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Photodynamic Therapy: Current and Emerging Applications

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Introduction

Donald F. Richey MD

For the general dermatologist, implementing photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) offers a key to new treatment programs in medical dermatology with an added bonus of cosmetic dermatology services.

In my medical-surgical-cosmetic practice, PDT with ALA (Levulan® Kerastick®, Dusa Pharmaceuticals) serves multiple functions. The technique is a tremendous adjuvant for the treatment of moderate to severe acne. Like isotretinoin (Accutane, Roche Pharmaceuticals), ALA PDT with blue light (BLU-U® Blue Light Photodynamic Therapy Illuminator, Dusa Pharmaceuticals) reduces the size of sebaceous glands. It also produces porphyrins, which have antibacterial actions. In some patients, ALA PDT can replace oral isotretinoin and oral antibiotics.

ALA PDT reaches 2 types of people not being treated for their acne. I call them non-believers and non-responders.

Non-believers are afraid a dermatologist will either prescribe oral antibiotics that will "destroy their immune system" or will put them on isotretinoin, which non-believers have heard horror stories about. Non-believers are basically against oral medications, so they "don't believe" that a dermatologist can help them.

Non-responders, though not against oral medications, have taken isotretinoin but still have advanced cystic scarring acne, or have taken oral antibiotics without improvement. These people are also looking for a treatment program that does not have the side effects of these medications.

The beauty of ALA PDT is that it offers a very nice topical treatment without the side effects of oral medications. I introduced the technique to new patients with advanced acne and established patients who were frustrated with their acne. (I held no seminars and did no advertising.) Both non-believers and non-responders are happy with ALA PDT as an add-on to their topical acne medications. The ALA PDT treatment of acne is reimbursed about 10% of the time.

Another application of ALA PDT with blue light is the treatment of actinic keratoses (AKs), especially in patients with multiple lesions. Since 15 or more lesions are beyond treatment with liquid nitrogen, the traditional therapy has been topical 5-fluorouracil (5-FU, Efudex, ICN Pharmaceuticals, Inc.). Most patients will accept treatment with 5-FU once but not twice because during the first course of therapy they had 3 weeks of severe redness, pain, and peeling. For these people, I needed a topical treatment for the entire face, neck, hands, or arms without the side effects of 5-FU.

ALA PDT with blue light knocks out these pre-cancerous lesions and patients have 2 to 3 days (rather than 3 weeks) of redness and peeling. People I've been treating for more than 2 years also love the textural change that occurs in their skin after treatment with ALA PDT. From a surgical point of view, this new skin smoothness is a real bonus.

For AKs, 2 treatments of ALA PDT at 2- to 4-week intervals has replaced 5-FU in my practice. Treatment of AKs with ALA PDT is reimbursed by insurance companies. In my practice, ALA PDT for moderate to severe AK is the first AK therapy in which patients actually ask for a repeat treatment.

For rejuvenating skin, I use the Levulan with intense pulsed light (IPL) rather than blue light. As an adjuvant treatment for this application. ALA PDT enhances outcomes associated with traditional IPL treatments and reduces subclinical sun damage. I also believe that ALA PDT can delay or prevent the development of AK and nonmelanoma skin cancers, as suggested by animal studies.[1,2]

Adverse Effects

If patients treated with ALA PDT are very sensitive to sunlight or UV Light, I tell them to wear sunblock indoors and outdoors for 48 hours. With their first treatment, they may get redness and peeling for a couple days as their sun-damaged skin exfoliates. I give them a moisturizing lotion and tube of cortisone ointment and tell them how to cool their faces with icepacks.

The BLU-U costs approximately $8,000, very economical compared to $20,000 for a light box for psoriasis or $75,000 to $100,000 for a laser. Any general dermatology practice could purchase a BLU-U unit. No new staff members are needed and it takes less than 1 hour to learn the technique. Dermatologists can begin the technique with acne, AKs, or photorejuvenation.

ALA PDT is a wonderful addition to a general dermatology practice because it places the physician at the cutting edge of technology. With the new federal restrictions on the use of Accutane, ALA PDT will probably replace this drug for acne. ALA PDT is also a good treatment alternative for acne patients who don't want oral medications, AK patients who want to avoid the skin irritation of 5-FU, and patients who want the skin textural changes for skin rejuvenation.

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North Valley Dermatology Center

Case Reports:
Broad area Photodynamic Therapy for Treatment of Multiple Basal Cell Carcinomas in a Patient with Nevoid Basal Cell Carcinoma Syndrome

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Abstract

We report a case of a 73-year-old man with nevoid basal cell carcinoma syndrome who was referred to us with multiple basal cell carcinomas on his face and chest. The patient underwent photodynamic therapy utilizing a 1-hour incubation of Levulan® Kerastick® δ-aminolevulinic acid 20% topical solution applied to the full face and illumination with a BLU-U® blue light source (10 J/cm^2) every 2 to 3 months for a total of 4 treatments. This treatment strategy resulted in multiple benefits, including reducing the number and size of his existing basal cell carcinomas, improving the appearance of previous surgical scars, and decreasing the rate of tumor development.

Case Report

A 73-year-old Caucasian male first presented in childhood with multiple jaw cysts requiring dental surgeries and tooth extractions. The patient began developing basal cell carcinomas (BCCs) as a young man during military service. A diagnosis of nevoid basal cell carcinoma syndrome (NBCCS) was made and subsequently the patient developed hundreds of BCCs that were treated by multiple excisions, resulting in extensive scarring. On 2 occasions, the patient received Photofrin systemic photodynamic therapy (PDT) for multiple lesions that cleared but resulted in further scarring. The requirement for nearly constant, painful therapy and the resulting disfigurement left the patient suicidal, according to his family and referring physician. At the time of referral, multiple BCCs were present and he was scheduled for a complex procedure to remove a large BCC on the margin of the right upper eyelid.

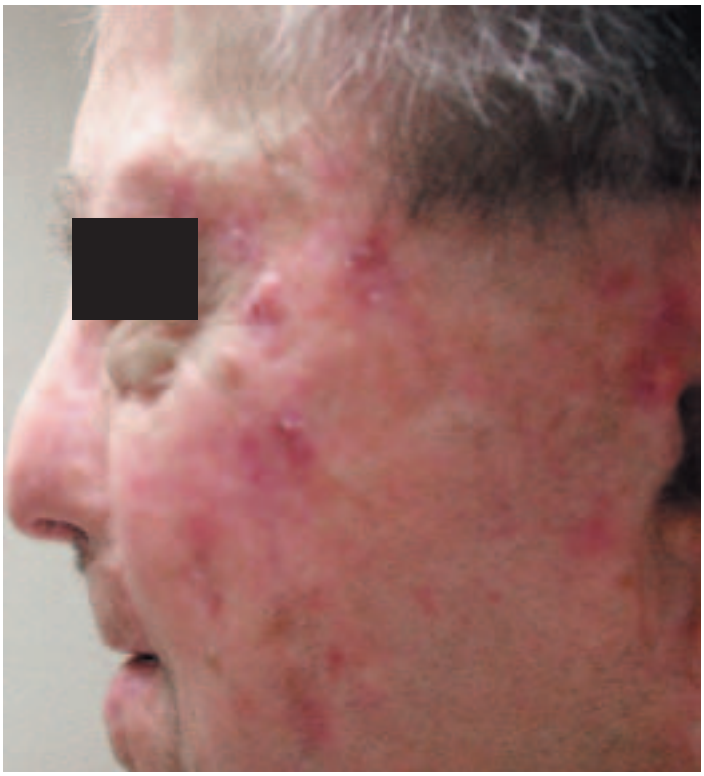
On initial examination in August 2003, we detected multiple translucent telangiectatic papules and scaly patches covering the patient's cheeks and preauricular areas, both ears, balding occipital scalp, and anterior chest (Figure 1). The patient underwent PDT consisting of 1-hour topical application of Levulan® Kerastick® δ-aminolevulinic acid 20% topical solution to the full face followed by illumination with a BLU-U® blue light source (maximum output of 417 nm, radiance 10 mW/cm^2 for 1,000 seconds, total dose 10 J/cm^2 per exposure) followed by oral prednisone 50 mg/day for 2 days to reduce acute photoxicity. After repeating this process every 2 to 3 months for a total of 4 full face PDT treatments, the patient and treating physicians noted significant improvement in the number and size of existing BCCs, decreased prominence of old facial scars and decreased pore size (Figure 2). At present, the patient is doing well, in excellent psychological health and continuing full face PDT treatments every 2 to 3 months.

Discussion

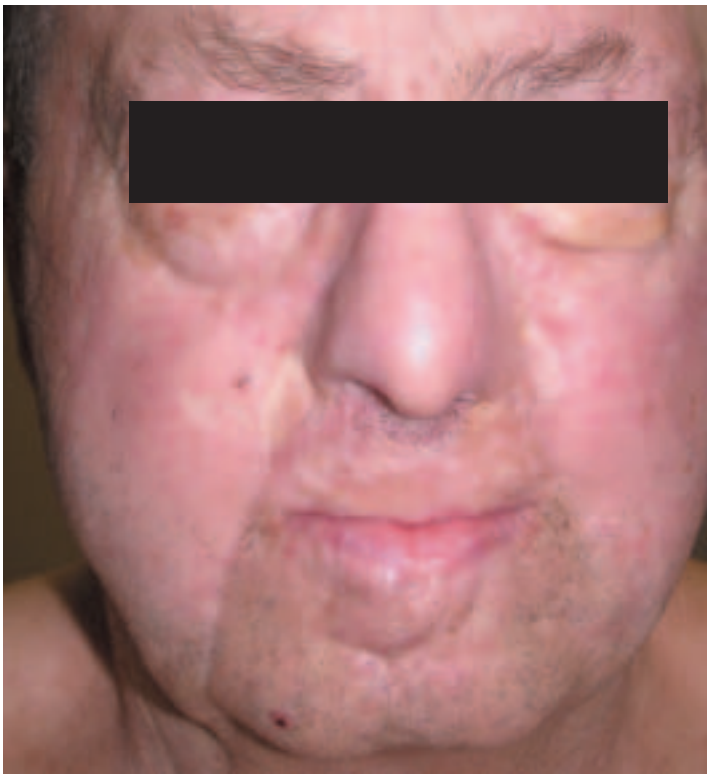
The use of photosensitizing chemicals for the treatment of skin disease dates back to ancient times when the Egyptians, Indians, and Greeks used psoralen-containing plant extracts and light to treat psoriasis and vitiligo.[1] The term photodynamic therapy (PDT) was coined by von Tappeiner in 1904 to describe oxygen-consuming chemical reactions induced by photosensitization.[2] Over the years, many photosensitizing agents have been developed but systemic agents such as porfimer sodium and topical agents such as δ-aminolevulinic acid (δ-ALA) have generated the most interest in part because they preferentially accumulate in neoplastic tissues.[3] Both agents are quickly metabolized to protoporphyrin-IX (PPIX),[4] a reaction that depletes cellular iron stores, halting the synthetic pathway leading to the production of heme and resulting in an accumulation of PPIX.[5] Upon exposure to light, PPIX drives the production of reactive oxygen species leading to local tissue destruction.

