tr>
<tr>
<td><strong>Safety Concerns</strong></td>
<td>Photosensitivity 24-48 hours s/p Tx</td>
<td>ACD, Photosensitivity Dermatitis</td>
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<tr>
<td><strong>Incubation Time</strong></td>
<td>14 – 18 hours label 1 hour recent articles</td>
<td>3 hours under occlusion</td>
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Studies showing greater than 68% clearance with MAL-PDT

- Szemies RM et al. JAAD 2002; 47:258-62
- Pariser DM et al. JAAD 2003; 48: 414-8

Better cosmetic outcomes and efficacy than cryotherapy

MAL-PDT vs. ALA-PDT for AKS

- MAL was less painful than ALA in treatment of AKs using same red light source. Kasche, A et al. J Drugs Dermatol 2006; 5: 353-6
ALA-PDT before and after 12 weeks

ALA-PDT before and after 12 weeks
ALA-PDT before and after 10 weeks full field short contact

ALA-PDT before and after 10 weeks
ALA-PDT full field short contact

2/19/2008  4/17/2008

ALA-PDT full field short contact

2/19/2008  4/17/2008
ALA-PDT full field short contact

2/19/2008 4/17/2008

ALA-PDT full field short contact

1/15/2008 3/26/2008
PDT treatment for Bowen’s Disease (BD) or SCC in Situ


- ALA treatment of BD utilizing a pulse dye laser light source was effective in 17 patients using 4 hour incubation and overlapping 7 mm diameter spots size with 82% complete clearance at 1 year. Britton JER, et al. Br J Dermatol 2005;153:780-4
**Bowen’s Disease**

- MAL-PDT was more effective in clearing lesions and showed a superior cosmetic effect compared to cryotherapy and topical 5-FU. Morton CA, et al. Arch Dermatol 2006; 142:729-35
- Various case reports have shown effectiveness of PDT to treat Bowen’s Disease of the nipple, sub-ungual SCC in situ, Bowenoid papulosis, and erythroplasia of Queryat.

**PDT treatment for Basal Cell Carcinoma**

- A review article of 12 studies showed a weighted clearance rate of 87% for superficial basal cell carcinomas treated with ALA-PDT, but only 53% clearance for nodular bcc. Peng Q, et al. Cancer 1997;79:2282-308
- MAL-PDT with broadband light and pre-treatment curettage used to treat group of 350 superficial and nodular BCC showed an overall cure rate of 79% after 35 months with a good to excellent cosmetic response in 98%. Soler AM, et al. BR J Dermatol 2001;145:467-71
Basal Cell Carcinoma

- ALA-PDT was compared with MAL-PDT with red light irradiance for treatment of nodular bcc. There was no difference in lesional response on histologic analysis after 8 weeks. Kuijpers D et al. J Drugs Dermatol 2006;5:642-5

- A study of 95 patients with 148 bcc lesions in “difficult to treat” sites, large size or recurrent were treated with MAL-PDT and red light. There was an 89% complete response rate at 3 months and an estimated complete response rate of 78% at 2 years. 84% were judged to have a good or excellent cosmetic response. Vinciullo C et al. Br J Dermatol 2005:152:765-72

Basal Cell Carcinoma

- A multicenter randomized trial for treatment of nodular bcc compared MAL-PDT and red light with standard surgical excision. A similar complete response of 91% vs. 98% was noted at 3 months, but fell to 83% vs. 96 % at 12 months and to 76% vs. 96 % at 5 years, PDT offered a more favorable cosmetic response. Rhodes LE, et al. Arch Dermatol 2007;143:1131-6
Basal Cell Carcinoma

- MAL-PDT compared with cryotherapy for superficial bcc showed similar complete response rates at 3 months and 5 years, but with superior cosmetic outcome for PDT. Basset-Seguin N, et al. Eur J Dermatol 2008;18:547-53

PDT for Basal Cell Nevus Syndrome

- Poster presentation at 2008 AAD meeting by Dept of Derm. Boston U. Five BCNS patients treated broadly with topical 20% ALA solution/blue light and tumors greater than 4 mm diameter were injected intraleisonally with solution diluted with lidocaine/epi resulted in clearing of most of the lesions and a reduction of new lesions seen up to 5 years follow-up
**Broad Area PDT in BCNS Patients**

G.S. 67 years old

Pretreatment  | After 3 Treatments


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**Intralesional Treatment of Nodular BCC in a Patient with BCNS**

Pretreatment  | 1 month

BluU lamp (417 nm) 10 J/cm²
ALA 20% diluted 1:1 in 1% lidocaine

No recurrence after 4 years.

