Photodynamic therapy for acne vulgaris: A critical review from basics to clinical practice

Part II. Understanding parameters for acne treatment with photodynamic therapy

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Photodynamic therapy requires a photosensitizer, oxygen, and activating light. For acne, pilosebaceous units are "target" structures. Porphyrins are synthesized in vivo from 5-aminolevulinic acid (ALA), particularly in pilosebaceous units. Different photosensitizers and drug delivery methods have been reported for acne treatment. There are a variety of porphyrin precursors with different pharmacokinetic properties. Among them, ALA and methyl-ester of ALA (MAL) are available for possible off-label treatment of acne vulgaris. In addition, various light sources, light dosimetry, drug incubation time, and pre- and posttreatment care also change efficacy and side effects. None of these variables has been optimized for acne treatment, but a number of clinical trials provide helpful guidance. In this paper, we critically analyze clinical trials, case reports, and series of cases published through 2009. (J Am Acad Dermatol 2010;63:195-211.)

Learning objectives: After completing this learning activity, participants should be able to analyze photodynamic therapy using 5-aminolevulinic acid and its derivates for acne treatment, predict the effectiveness and outcomes of photodynamic therapy using different parameters and/or different porphyrin-related photosensitizers, and assess and manage the side effects of porphyrin-based photodynamic therapy for acne.

Key words: adverse effects; 5-aminolevulinic acid; lasers; light; methyl 5-aminolevulinate; photochemotherapy; porphyrins; therapeutics.

Over the past decade, several papers have been published about photodynamic therapy (PDT) using 5-aminolevulinic acid (ALA) or methyl-aminolevulinate (MAL) for acne vulgaris. Despite the enthusiasm for new treatment alternatives, it is clear that there is no consensus about treatment parameters to target of acne sebaceous glands.

PDT drug delivery methods, choice of photosensitizer, skin preparation, light sources, and light dosimetry/irradiance may affect efficacy and side effects. Understanding the science behind treatment methods may increase efficacy and long-term acne remission. This review is a critical analysis of all clinical papers on the subject of PDT for acne. Table I summarizes the clinical studies, case reports, and series of cases published through 2009 regarding PDT for acne.

5-AMINOLEVULINIC ACID VERSUS 5-AMINOLEVULINIC ACID DERIVATIVES

Key points

- **5-aminolevulinic acid (ALA) and ALA derivatives have different mechanisms of cell uptake and transport**
- **While ALA is hydrophilic, most ALA derivatives are lipophilic, making it easier for pas-**

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Funding sources: None.
Conflicts of interest: The authors, editors, JAAD CME council members, and peer reviewers have no relevant financial relationships.

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0190-9622/$36.00

doi:10.1016/j.jaad.2009.09.057

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Key points

- **5-aminolevulinic acid (ALA) and ALA derivatives have different mechanisms of cell uptake and transport**
- **While ALA is hydrophilic, most ALA derivatives are lipophilic, making it easier for passive cell transport. However, ALA derivatives**

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need an extra step of metabolism to be converted into ALA and then into porphyrins

- **In general, high-dose photodynamic therapy with long incubation, high fluence red light activation works similarly for both ALA and ALA derivatives**
- **Oral administration of ALA has been reported for acne treatment, but can be associated with systemic side effects and generalized phototoxicity**

CAPSULE SUMMARY

- Porphyrin precursors (5-aminolevulinic acid [ALA] or esters of ALA) delivered topically or orally have been studied for photodynamic therapy (PDT) of acne.
- PDT for acne has not been optimized, including topical preparation, dose-response, conditions for metabolism to porphyrins, and light exposure.
- Ester derivatives of ALA, such as methyl-ester of ALA (MAL), are converted into ALA after uptake to skin. Different biodistributions occur among ALA derivatives because of lipophilicity and cell membrane transport mechanisms.
- Porphyrin precursors require an incubation period for metabolism. Longer incubation times ($\geq$3 hours) are associated with long-term acne remission.
- When used with high-dose conditions (long incubation time, high fluence red light exposure), ALA PDT and MAL PDT have been shown to produce similar effects for acne treatment.
- For PDT activation, continuous wave, high intensity red light sources have deeper penetration and are more likely to produce sebaceous gland destruction compared with blue light or pulsed light sources.
- Topical ALA PDT or MAL PDT is often painful, causes inflammatory side effects, and may cause residual photosensitivity.

In the United States and South America, 5-ALA is available in 20% hydroalcoholic solution and marked as Levulan Kerastick (Dusa Pharmaceuticals, Wilmington, MA) for treatment of actinic keratosis followed by blue light exposure. Methyl aminolevulinate hydrochloride is the methyl-ester of ALA (MAL) in a cream formulation. MAL is marketed as Metvix (produced by Photocure ASA, Oslo, Norway, and marketed by Galderma SA in Europe, Australia, and South America for the treatment of actinic keratosis and, depending on the country, for treating Bowen disease and superficial basal cell carcinoma) or as Metvixia (in the United States, marketed by Galderma SA for the treatment of actinic keratosis with red light exposure). It is labeled either as 16% or 16.8% concentration in different countries, depending whether the hydrochloride is included in molecular weight. Lower concentrations of MAL (2, 4, and 8%) are being tested in phase I and phase II clinical trials for acne treatment, but no publications are available thus far. More recently, the hexyl-ester of ALA has been approved in Europe for bladder cancer treatment (Hexvix 85-mg powder for intravesical use; produced by Photocure ASA, Oslo, Norway, and marketed by Galderma SA), but this compound has not yet been studied for acne. Other derivatives are not yet marketed.