Figure 1. Pre-Treatment

a. Left profile.



b. Full face.



δ-ALA is more advantageous that available systemic photosensitizers for treating skin neoplasms because it can be directly applied and does lead to long-term photosensitivity. In 1999, the United States Food and Drug Administration (FDA) approved a PDT modality for the treatment of nonhyperkeratotic actinic keratoses which utilizes 20% topical hydroalcoholic solution of δ-ALA and a blue light source of 417 nm peak output,[6] with most energy in the Soret band (400-410nm) in which porphyrins absorb maximally.[7] In light of recent studies showing effective treatment of nodular and superficial BCCs with δ-ALA-PDT using red light (630-635 nm)[8] and an incoherent blue light source (400-450 nm),[9] we attempted to treat multiple BCCs in 2 women aged 21 and 47 years with NBCCS using the FDA approved blue light source for δ-ALA-PDT.[10] Rather than the FDA-approved protocol of 14- to 18-hour δ-ALA incubation and application restricted to visible lesions,[11] the topical solution of δ-ALA was applied 1 to 3 hours prior to light treatment (10 J/cm^2) and after the first course, the entire face (broad area PDT), rather than the visible BCC lesions only, was treated. Initially, 2 consecutive treatments 1 week apart were administered as a therapeutic course and the patients underwent 2 courses of δ-ALA 3 months apart.[10]

Between the 2 patients, a total of 9 superficial and 16 nodular BCCs on the face and 27 superficial BCCs on the lower extremities were treated. After 2 to 4 exposures, complete clinical resolution was noted in 8/9 (89%) of superficial BCCs and 5/16 (31%) of nodular BCCs on the face, and in 18/27 (67%) of superficial BCCs on the lower extremities with excellent cosmetic results.[10] The remaining 21 lesions showed partial clinical resolution that continued with further therapy over the subsequent 9 months.

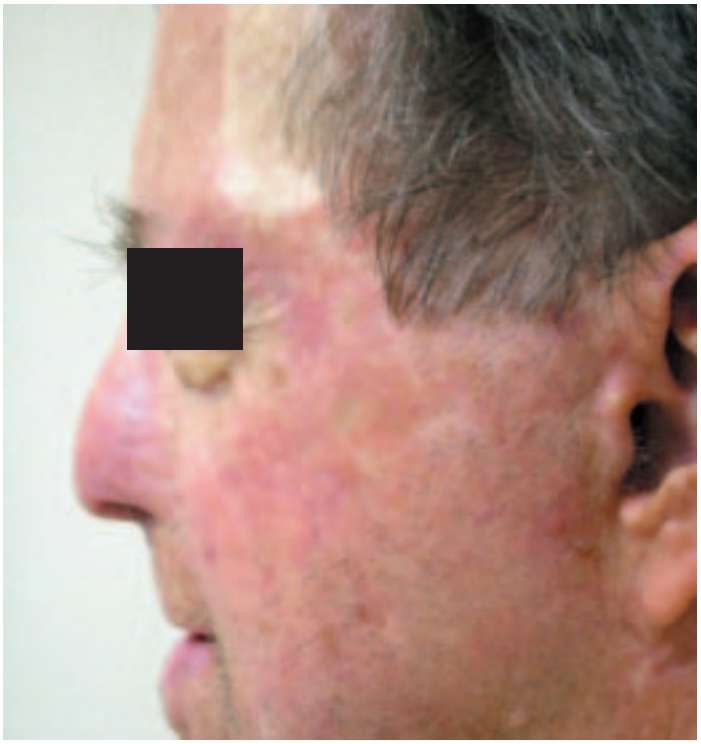
As in the 2 initial patients, broad area PDT produced several benefits for the present patient beyond those achievable by PDT limited to lesions visible lesions. In addition to resolution of the BCCs, both the patient and treating physicians noted a decrease in the prominence of old facial scars, decreased pore size, and decreased severity of diffuse photodamage, a benefit also noted in a study of 18 middle-aged subjects with moderate actinic keratoses and diffuse photodamage but no recognized photodermatosis, after a single δ-ALA-PDT treatment.[12] Furthermore, the current patient who continued broad area PDT every 2 to 4 months over the last year has noted a significant decrease in the rate of new tumor development as he has not required any surgical cancer treatments. Broad area δ-ALA-PDT may offer patients with NBCCS and other cancer-prone conditions a non-invasive method to treat existing malignancies, prevent new lesions, and improve the appearance of previous surgical sites.

Acknowledgements

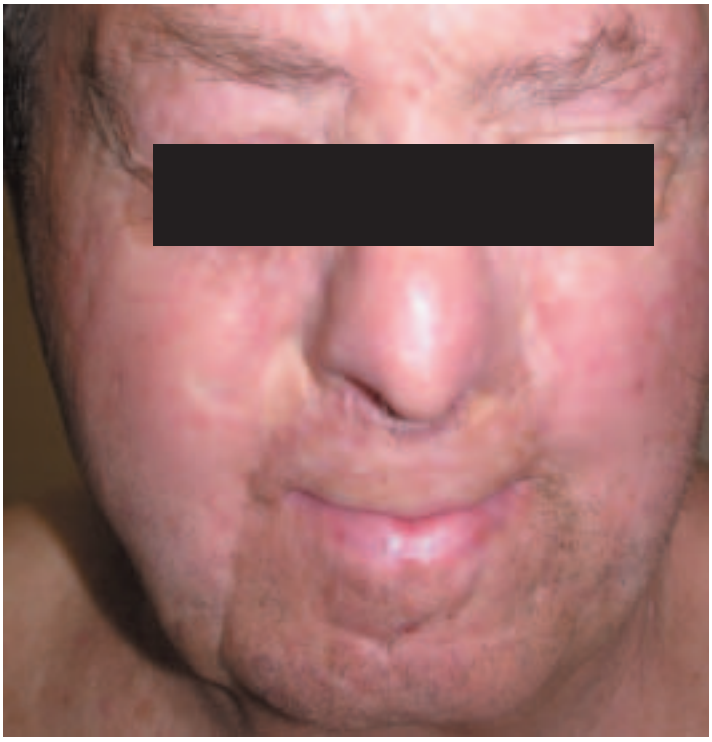
The authors are grateful to Ms. Andrea Macone and Ms. Allison Chapas for assistance with the digital images. This patient was previously presented at the December 2003 New England Dermatology Society Clinical Meeting.

Figure 2. Post 4 Broad Area PDT Treatments.

a. Left profile.



b. Full face



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Case Reports: Photodynamic Therapy for the Treatment of Erythema, Papules, Pustules, and Severe Flushing Consistent With Rosacea

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Abstract

We report a case of a 45-year-old woman who presented with facial erythema, papules, pustules, and severe flushing consistent with rosacea. The patient had failed standard pharmacologic treatments. The patient's flushing was so severe that she had undergone an elective sympathectomy. She received 6 sessions of photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA as Levulan® Kerastick®, Dusa Pharmaceuticals) given at 2-week intervals. Improvement was evident after the second treatment and was considered "excellent" after the sixth treatment. Improvement continued and no flares were observed 1 month after the final treatment.

A 45-year-old white woman presented with a 5-year history of erythema, papules, pustules, and severe flushing of the central face. Symptoms were consistent with rosacea (Figure 1). The patient was receiving no topical or systemic medications at presentation, though she had previously received multiple topical and oral therapies (metronidazole, sodium sulfacetamide, and tetracycline). She had undergone elective sympathectomy due to the severity of flushing. The failure of previous pharmacologic treatments led to our decision to use photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) with pulsed dye laser (PDL) activation.

The patient's central face was first cleaned with acetone. ALA (Levulan® Kerastick®, Dusa Pharmaceuticals, Wilmington, Mass.) was applied once, allowed to dry, applied again, and allowed to remain in contact with skin for 15 minutes. The area was treated with ultrasound for 15 minutes to increase penetration of ALA. The treated area

Figure 1. A 45-year-old woman who presented with facial erythema, papules, pustules, and severe flushing that suggested rosacea.