Courtesy of Barbara A. Gilchrest, M.D.
10-year-old boy with BCCs and Basaloid Follicular Hamartomas A) 24 hours post-PDT and B) After 2 ALA PDT Treatments


PDT for Photorejuvenation

- Several studies done to assess treatment for AKs have shown promise for reducing the appearance of fine lines and wrinkles, photoaging, telangectasia, and melasma
Photorejuvenation

- ALA with blue light resulted in 83% response rate of AKs and significant reduction in crow’s feet, skin roughness, hyperpigmentation, and facial erythema. Gold MH Cutis 2002;69(6 Suppl);8-13

Photorejuvenation

- ALA-PDT one hour incubation followed by blue light cleared 90% of AKs with 72% improvement in skin texture and 59% reduction of pigmentary changes. Goldman MP, J Lasers Surg Med 2002;14(S) et al. 2002;14(S):24
Photorejuvenation


PDT for Skin Cancer Prevention
Organ Transplant Recipients

- MAL-PDT red light treated sites compared with control sites in renal transplant recipients with AKs showed longer time to develop new lesions in MAL treated sites and by 12 mos. 62 % of treated sites were free of new lesions compared with 35 % of control. Wulf HC. Acta Derm Venereol 2006;86:25-8
PDT for Acne

- Most reports show better efficacy for red light or IPL over blue light irradiation.
- ALA red light treated areas on the back showed a reduction of inflammatory lesions at 10 weeks with one treatment and a greater reduction after 20 week with four treatments compared to controls. Hongcharu W et al. J Invest Dermatol 2000;115:183-92

Acne

Acne

- ALA-PDT irradiated with PDL vs. PDL alone for facial acne showed a 77% lesional clearance rate for PDT treated patients vs. 32% for PDL only patients at 6 mos after a mean of 2.9 treatments. Alexiades-Armenakas M. j Drugs Dermatol 2006;5:45-55

- MAL-PDT red light for two treatments vs. controls for moderate to severe facial acne showed a 69% reduction in inflammatory lesions with PDT vs. no change in the control group. Moderate pain during treatment, followed by erythema, pustules, and desquamation. Weigell SR, WulfHC. Br J Dermatol 2006; 154:969-76
ALA-PDT with blue light for acne

ALA-PDT for Acne using IPL

ALA-PDT for Rosacea using PDL
PDT for Sebaceous Hyperplasia Papules

- Several case reports and case series report a therapeutic benefit for PDT using ALA or MAL with various light sources

PDT for Viral Warts

- Clearance rates of 56-100% for PDT using ALA or MAL with various light sources have been noted in case series and comparison trials of refractory warts. Recent studies support the potential of PDT for plantar warts, but with outcomes dependent on adequate paring and the use of a keratolytic agent pre-PDT
PDT for Cutaneous T-Cell Lymphoma

- Several case reports and case series successfully utilizing ALA-PDT and MAL-PDT for early stage localized CTCL have been published. While topical PDT can elicit a response further studies are needed to define optimal treatment parameters.

Other applications for PDT based on case reports and small case series

- Actinic cheilitis
- DSAP
- Extramammary Paget’s
- Rosacea/Perioral dermatitis
- Hailey-Hailey
- Darlers
- NLD
- Molluscum contagiosum
- Flegel’s disease
- Toenail onychomycosis
- Hidradenitis suppurativa
- ALA,MAL,red,broad
- ALA,MAL,red,PDL
- ALA,MAL,red
- ALA,MAL,red,blue, PDL
- ALA,red
- ALA,red,blue
- MAL,red
- ALA,blue
- ALA,red
- Urea occlusion, ALA,red-PDL
- ALA,blue
Summary of applications for PDT

- Excellent for ALA or MAL for treating thin to moderate AKS, Bowen’s Disease, Superficial BCC, and photorejuvenation with any light source.
- Good emerging evidence for ALA or MAL for thin nodular BCC with red light.
- Good emerging evidence for ALA or MAL for treatment of warts and skin cancer prophylaxis in OTR recipients.
- Fair emerging evidence for ALA or MAL for acne, rosacea, extramammary Paget’s, and CTCL.
- Many other conditions reported to be affected by PDT in case reports need further confirmation.