Mechanisms of ALA cell uptake involve transmembrane channels and active transport. ALA is a naturally occurring amino acid with a balance of hydrophilic and lipophilic properties that allows diffusion in and out of biomembranes.[1] ALA is a largely hydrophilic zwitterion (a neutral molecule carrying both positively and negatively charged groups) which facilitates plasma membrane penetration.[2] ALA esters were developed to increase drug penetration by adding aliphatic alcohols to the carbohydrate chains and modifying the alkyl chain length, and to formulate new, patentable molecules. However, if a highly lipophilic drug is added to a lipophilic vehicle (cream or ointment), it tends to be retained in the vehicle rather than partitioning into skin, and uptake is reduced.[1] Those ALA derivatives with long lipophilic side chains may also suffer delay in uptake because of retention in stratum corneum and/or a higher molecular weight.[1] Figure 1 summarizes the lipophilic properties of ALA and its derivates.[1] Ultimately, only the ethyl, propyl, and methyl esters of ALA have successfully improved porphyrin formation upon topical application to intact skin in vivo.[1,3] Some studies using the topical hexyl ester of ALA in skin failed, possibly because it was used within a lipophilic vehicle, suggesting that a hydrogel vehicle may be more appropriate for the more lipophilic esters.[1]

In addition to differences in uptake related to physicochemical properties, it was also observed in different cultured cell lines that uptake of ALA and its various esters follow different active transport pathways. 5-ALA is a beta amino acid that enters cells in part via active transport mechanisms, such as PEPT1

Table I. Publications between 2000 and 2008 of 5-aminolevulenic acid and methyl aminolevulinate hydrochloride photodynam of acne vulgaris

	Hongcharu, 2000[18]	Itoh, 2000[40]	Itoh, 2001[23]	Goldman, 2003[35]	Pollock, 2004[41]	Gold, 2004[26]	Taub, 2004[27]	
Drug	20% ALA topical	20% ALA topical	20% ALA topical	20% ALA topical	20% ALA topical	20% ALA topical	20% ALA topical + salicylic acid peelings over 4 weeks	Or
Control group?*	Yes; blinded assessment	Yes (compared to rest of the face that was not treated); not blinded assessment	No; not blinded assessment	No (compared to blue light only group), not blinded assessment	Yes (same patients received treatments and controls); not blinded assessment	No; not blinded assessment	No; not blinded assessment	No
No. of patients/ acne location	22/Back	1/Face	13/Face	22 (12 blue light vs 10 ALA-PDT)/Face	10/Back	15	18	51
Acne type	Inflammatory, mild to moderate	Inflammatory	3 Comedonal (NI); 10 inflammatory	Inflammatory, mild to moderate	Inflammatory, mild to moderate	Inflammatory, moderate to severe	Inflammatory, moderate to severe	Int
Pretreatment	70% Isopropyl alcohol	Not mentioned	Not mentioned	2% Salicylic acid cleanser	Not mentioned	Cetaphil cleanser	Acetone scrub and alcohol scrub	No
Time of incubation	3 hrs under occlusion	4 hrs under occlusion, light covered	4 hrs under occlusion, light covered	15 min	3 hrs under occlusion	1 hr	15-30 min, not standardized	4 h
Light sources	Broad-spectrum (550-700 nm), 150 J/cm^2	Pulsed excimer dye laser (635 nm), 5 J/cm^2	Broad-spectrum (600-700 nm) halogen lamp at 17 mW/cm^2, 13 J/cm^2	Blue 417 ± 5 nm, 10 mW/cm^2, 3.6 J/cm^2	Diode laser (635 nm), 25 mW/cm^2, 15 J/cm^2	IPL (430-110 nm), 3-9 J/cm^2 + heat	Blue (417-420 nm) OR blue 417 ± 5 nm (1.8-4.2 J/cm^2 at 10 mW/cm^2) OR IPL (400-980 nm), 18-25 J/cm^2 + radiofrequency 18-20J/cm^2, no standardized fluences	Me
No. of PDT sessions	Two randomized groups: 1 vs 4 sessions (1-wk apart)	1	1	2	3 (1-wk apart)	4 (1 wk apart)	2-4 (4-8 wks apart), not standardized	2 (
Total follow-up time	20 wks after the last treatment	32 wks	24 wks after the last treatment	2 wks	3 wks	12 wks	4-32 wks, not standardized	12

Table I. Cont'd

	Hongcharu, 2000[18]	Itoh, 2000[40]	Itoh, 2001[23]	Goldman, 2003[35]	Pollock, 2004[41]	Gold, 2004[26]	Taub, 2004 [27]	
Efficacy rate[†]	Four sessions better than 1. After 20 wks, reduction of ~50% of acne after 4 sessions ($P < .05$). ~30% reduction with only one session. Global acne improvement, sebum reduction, and autofluorescence statistically significant compared to other control sites	Complete remission, with no new lesions	100% of patients with some improvement; 13/13 patients with no new lesions after 1 mo; 5/13 without new lesions after 3 mos and 6 mos all patients had new lesions	68% (PDT) reduction of inflammatory lesions vs 40% (blue light) and 62% reduction of NI lesions. 32% (ALA-PDT) vs 25% (blue only) improvement in severity of acne	Reduction of acne count from 11.6 lesions to 3.6 at the end of the study; NI lesions not evaluated	20% of patients had no improvement with treatment; 80% of patients showed 71.8% of improvement; NI lesions not mentioned	27% of patients had no improvement with treatment. Results not comparable because of the lack of standardization	7.8
Recurrence			New lesions after 3-6 mos				11% recurrence in 1 or 2 mos; results not comparable because of the lack of standardization	

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