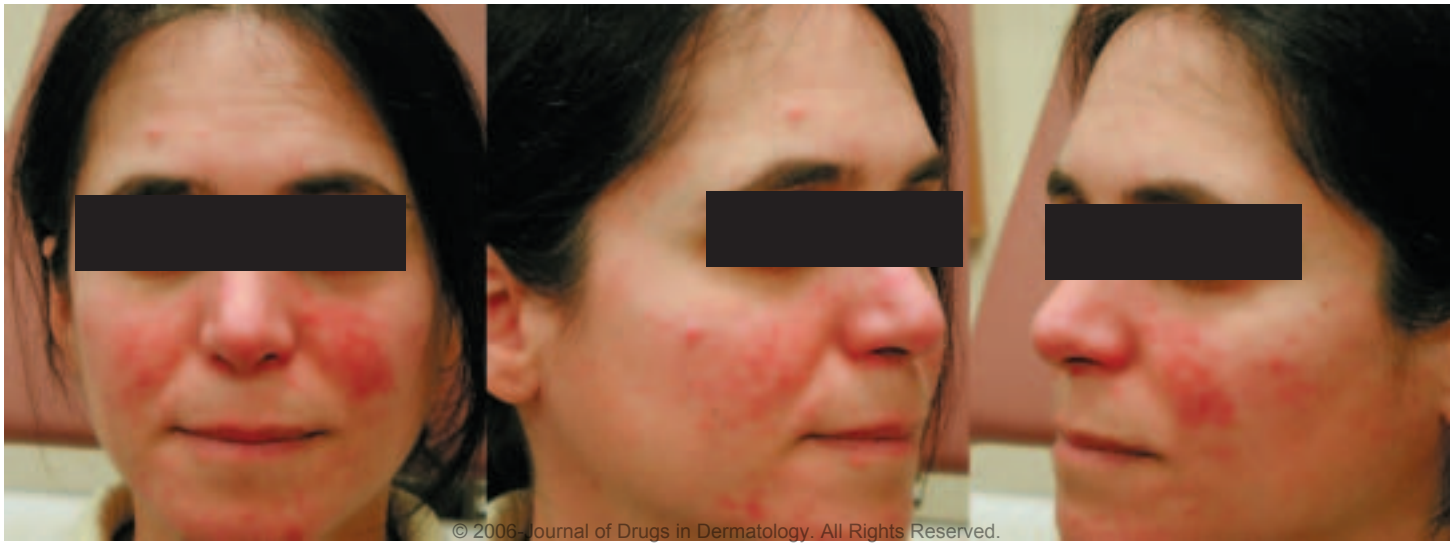
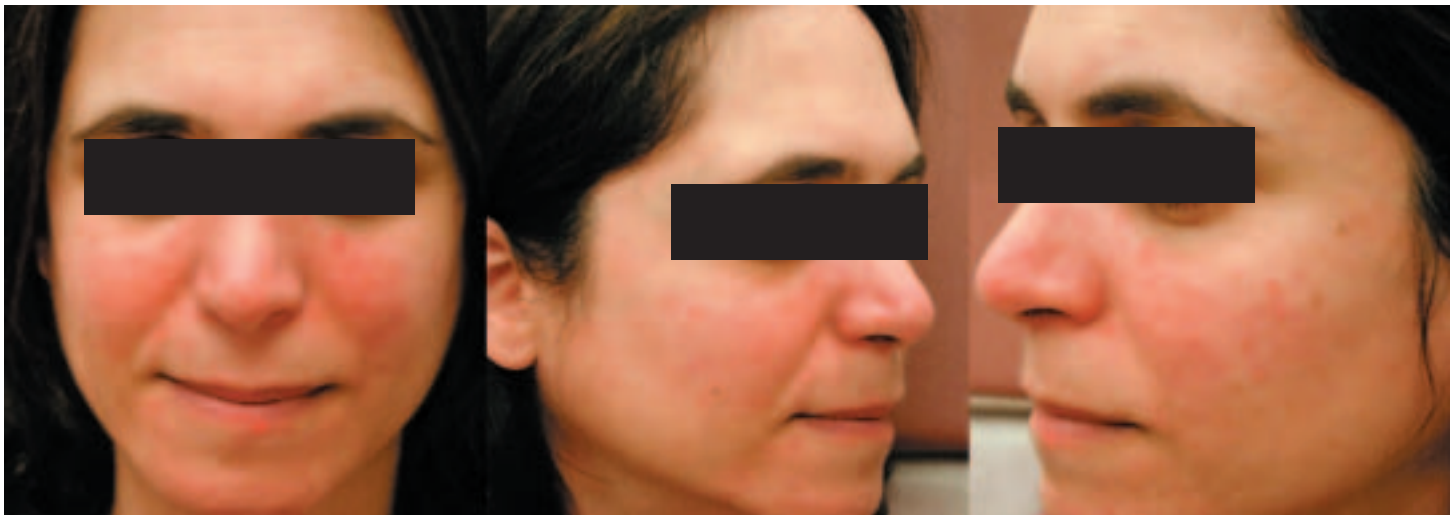


Figure 2. A 45-year-old woman treated 6 times over 12 weeks by photodynamic therapy with 5-aminolevulinic acid. eduction in facial erythema, papules, pustules, and severe flushing was noticeable after the second treatment. Improvement was considered "excellent" after the final treatment.



was irradiated with a PDL (595 nm, 40 ms pulse duration) (VStar®, Cynosure, Inc., Chelmsford, Mass.) accompanied by a continuous flow of chilled air (SmartCool®, Cynosure, Inc.; Zimmer Elektromedizin GmbH, Germany). The initial 3.4 J/cm^2 fluence was increased 0.5 to 1.0 J/cm^2 with successive treatments to a maximum of 7.5 J/cm^2. After irradiation, the patient was instructed to wash her face with soap and water and apply sunscreen. Treatment was repeated every 2 weeks for a total of 6 treatments. Improvement was evident after the second treatment and considered "excellent" after the final treatment (Figure 2). Improvement continued and no flares were observed 1 month after the final treatment.

Discussion

Symptoms associated with rosacea include facial erythema, papules, pustules, and severe flushing. Standard treatment consists of topical metronidazole or sulfacetamide. In moderate to severe cases, other antibiotics may be added to control papules and pustules and to arrest progression to rhinophyma or ocular rosacea.[1] Guidelines for classifying, managing, and treating rosacea have been presented.[2]

Pharmacologic therapy is effective against papulopustular lesions of rosacea but its effect against erythema, flushing episodes, and telangiectasias is limited.[3-6] For patients who either don't respond to antibiotics or don't wish to take antibiotics for long periods, lasers,[3,5,7-10] intense pulsed light,[1,11] radiofrequency (RF),[12] and a combination of RF and optical energy[13-16] are alternative treatment modalities. Temporary purpura is a common side effect in laser treatments.[1]

PDT has been used by Nybaek and Jemec to treat 4 patients with rosacea.[17] PDT uses a photosensitizer, light source, and oxygen to selectively destroy cells. ALA, the most extensively studied photosensitizing agent, is an intermediate in porphyrin biosynthesis. Topically applied ALA penetrates the skin and is converted to protoporphyrin IX (PpIX), photosensitizer which can be activated by light to form a cytotoxic intermediate that selectively destroys target cells.[18,19] ALA-induced PpIX can be activated by a variety of light sources.[20,21] Methyl aminolevulinate (MAOP), a derivative of ALA with higher lipophilicity, has also been used as a photosensitizing agent.[22]

Nybaek and Jemec[17] reasoned that since overlap in therapeutic choices for acne and rosacea was considerable and that ALA PDT was effective against acne,[23] PDT might be an effective treatment of rosacea in patients in whom tetracycline and metronidazole were ineffective or continuous antibiotic treatment was unacceptable. Four patients received 2 or 3 PDT sessions with MAOP (Metvix™, PhotoCure ASA, Norway) incubated for 3 hours followed by activation with 632-nm red diode light (37 J/cm^2) from a Curelight128® (PhotoCure ASA). Treated areas cleared in 3 of the 4 patients. Remission lasted 9 months in 1 patient and 3 months in 2 patients. The authors concluded that PDT may be useful in certain cases of rosacea.

Our study differs from that of Nybaek and Jemec in several important respects. First, Nybaek and Jemec used MAOP photosensitizing agent whereas we used ALA. Metvix Cream is approved in Europe for the treatment of actinic keratosis (AK) of the face and scalp and basal cell carcinoma unsuitable for conventional therapy. Metvix also has FDA clearance for the treatment of AKs, but is not available in the US at the time of this writing.

ALA as Levulan Kerastick has FDA clearance for the treatment of nonhypertrophic AKs of the face and scalp and has been studied extensively for the treatment of acne, photoaged skin, sebaceous hyperplasia, skin cancer, and other cutaneous lesions.[20,21] In our hands, a 15-minute ALA-incubation time with a 15-minute ultrasound treatment to enhance ALA penetration was sufficient to obtain good results. In contrast, like Nybaek and Jemec, the authors of 5 large studies[24-28] reported MAOP incubation times of 3 hours.

In our study, fluences did not exceed 7.5 J/cm^2 for each of 6 treatments. Fluences reported by Nybaek and Jemec, whose patients were treated only 2 or 3 times, were considerably higher at 37 J/cm^2. In the study of Taub,[1] fluences ranged from 27 to 36 J/cm^2 for 1 to 7 treatments. These results suggest that optimal PDT parameters for rosacea require further study.

We conclude that ALA PDT with PDL activation may be an option for the treatment of erythema, papules, pustules, and severe facial flushing in patients who fail conventional pharmacologic therapy or patients who wish to avoid antibiotic therapy for extensive periods.

Disclosure

Dr. Katz is member of the physician advisory board and is a stockholder of Dusa Pharmaceuticals, Inc.

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Case Reports: Treatment of Hyperpigmentation-Melasma with Photodynamic Therapy

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Abstract
Hyperpigmentation-melasma was treated in a 31-year-old female with the application of aminolevulinic acid HCL 20%-single use Levulan® Kerastick® followed by exposure to 10 J/cm^2 of nonlaser blue light. The results have been excellent and long-lasting.

Case Report

A 31-year-old fair-skinned female presented with dark patches on the zygomata, numerous ephelides, and malar hyperpigmentation (melasma) (Figures 1-2). She had a history of eczema as a child, a history of irritable bowel syndrome (IBS), no allergies, and no children. She took Orthotricyclen for 10 years, and Zelnorm 5. A BLU-U/ALA peel was done to eliminate the dark pigmentation and a single use Levulan® Kerastick® (ALA) (aminolevulinic acid HCL 20%) for topical solution was applied to the entire face. She returned the next morning and was exposed to 10 J/cm^2 of nonlaser blue light for 17 minutes (Figure 3). One week later, there was evidence of peeling of the erythematous and darkened areas (Figure 4). Healing was noted after 2.5 weeks with excellent results (Figures 5-6). She was instructed to use a broad-spectrum SPF 30 sunscreen and reapply every 2 hours while avoiding the sun between 10 am and 4 pm (Figure 5). She remains improved to date (Figure 7).

Figure 1. Pigmentation Pre-Treatment.

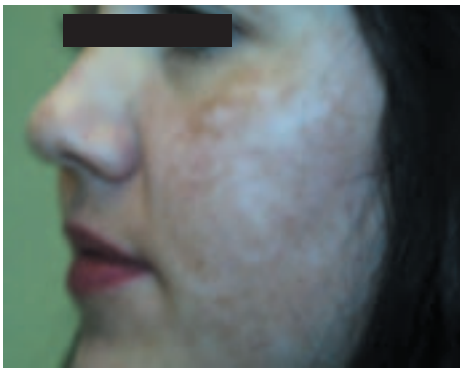


Figure 2. Pigmentation Pre-Treatment.

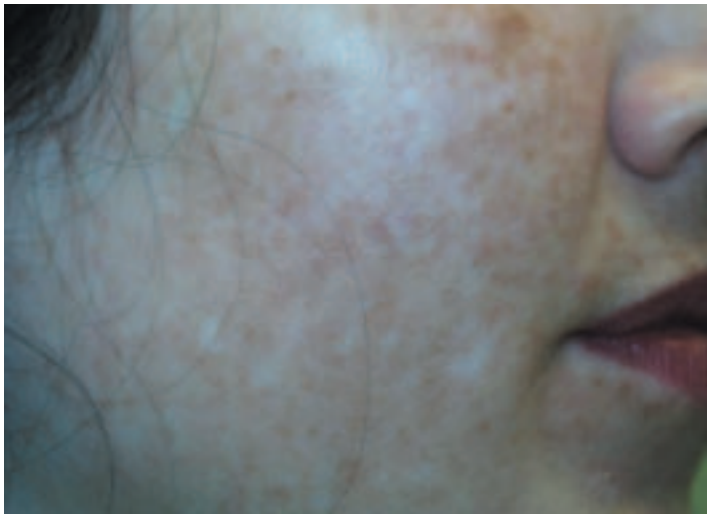


Figure 3. Initial Reaction after Treatment.

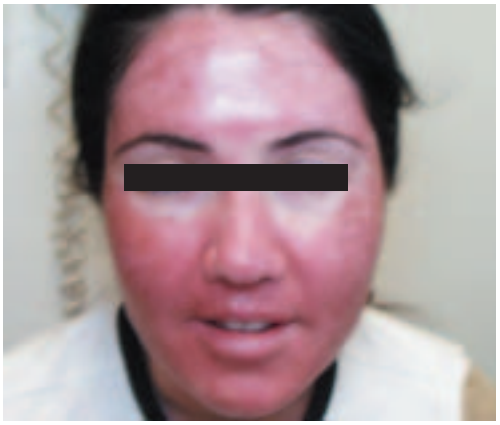


Figure 4. Peeling, Erythema, Darkening—1 Week Post-Treatment.

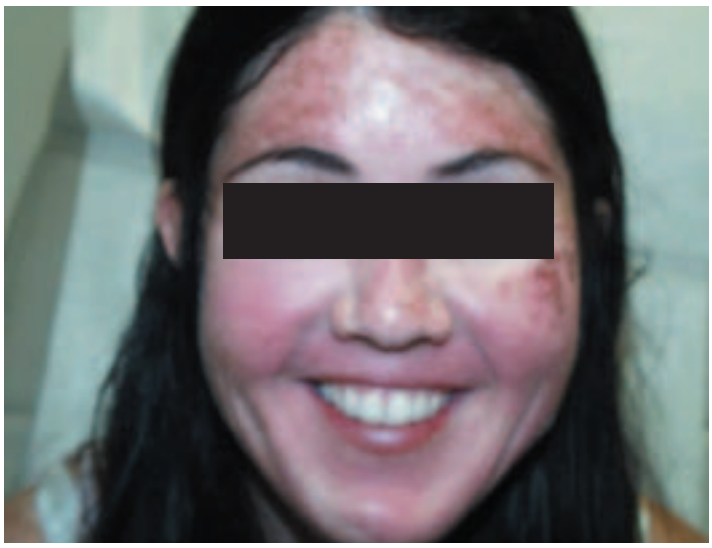


Figure 5. Complete Healing—Approximately 2.5 Weeks Post-Treatment.

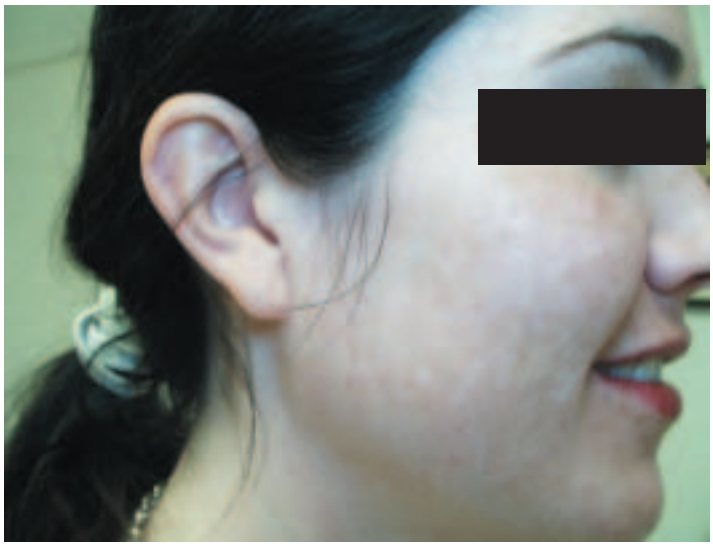


Figure 6. Complete Healing—Approximately 2.5 Weeks Post-Treatment.

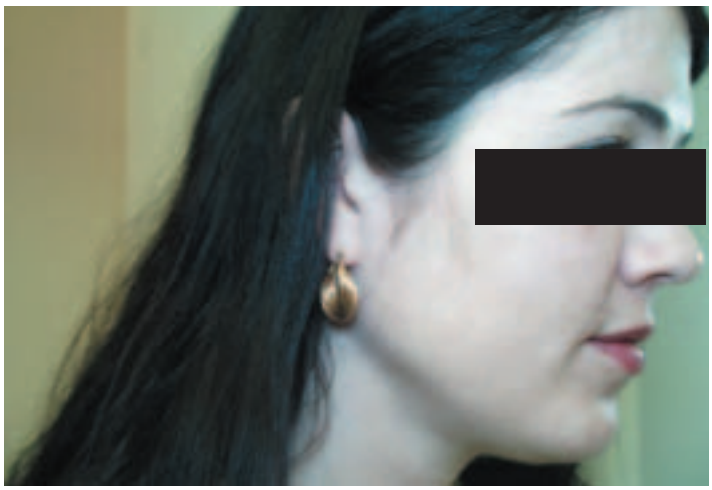
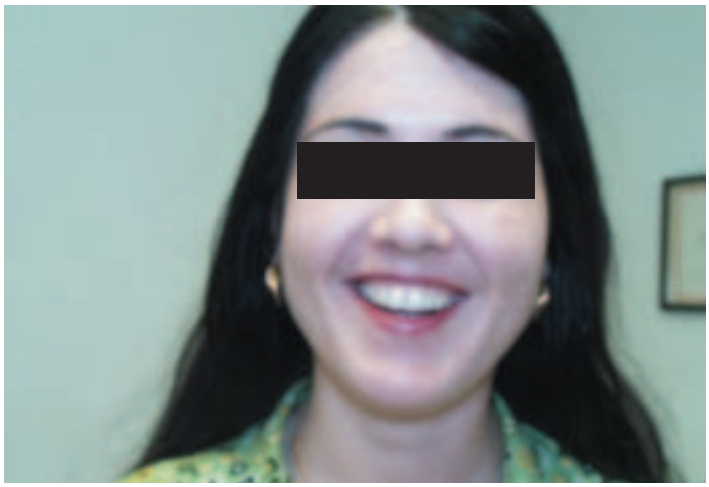


Figure 7. Long-Term Improvement—9 Months Post-Treatment.



Discussion

Melasma may be epidermal, dermal, or mixed. Its pathogenesis is unknown and therapy is often difficult.[1-3] Topical treatments such as hydroquinone,[4] tretinoin,[5] azelaic acid,[6] and combination therapies[7-9] may be successful in epidermal melasma;[3] results with chemical peels are variable.[10,11] Chemical peels[12] and dermabrasion[13] have been successful in dark-skinned patient with recalcitrant melasma. Intense pulsed light[14] and lasers[2,3,15-17] have been used for the treatment of refractory melasma. Complications associated with lasers include hypertrophic scarring, atrophy, and hypo- and hyperpigmentation.[18]

To the author's knowledge, this is the first report to describe the use of ALA PDT in the treatment of freckles and melasma. Topically applied ALA photosensitizing agent, an intermediate in the biosynthesis of heme, penetrates the skin and is converted in the epidermis to protoporphyrin IX (PpIX), a photosensitizer which can be activated by light to form a cytotoxic singlet oxygen.[19,20] ALA-induced PpIX can be activated by a variety of light and laser sources.[21,22]

In this study, excellent cosmetic results were obtained with a single ALA PDT session. The treatment procedure was similar to that reported for actinic keratosis (AK).[23] Since ALA PDT typically results in peeling of the outer layers of skin, it was reasonable to assume that the treatment would remove freckles and melasma-associated pigment in these layers. The patient in this report was very satisfied with the results, which have lasted for at least 9 months.

The author concludes that ALA PDT with blue light may be a treatment alternative to topical therapies for melasma patients unwilling to wait long periods for results. The results of this study warrant additional studies in more patients and with other light sources.

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PHOTODYNAMIC THERAPY FOR PERIORAL DERMATITIS

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Abstract

Background: Treatment of perioral dermatitis (POD) consists of topical steroids, oral antibiotics, and topical antibiotics.

Objective: To evaluate the safety and efficacy of photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA) in the treatment of POD.

Methods: A split-face 21-patient study was conducted in which one side of the face was treated 4 times weekly with ALA PDT (30-minute ALA incubation) with blue light activation and the other side with topical clindamycin. Lesions were counted and photographs were taken before and after the final treatment. Patient satisfaction was also evaluated.

Results: Fourteen patients (66.7%) completed the study. Facial sides treated with ALA PDT achieved a mean clearance of 92.1% compared to 80.9% for the clindamycin-treated sides. The difference was significant (P=0.0227). The mean patient satisfaction level for the ALA PDT-treated side was 4.4 (1-5 scale).

Conclusion: ALA PDT may be a promising alternative to antibiotics for the treatment of POD.

Introduction

A chronic condition with unpredictable flare-ups, perioral dermatitis (POD) occurs mostly in women aged 16 to 45 years. The disease has also been observed in children 7 months to 13 years of age.[1] In children, POD affects boys and girls equally[2] and lesions often appear in the periocular and perinasal areas of the face.[3] POD has been reported in Western Europe, Scandinavia, Australia, and North America.[1]

POD presents as small erythematous papules and papulopustules around the mouth. Lesions are usually absent in a narrow area close to the vermilion but may occur on the chin, nasolabial folds, and periorbital areas. Eyelids may also be involved and pruritus may be present.[1]

The pathogenesis of POD is not completely understood. A variety of agents including hormonal factors, infective agents, glucocorticoids, fluorinated steroids, contraceptive pills, hydrocortisone butyrate, amalgam dental fillings, fluorinated and tartar-control toothpastes, and cosmetics have been associated with this common dermatosis. The occlusive effects of moisturizing creams, which cause skin flora to proliferate, have also been implicated.[1] POD pathogenesis has been related to dry skin and barrier (skin) function impairment.[4] POD has also been reported in renal transplant recipients and patients with ulcerative colitis receiving systemic corticosteroids.[5] Inhaled steroids have caused POD in asthmatic children.[1]

Patients with POD are intolerant of sunlight, but this is not always a prominent feature. Untreated, POD may persist for months or years, especially in patients who use topical steroids frequently.

Treatment options for POD consist of both topical and systemic agents. Topically, clinicians may substitute a low-potency steroid (hydrocortisone cream) to prevent a flare-up.[6,7] Other choices include erythromycin as a solution (1.5%-2%) or in combination with hydrocortisone,[7] metronidazole cream (1%)[8] or gel (0.75%),[9] isotretinoin (granulomatous POD),[10] sulfacetamide and hydracortisone,[11] tetracycline,[6-8,12-14] clindamycin,[1] or azelaic acid.[15] For treatment of POD lesions on the face, the authors have used low-potency nonfluorinated corticosteroids, topical antibiotic solutions, and oral antibiotics (tetracycline or related agents).

Oral tetracycline is the most effective antibiotic for the treatment of POD,[1] but its use (and that of other antibiotics) is contraindicated in children less than 8 years of age and in pregnant women, in whose age group POD is most prevalent. Tetracycline may also cause nausea, vomiting, and phototoxicity.[15] Other systemic choices include doxycycline, minocycline, erythromycin, cotrimoxazole, and combinations of sulfamethoxazole and trimethroprim.[1,16]

Oral tetracycline in combination with topical sulfacetamide-hydrocortisone lotion has resulted in complete clearing.[11] Erythromycin (oral or topical) or topical metronidazole may be substituted for tetracycline, but both are less effective.[7] In addition, since patients with POD often have unusually high skin sensitivity, topical medications may be poorly tolerated.[15]

Finally, POD is not among the FDA indications for tetracycline, erythromycin, and topical metronidazole.[17]

These limitations, along with reluctance or refusal of patients to take oral or topical antibiotics, prompted us to search for a safe and effective treatment of POD that might eliminate or reduce the need for antibiotics. Our search led to photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA).

ALA PDT augments the effects of light therapy. A precursor of porphyrins, topically applied ALA penetrates the skin and is converted in tissues to protoporphyrin IX (PpIX), which can be activated by various light sources to form cytotoxic singlet oxygen.

The major advantage of ALA PDT is its selectivity. Topically applied ALA penetrates the stratum corneum of abnormal epidermal cells more rapidly than it penetrates the stratum corneum of normal epidermal cells. As a result, ALA-induced PpIX accumulates preferentially in abnormal cells. Since PpIX accumulates only in the epidermis, exposure to light of the appropriate wavelength destroys abnormal cells only in the epidermis.[18]

The U.S. Food and Drug Administration (FDA) has cleared Levulan® Kerastick® (5-aminolevulinic acid HCl, Dusa Pharmaceuticals, Inc., Wilmington, Mass.) for the treatment of multiple non-hypertrophic actinic keratoses on the head and scalp and the BLU-U® Blue Light Photodynamic Therapy Illuminator for the treatment of actinic keratoses. ALA PDT has also been used in our practice[19] and by others[20-22] to treat sebaceous hyperplasia and by many[23-28] to treat acne vulgaris. The technique has also been used to treat photodamage, basal cell carcinoma, Bowen's disease, squamous cell carcinoma, and other cutaneous diseases.[29]

The purpose of this article is to evaluate the efficacy and safety of ALA PDT in the treatment of POD.

Materials and Methods

Twenty-one patients (19 women) aged 10 to 70 years (mean 36.5) with Fitzpatrick skin types II to IV and recurrent POD participated in a prospective split-face study conducted over 6 months. Patients had lesions consistent with POD for 0.5 to 120 months (mean 5.0, 120 months omitted from calculation of mean) and no other skin diseases. In all patients, lesions were present for more than 1 month and diagnosis of POD was made at least 1 month before treatment. One side of the face was treated with ALA PDT and the other side with topical clindamycin. In most cases, the side with the highest number of lesions was treated with ALA PDT. Before entering the study, patients had previously taken OTC topical antibiotics, corticosteroids, or both. Patients had at least 3 facial lesions (identified by clinical observation) on each side of the face. Women who were pregnant or breast feeding were excluded. All patients gave signed informed consent.

The ALA PDT-treated side of the face was washed with acetone before applying ALA (Levulan Kerastick) photosensitizing agent. Epidermal pain or irritation due to acetone application was not observed. ALA was applied only to areas of lesions. The clindamycin-treated side was treated daily with clindamycin phosphate gel (Clindagel, Galderma), but not washed with acetone before application of clindamycin. ALA was not occluded during its 30-minute contact with lesions. ALA was wiped away and lesions were immediately treated with 410-nm blue light (BLU-U®) for 8 minutes. Pain during exposure to light was minimal and did require anesthesia or cooling. Patients who completed the treatment program received an average of 3 weekly treatments (range 1-4), each over 1 month. After treatment, patients were instructed to avoid sun exposure for 48 hours. Corticosteroid treatment (topical and systemic) was not permitted. Patients requiring topical corticosteroid to counteract photosensitivity reactions were dropped out of the study.

Responses were considered complete if no lesion could be seen at the treatment site. Patients graded satisfaction with treatment on a scale of 1 to 5, with 5 denoting complete satisfaction. Results of treatment were evaluated by (1) comparing pre- and posttreatment photographs, (2) clinical evaluations of the extent and number of POD lesions before and after treatment, and (3) evaluating a patient-satisfaction survey after treatment.

Results

Results are presented in Table 1. Fourteen patients (66.7%) completed the study. All received 4 treatments to achieve complete or nearly complete clearance by either modality. The mean baseline lesion count for the ALA PDT-treated side (18.5) was significantly higher (p=.0126) than the corresponding mean for the clindamycin-treated side (12.8). The mean posttreatment lesion counts (1.4 [ALA PDT] and 2.3 [clindamycin]), however, did not differ significantly (p=.1440). Mean lesion counts before treatment differed significantly from posttreatment lesion counts by both treatment modalities (p<.0001 and p=.0001 for ALA PDT and clindamycin, respectively).

The facial sides treated with ALA PDT achieved a mean clearance of 92.1% compared to 80.9% for the clindamycin-treated sides. (Clearing of lesions is defined as the absence of erythema or palpable lesions.) The difference was significant (P=.0227). In 9 of the 14 patients, clearance was greater with ALA PDT. Equal clearance rates were seen in 2 patients. In 3 patients, clearance was greater on the clindamycin side of the face. Most patients who had low clearance rates achieved it on both sides of their faces. The mean patient satisfaction level for the ALA PDT-treated side was high at 4.4. Mild postinflammatory hyperpigmentation occurred in 3 patients and was treated successfully with hydroquinone (4%). Seven patients (33.3%) did not complete the study due to skin photosensitivity irritation caused by failing to avoid sun exposure for 48 hours after treatment.

Figures 1 and 2 show the treatment results for patients 12 and 3, respectively. Figure 1b shows complete clearance of the ALA PDT-treated papules on the right nasolabial area and partial clearance of the clindamycin-treated lesions on the left lower chin (1-2 lesions). The 1-mm papules (n = 3-5) below the nares (bilateral) appeared after the treatment period and were not treated by either modality.

Figure 2b shows complete clearance of the ALA PDT-treated papules on the right nasal ridge, chin, and right angle of the mouth. Lesions on the right upper lip (n=4) are partially resolved. On the clindamycin-treated side, 11 inflammatory papules were present on the lower left nasolabial fold before treatment and 5 remained after treatment.

Table 1. Lesion Counts and Clearance Rates of Patients with POD* Treated with ALA PDT† and Clindamycin in a Split-Face Study.

Patient	Age/Sex	Duration (mo.) of POD	No. of Lesions ALA PDT Baseline/1 Mo.	No. of Lesions Clindamycin Baseline/1 Mo.	Clearance (%) ALA PDT/Clindamycin	Satisfaction Level (1-5 Scale)
1	31/F	3	12/0	8/1	100/88	5
2	14/M	1‡	10/0	11/2	100/82	4
3	89/F	6	9/0	11/5	100/55	5
4	27/F	0.5‡	17/0	20/1	100/95	5
5	10/M	2	14/0	10/0	100/100	4
6	49/F	2	30/3	5/2	90/60	5
7	50/F	3	10/4	6/3	60/50	4
8	30/F	6	17/0	12/0	100/100	5
9	35/F	3	17/1	5/0	94/100	5
10	48/F	10	9/1	3/0	89/100	5
11	41/F	24	31/3	23/1	90/96	4
12	42/F	3	30/3	30/5	90/83	4
13	49/F	120§	36/0	22/5	100/77	5
14	47/F	2	17/4	13/7	76/46	2
Mean	40.1	5.0	18.5/1.4	12.8/2.3	92.1/80.9	4.4
SD	19.1	6.4	9.3/1.6	8.0/2.3	11.6/20.1	0.8
95% CI	29.1-51.2	0.8-8.5	13.3-23.9/0.4-2.3	8.2-17.4/0.9-3.6	85.4-98.8/69.3-92.4	3.9-4.9
Diff. Between Means	—	—	17.1	10.5	11.2	—
Paired T statistic	—	—	7.1	5.3	2.6	—
P (2-tailed)	—	—	<0.0001	0.0001	0.0227	—

* Perioral dermatitis.
† 5-Aminolevulinic acid-photodynamic therapy.
‡ Patients presented with a 1- and 0.5-month histories of lesions consistent with POD. Diagnoses were established for both at least 1 month later.
§ Omitted from statistical calculations.

Discussion

To the authors' knowledge, this is the first study to evaluate the use of ALA PDT for the treatment of POD. Our results show that for 11 of 21 patients (55.4%), equal or greater clearance of POD lesions was achieved with 4 ALA PDT treatments spaced 1 week apart compared to daily topical applications of clindamycin. The results of the ALA PDT-treated sides were more consistent as shown by the 11.6 SD compared to the 20.1 SD of the clindamycin-treated sides. Thirteen of the 14 patients who completed the study expressed satisfaction at the 4 or 5 level with the ALA PDT treatment. The single patient with a 2 satisfaction level achieved a low clearance rate by both treatments.

Refractory lesions were dispersed and had no unique physical characteristics. No relationship was apparent between response to treatment and number of lesions at baseline, duration of treatment, Fitzpatrick skin type, dryness or oiliness of skin, use of cosmetics, allergies, use of topical steroids, or noncompliance. We suggest that clearance is due

Figure 1. (left) A pretreatment photograph of a 42-year old woman (Patient 12, Table 1) who presented with a focal grouping of erythematous papules on the right nasolabial area and discrete lesions on the left lower chin and at the right angle of the mouth. Lesions had been present for 6 months. The right side was treated by photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA) and the left side was treated with clindamycin. The "shiny" appearance is due to the ALA application. (right) The same patient after 4 treatments.

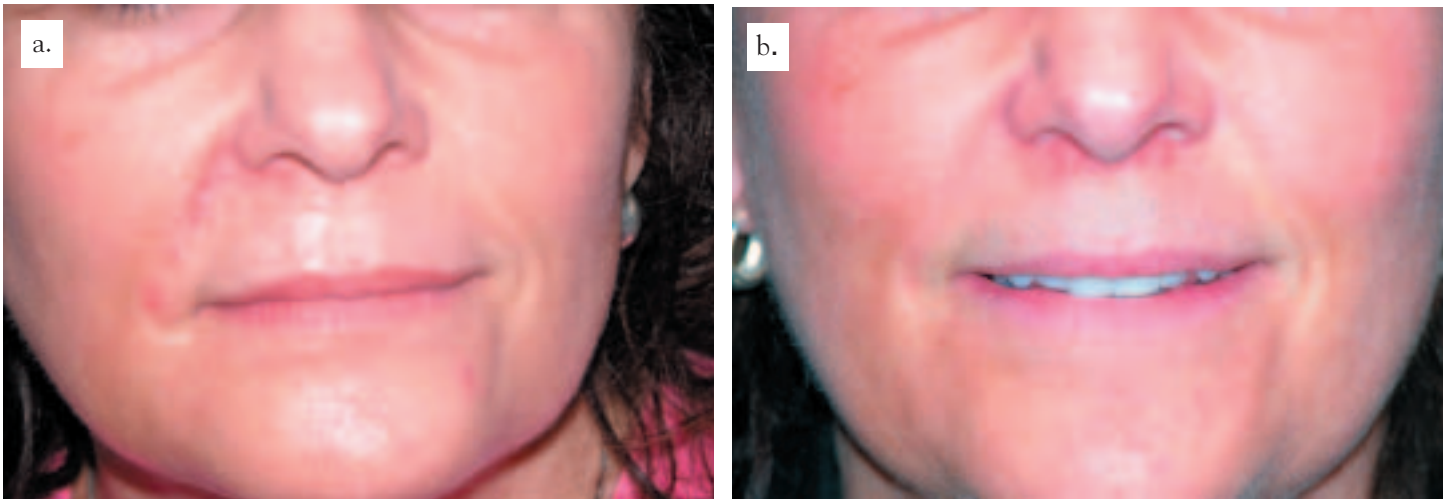
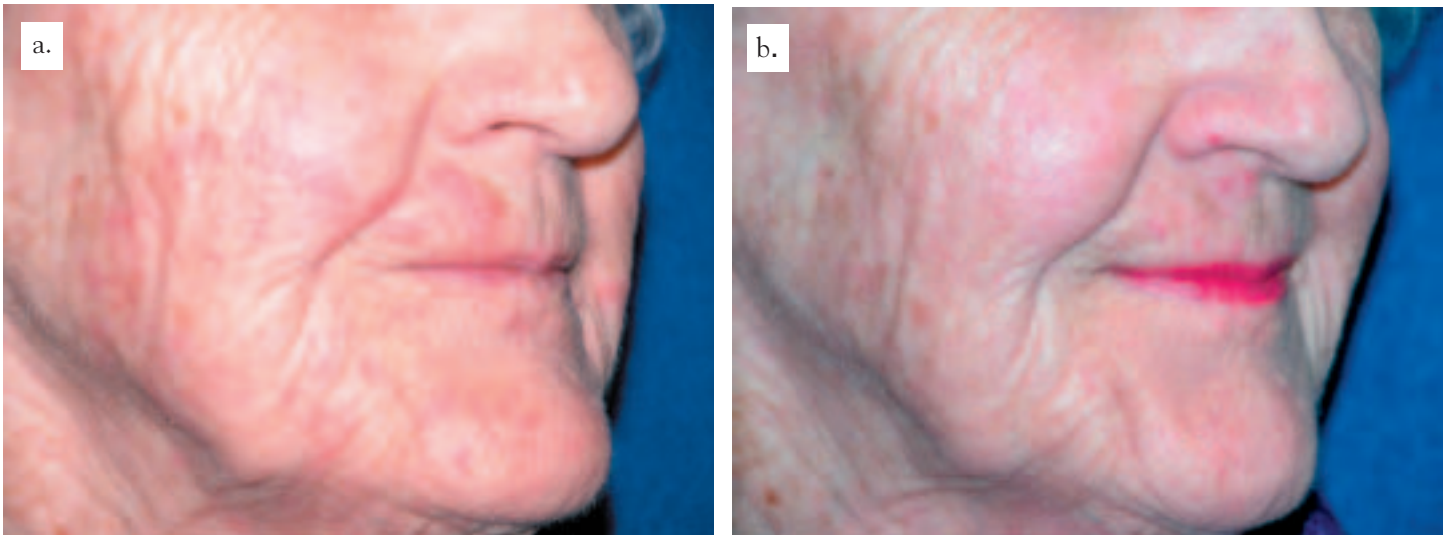


Figure 2. (left) A pretreatment photograph of an 89-year-old woman (Patient 3, Table 1) who presented with a cluster of erythematous papules (1-2 mm) on the right nasal ridge, right upper lip, right chin, and right angle of the mouth. Lesions had been present (sporadically) for 5 years; her most recent outbreak occurred 6 months before the study. Photograph was taken before the first treatment session. The right side of the face was treated by photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA) and the left side was treated with clindamycin. (right) The same patient after 4 treatments.



to absorption of ALA by (sebaceous) glands and destruction of both overactive glands and bacteria by cytotoxic singlet oxygen generated by ALA-induced PpIX.

Seven patients (33.3%) withdrew from the study due to skin irritation caused by post-treatment photosensitization. They tolerated ALA PDT well but failed to comply with instructions to avoid sun exposure for 48 hours after treatment. In all patients the irritation was resolved by topical corticosteroid treatment. Expense and lack of coverage by insurance companies may be other drawbacks to this modality.

The primary strength of this study is the clarity and consistency of the results as revealed by the photographs, lesions count data, and statistical analysis. The data show that ALA PDT may be a treatment alternative for POD in patients who cannot or prefer not to take antibiotics for extended periods. The age range of patients (10-89 years) was wide; all but 2 patients were women, a typical POD

population, and 2 children (ages 10 and 14) were included. The small number of patients and the absence of data on long-term benefits are the primary limitations of this study.

The importance of ALA PDT in dermatology is expected to increase. The technique has been made more practical by shortening ALA incubation times. Erythema, edema, and crusting after treatment are being minimized as researchers refine treatment parameters. In exploring off-label uses of ALA PDT in both medical and cosmetic dermatology, investigators have shown that red light, pulsed dye lasers, and pulsed light as well as blue light can be used to activate ALA-induced PpIX.[29,30]

Conclusion

Given once weekly for approximately 4 weeks, ALA PDT offers a treatment option for POD in patients who cannot or prefer not to take systemic medication or apply topical medication daily for extended periods. Further studies comparing ALA PDT with other antibiotics and determining the duration of benefit are warranted to confirm our results.

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CURRENT TREATMENTS OF ACTINIC KERATOSIS

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Abstract

Actinic keratosis (AK) lesions should be treated because they may evolve into lesions clinically indistinguishable from those of invasive squamous cell carcinoma which require expensive therapy. Treatment options for AK include cryosurgery, curettage and excisional surgery, dermabrasion, chemical peels, laser resurfacing, 5-fluorouracil (5-FU), imiquimod, diclofenac, and tretinoin, each with advantages and limitations. Clinical trial results show that photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) is an effective and safe treatment of nonhypertrophic AK lesions of the scalp and face. ALA-induced protoporphyrin IX may be activated by a variety of light sources. ALA incubation times of 1-hour make ALA PDT a practical procedure for the treatment of AK lesions. Clinical trials show that PDT with methyl aminolevulinate (MAOP) is also a safe and effective treatment of AKs of the face and scalp; MAOP is available in Europe but not in the US at the time of this writing. ALA PDT offers efficacy against multiple AKs without the adverse effects of 5-FU or imiquimod.

Introduction

Skin undergoes both chronological and sun-induced aging.[1] Aging due to chronic exposure to ultraviolet (UV) light of the sun—called photoaging—is cumulative and superimposed onto chronological aging. Actinic keratosis (AK) has been described as a "key event" as photoaged skin evolves into invasive squamous cell carcinoma (SCC).[2] UVB (>280-315 nm) is responsible for UV-induced carcinogenesis.[3,4]

AK is the second most frequent reason that people consult a dermatologist.[5] AK is characterized by dysplasia of keratinocytes in the epidermis.[6] Risk factors for AK and SCC include long-term sun exposure, advanced age, fair skin, immunosuppression, and genetic diseases such as xeroderma pigmentosum.[7-9] Lesions typically present as red, scaling papules or plaques 1 to 3 mm in diameter. Lesions may be numerous, diffuse, and up to several centimeters in size, particularly on sun-exposed areas of the skin. They occur on a bald scalp, face, back of the hand,[7] forearm, and neck.[3] They may thicken and progress to lesions clinically indistinguishable from those of SCC. Clinical variants include pigmented AK, cutaneous horn, lichen planus-like keratosis, and actinic cheilitis.[7]

AK has traditionally been considered premalignant. However, AK lesions may progress from the epidermis to the dermis[8] and metastasize, and thus are similar to lesions of Bowen's disease (SCC *in situ*), intraepithelial Merkel cell carcinoma, sebaceous carcinoma, and melanoma.[6] Estimates of the risk that an AK lesion will progress to invasive SCC range from 0.025% to 16% per year.[10] Hurwitz and colleagues[11] reported that 97% of SCCs were associated with nearby AKs whereas Dinehart and colleagues[12] reported that nearby AKs were found in 44% of skin lesions that had metastasized. Jeffes and Tang[8] estimated that 60% of SCC lesions probably arise from AKs.

AK and SCC lesions share many features of malignancy. In both types of lesions, keratinocytes have lost polarity, nuclei are pleomorphic, cellular maturation is disordered, and high numbers of atypical and pleomorphic mitotic figures are present.[13] In addition, mutations of p53 genes are identical.[14] P53 mutations are found in most AKs, more than 90% of SCCs, and most basal cell carcinomas (BCCs).[4]

The development of SCC lesions has been studied in mice. SCC lesions develop in 3 stages: initiation, promotion, and progression.[15] Initiation occurs when UV radiation or a carcinogen causes mutation of specific genes in epidermal cells. Promotion occurs as initiated epidermal cells proliferate and result in the development of clonal benign lesions. Progression occurs (rarely) when further DNA damage causes benign cells to become SCC cells. It is recognized that apoptosis (the mechanism by which skin cancer is prevented) is regulated by 3 genes (p53 [tumor suppressor], bcl-2 [inhibition of apoptosis], and Fas [apoptosis signaling].[16] When p53 becomes mutated, the apoptotic process is upset.[4] It is not known why some UV-induced AK lesions progress and others do not.[16] A recent study[16] suggests that an inflammatory response may be associated with progression of AK to SCC.

Treatment

Actinic keratosis is regarded by some investigators as an *in situ* malignancy that may regress, remain unchanged, or progress.[6] Although the destiny of a given lesion is uncertain, all AK lesions should be treated to prevent progression to invasive SCC and more costly therapy.[17]

Destructive Treatments

A variety of medical and surgical options are available for the treatment of AK. Physicians and patients must consider efficacy (short and long term), tolerability, convenience, cosmetic outcome, and cost. More than 90% of AKs treated in the US are treated by destructive therapies (eg, cryosurgery).[5]

When the number of AK lesions is less than 15, cryosurgery with liquid nitrogen has been the standard treatment[18,19] because its reported cure rate is 98%[5,20,21] and local anesthesia is usually not required.[18] A recent prospective, multicentered trial[22] of 90 typical patients with AK, however, showed that

complete response (CR) rates for cryosurgery are considerably lower than 98% and that success of treatment depends on the duration of freezing. In this study, CR rates were 39%, 69%, and 83% at <5 s, >5 s, and >20 s freeze times, respectively. For individual lesions, the overall response rate was 67.2% (60.4%-74.1%, 95% CI). Adverse events, although mild and well-tolerated, included pain during treatment and hypopigmentation after healing.

Curettage (with or without electrosurgery) and excisional surgery are alternatives to cryosurgery. Unlike cryosurgery, curettage and excisional surgery allow for tissue samples to rule out SCC. On the other hand, scarring may occur and local anesthesia is usually required with curettage.[18] Another disadvantage is that curettage, excisional surgery, and cryosurgery are ineffective against subclinical AKs.

Dermabrasion, chemical peels, and laser resurfacing are less commonly used modalities for AK removal. Patients treated with dermabrasion remained free of AK lesions for at least 4 years, much longer than patients receiving cryosurgery, 5-fluorouracil (5-FU), or chemical peels.[23]

Topical 5-Fluorouracil and Other Therapies

Topical therapies, particularly 5-FU, are appropriate when many AKs are present. 5-FU has been the standard of care for diffuse AKs[24] because it is easy to apply, effective, and inexpensive for multiple, diffuse, and microscopic lesions.[25] 5-FU inhibits DNA synthesis in hyperproliferative keratinocytes without damaging normal skin cells.[26,27] 5-FU is also associated with significant erythema, crusting, and scaling. Although 5-FU accounts for less than 4% of treatments of AK, some Medicare carriers require that AKs be treated with 5-FU before other modalities are used.[28] Patients for whom 5-FU is indicated must be carefully selected for their ability to cope with "normal" adverse effects (pain, pruritus, burning, erythema, inflammation, erosions) and be willing to apply the medication twice daily for 2 to 4 weeks. Patients must avoid sunlight during treatment and take care when applying the medication near the eyes, nose, and mouth. 5-FU can worsen rosacea and acne and allergic reactions to 5-FU or vehicle may be severe.[5,18]

Formulations of 5-FU have been developed in an effort to reduce skin irritation. Weiss and colleagues[29] found that a once-daily dosing of 0.5% fluorouracil cream with a microsphere vehicle was effective against AKs, although facial skin was still irritated. In 2 other studies comparing the 0.5% formulation to the 5% formulation, AK clearances were similar with both formulations but side effects were also comparable.[5]

5-FU is available commercially as Efudex® (Valeant Pharmaceutical International), Fluoroplex® (Allergan Inc.), and Carac® (Dermik Laboratories).

New Topical Agents

Imiquimod (Aldara®, 3M Pharmaceuticals) is FDA cleared for the treatment of AKs, superficial BCCs, and condylomata acuminate.[30] As an immune response modifier, imiquimod stimulates the production of interferon α, tumor necrosis factor α, and interleukin 12. The resulting cytokine cascade may elicit a cytotoxic T-lymphocyte immune response. Imiquimod may also stimulate the release of cytokines from macrophages, monocytes, and dendritic cells.[30,31] When given 3 times weekly for 16 weeks in 2 phase 3 trials, imiquimod reduced baseline lesion counts by 86.6% compared to 14.3% in vehicle-treated groups. Complete clearance was achieved in 48.3% for imiquimod-treated patients compared to 7.2% for vehicle-treated patients.[31] Adverse effects were similar to those associated with 5-FU treatment.

A non-steroidal anti-inflammatory drug, diclofenac (3% in 2.5% hyaluronan gel, Solaraze®, Doak Dermatologics) applied daily for 90 days in patients with AK resulted in complete resolution of 40.5% of patients in a randomized, double-blinded, placebo-controlled trial.[32] The treatment was well-tolerated with mild skin effects in both groups. Efficacy was reduced, however, if the drug was used for periods less than 3 months.[5]

Tretinoin (Retin A®/Renova® [OrthoNeutrogena]), adalpene (Differin®, [Galderma]), and tazarotene (Tazorac®/Avage® [Allergan Inc.]) are other topical options. Tretinoin has been shown to reduce AK lesion counts by 50% or less after long-term therapy[33,34] and may be appropriate as a prophylactic medication.[5,33]

Photodynamic Therapy with 5-Aminolevulinic Acid

The use of ALA PDT for the treatment of AK began to take hold when Kennedy and coworkers introduced topical ALA as a photosensitizing agent.[35,36] ALA was applied to the skin and allowed to remain in place (incubate) for 3 to 6 hours. ALA-induced PpIX was activated by filtered light from a slide projector. A CR (ie, no evidence of tumor) was obtained in 9 of 10 AK lesions.

The work of Kennedy and colleagues stimulated researchers to experiment with a variety of light sources to activate ALA-induced PpIX (Table 1). Investigators have used a xenon lamp[37] argon pumped dye laser,[38,39] filtered halogen lamp,[40,41] slide projector,[42,43] Waldmann halogen,[44,45] non-laser blue light,[46,47] long-pulse pulsed dye laser,[48] and pulsed light[49] for activation. ALA incubation times ranged from 3 to 24 hours and most protocols required occlusion to assure adequate penetration of ALA and conversion to PpIX. In most cases, CR rates for AK lesions exceeded 75% with a single treatment. Adverse effects included localized erythema and edema as well as mild stinging and burning during light treatment. Hypertrophic lesions responded incompletely to treatment.[39,40]

Clinical Trials

The encouraging results of these early studies led to a phase 1 study of ALA mixed in a proprietary emollient vehicle (Dusa Pharmaceuticals) at 3 concentrations. In their Phase 1 study, Jeffes and colleagues[39] showed that topical ALA (10%, 20%, 30%) with activation by 630-nm (red) laser light achieved complete clearance of nonhypertrophic AK lesions on the face and scalp (Table 1). The treatment was well-tolerated.

Table 1. ALA-PDT in the treatment of AKs.

Reference	Light source	Light Dose (J/cm²)	Dose rate (mW/cm²)	ALA (20%) incubation time (hr)	No. of lesions treated	CR rate* (%) (Follow-Up Time)
Kennedy et al[35] and Kennedy et al[36]	slide projector (filtered light) >600 nm	150-300	15-150 (3.5-30 min)	3-6	10	90 (18 mo)
Wolf et al[42]	slide projector (unfiltered & filtered to remove <570 nm)	30-100	50-100 (5-20 min)	4-8 (occluded)	9	100 (3-12 mo)
Morton et al[37]	xenon lamp (615-645 nm)	94-156	55-158	4 (occluded)	4	100 (12 mo) (one AK lesion required retreatment after 2 mo.)
Calzavara Pinton[38]	argon-pumped dye laser (630 nm)	60-80	100	6-8 (occluded)	50	100 (treatment every other day until lesion cleared)
Fijan et al[40]	halogen lamp, red filter	up to 300	150-250 (20 min)	20 (occluded)	43	81.4 (up to 20 months)
Szeimies et al[44]	Waldmann halogen, red light (580-740 nm)	150	160	6 (occluded) (10% ALA)	36	71 (28 days)
Fink-Puches et al[43]	slide projector, unfiltered and filtered (eliminate <515, 530, 570, 610 nm), UVA	5.4-120 (760 UVA)	50 – 100 (38 for UVA)	4-24 (occluded)	251	64
Jeffes et al[39]	Argon pumped dye laser (630 nm)	10-150	up to 150	3 (occluded) (0%-30% ALA)	218	91 (8 weeks, face and scalp; 45% trunk and extremities) with 30% ALA
Kurwa et al[41]	Halogen lamp, filtered (580-740 nm)	150	53-100	4 occluded)	not stated	73 (mean reduction in lesional area)
Markham et al[45]	Waldmann halogen, visible light (580-740 nm)	20	20 (16 min, 40 s)	4 (occluded) (conc. % not reported)	4 (cases, scalp only; diffuse)	75 (6 mo.)
Jeffes et al[46]	non-laser fluorescent blue light (417 nm)	2-10	3-10	14-18	70	66 (8 weeks)
Alexiades-Armenakas et al[48]	Long-pulsed pulsed dye laser (595 nm)	4-7.5 (10 ms duration)	—	3-18	3622	93 (head), 71 (extremities), 65 (trunk) (4 mo.)
Piacquadio et al[47]	Blue light (417 nm)	10	9-11	14-18	1403	83 (8 wk), 91 (12 wk)

*Patients received a single treatment unless stated otherwise.

ALA = δ-aminolevulinic acid; PDT=photodynamic therapy; CR = complete response, the complete removal of tumor at the treatment site.

Adapted and updated with permission from Taub AF. Photodynamic therapy in dermatology: history and horizons. *J Drugs Dermatol.* 2004;3(1 Suppl):S8-S25.

Red light was selected to maximize penetration depth and PpIX activation.

Two years later Jeffes and colleagues[46] reported phase 2 clinical trial results with 20% ALA as Levulan® (Dusa Pharmaceuticals) and blue (nonlaser) fluorescent light (BLU-U® Blue Light Photodynamic Therapy Illuminator, Dusa Pharmaceuticals) rather than red laser light to activate PpIX. The multicenter, randomized, investigator-blinded, vehicle-controlled trial was directed at superficial AK lesions of the face and scalp of 36 patients. The new ALA formulation (Levulan) did not require occlusion to facilitate penetration and conversion of ALA to PpIX. ALA was incubated for 14 to 18 hours.

Blue light was selected for this trial because (1) absorption by PpIX (and subsequent activation) is greater at 417 nm than at 630 nm, (2) laser light is impractical for the treatment of multiple lesions, and (3) the dysplastic keratinocytes of superficial AK are limited to the epidermis. In other words, the increased activation of PpIX by blue light (2, 5, 10 J/cm^2) is a greater advantage than the deeper penetration depth of red light.

The authors reported complete clearance of 66% of AK lesions 8 weeks after a single treatment. Re-treatment of the 16 remaining AKs increased the overall clearance rate to 85% at 16 weeks after the initial treatment. Burning and stinging during light exposure and posttreatment erythema had disappeared within 1 week and 4 weeks, respectively. This study showed that 10 joules/cm^2 of blue light provided maximum clearance of superficial AK lesions.

The results of 2 independent, identical, phase 3 trials have been reported.[47,50] In these studies, 243 patients with 4 to 15 nonhyperkeratotic AK lesions on the face or scalp were randomized to receive either 20% ALA (Levulan) or vehicle that remained in contact with skin for 14 to 18 hours before irradiation with blue light (BLU-U). Follow-up was at 24 hours and 1, 4, 8, and 12 weeks after treatment. Lesions not cleared 8 weeks after the treatment were treated again.

The results are illustrated in Figure 1. After 8 weeks and 12 weeks, respectively, 77% and 89% of patients in the ALA group had at least 75% clearing of lesions, compared to 18% and 13% of patients in the vehicle group. The 89% of ALA-treated patients at week 12 includes patients (30%) re-treated at 8 weeks. After 8 weeks and 12 weeks, respectively, 66% and 73% of patients in the ALA group had 100% clearing of lesions, compared to 11% and 8% of patients in the vehicle group. Individual lesion response rates for the ALA PDT group are shown in Table 1. Cosmetic outcome of treated lesions was rated (by investigators) as good to excellent in 92% of lesions.[50]

Stinging or burning during light exposure decreased or resolved within 24 hours after exposure. Erythema and edema at the treated sites occurred in most patients and improved or resolved within 1 to 4 weeks after treatment. No patient withdrew from the study due to adverse events.

The authors concluded that topical ALA PDT was effective and safe for the treatment of multiple AKs of the scalp and face.

In phase 3 trials, 92% of investigators and 94% of patients regarded cosmetic outcome as good to excellent.[51] Noncutaneous effects associated with treatment were not observed. Temporary localized side effects were reported in both the ALA and vehicle groups.[52]

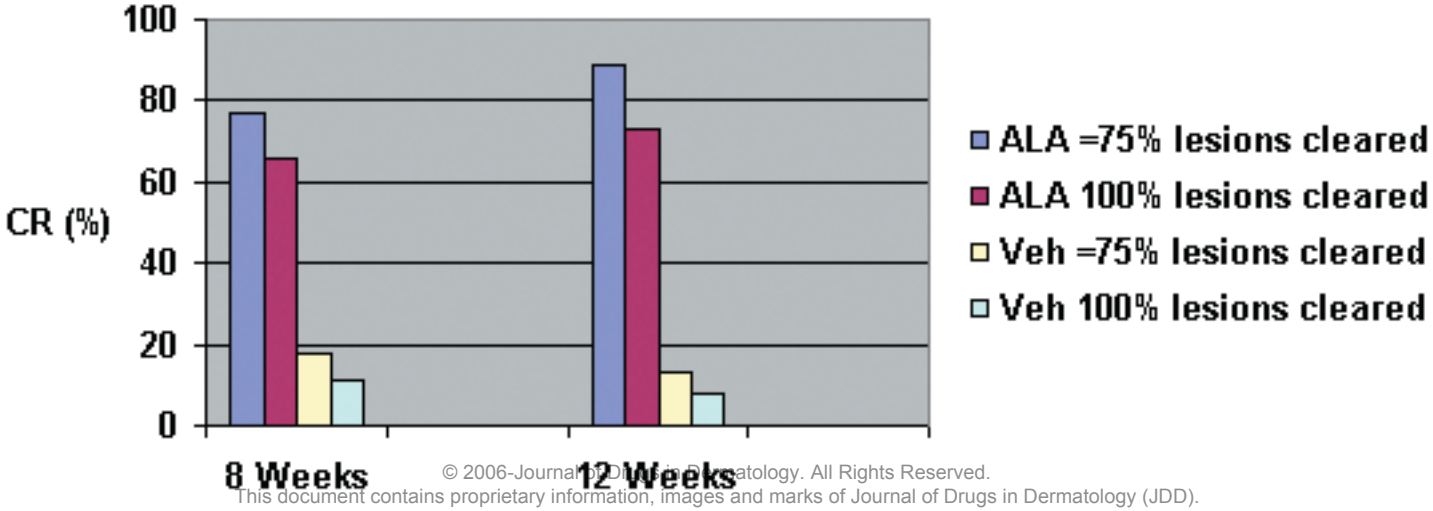
Recurrence Rate

The efficacy and recurrence rate of AK lesions receiving ALA PDT has been reported by Fowler and colleagues.[19] In this study, 69% of 32 lesions in 4 patients were still clear, 9% recurred, and 22% were "uncertain" 4 years after ALA PDT.

Short Incubation

After clinical trials had established the safety and efficacy of ALA PDT, researchers searched for ways to make the procedure more practical for patients seen in the dermatology

Figure 1. Complete response rates of patients 8 weeks and 12 weeks after treatment.[47]
CR = complete response; ALA = 5-aminolevulinic acid; Veh = vehicle.



practice. For example, Touma and colleagues[53] experimented with shorter ALA incubation times in patients with nonhypertrophic AK lesions and facial photodamage. Eighteen patients were randomized to receive topical 20% ALA for 1, 2, or 3 hours before treatment with 10 J/cm^2 blue light. Patients were evaluated at 1 day, 1 week, and 1 month after treatment. Clearance of AK lesions was similar in all 3 groups, indicating that 1-hour ALA incubation was sufficient to clear nonhypertrophic AKs. Improvements were notable in sallowness, fine wrinkling, and mottled hyperpigmentation as well. (In a later report,[54] Touma and colleagues reported that in 1 month, 96%, 94%, and 85% of the target AKs had been removed for the 1-, 2-, and 3-hour ALA incubation groups, respectively).

In a full-face study,[55] Gold incubated ALA for 30 to 60 minutes before treating facial AK lesions of 10 patients with intense pulsed light. After 3 treatment sessions spaced 1 month apart, more than 85% of targeted lesions had responded. Improvement was also evident in crow's feet, tactile roughness, mottled hyperpigmentation, and facial erythema.

In a single-treatment study of 32 patients with multiple AKs and moderate photodamage,[56] Goldman allowed 1 hour ALA incubation before exposing lesions to blue light. 6 months later, 90% of AK lesions had cleared as shown by lesion counts. Skin texture and pigmentation had also improved in most patients, and 62.5% of patients reported less pain with this treatment than with cryotherapy. A patient treated with this protocol is shown in Figure 2.

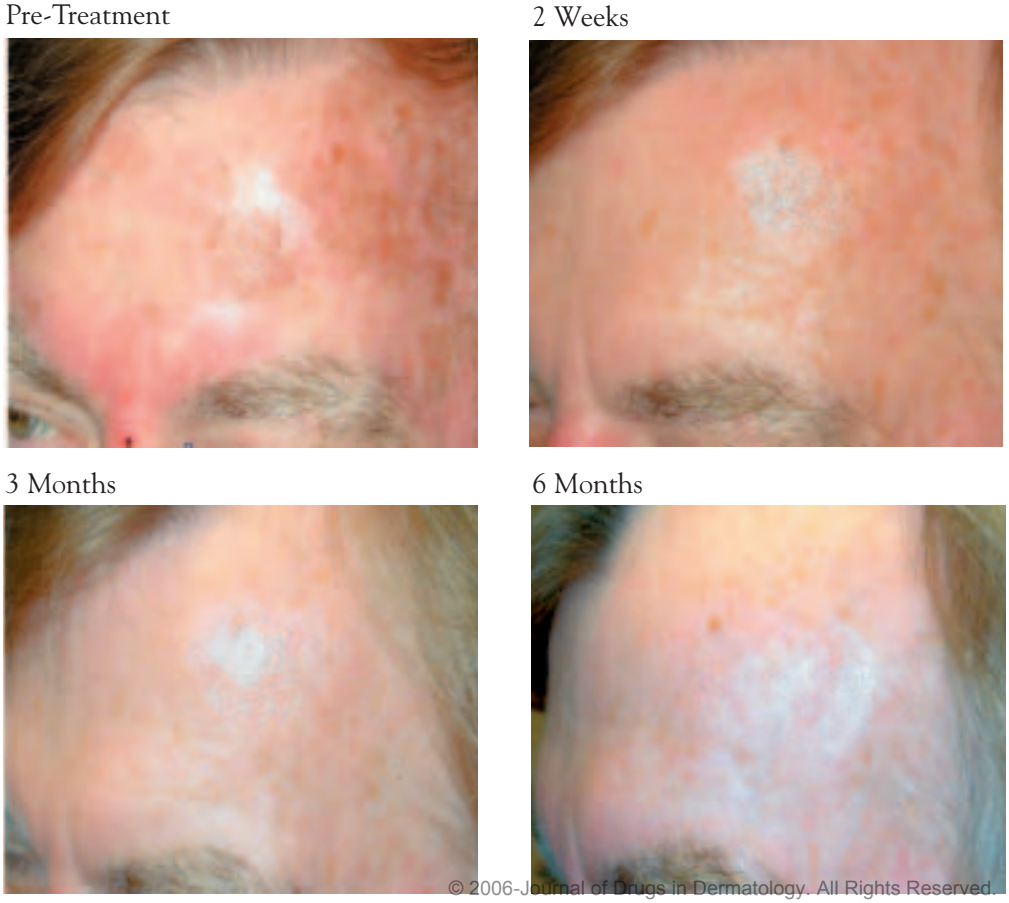
Avram and Goldman[57] retrospectively studied 17 patients treated with ALA PDT for AK, telangiectasias, blotchy pigment, fine wrinkles, and skin coarseness. ALA had incubated for 1 hour before treatment with intense pulsed light. After a single treatment, 68% of AK lesions had cleared and telangiectasias, pigmentary irregularities, and skin coarseness had improved by 55%, 48%, and 25%, respectively. Erythema and edema were mild and temporary.

Together, these studies showed that short-contact ALA PDT is an efficacious and safe treatment of nonhyperkeratotic AKs.

Long-Pulsed Pulsed Dye Laser Activation

Using nonpurpuric treatment parameters, the long-pulse pulsed dye laser (LP PDL) may provide efficacy and safety with minimal discomfort in the ALA PDT treatment of AK.[48] In a recent prospective study, 41 patients with AK lesions received a single ALA PDT treatment with 595-nm LP PDL activation. For comparison, 5 additional patients were treated

Figure 2. Clearance of AK lesions with improvement in skin texture and pigmentation on the left forehead of a patient treated with short-contact ALA PDT.[56]



once with LP PDL alone. Patients receiving ALA PDT were randomized to either 3-hour or 14- to 18-hour ALA incubation. Patients were followed for 10 days, 2, 4, 6, and 8 months after treatment.

Overall ALA PDT results are shown in Table 1. Head lesions (*n*=2,620) showed 99.5% clearance at 10 days, 98.2% clearance at 2 months, 92.9% clearance at 4 months, 91.6% clearance at 6 months, and 90.3% clearance at 8 months. Lesions on extremities (*n*=949) had lower clearance rates (70.9%-100%), as did lesions on the trunk (*n*=53) (65%-85%). Efficacy and safety were the same with 3-hour and 14- to 18-hour ALA incubation. Lesion count did not decrease in patients treated with laser alone.

ALA PDT with LP PDL may also provide safety and efficacy in the treatment of actinic cheilitis (AC).[58] In a proof-of-concept pilot study, 19 patients with AC received 1 to 3 treatments spaced 1 month apart. Two control patients received LP PDL treatment alone. In 68% of ALA PDT patients, complete clearance was achieved after a mean of 1.8 treatments and a mean follow-up time of 4.1 months (range 1-12 months). Seven of the 19 patients achieved 100% clearance after a single treatment. No clearance was apparent in control patients at 1 month.

The authors concluded that ALA PDT with LP PDL at non-purpuric parameters is a safe and effective treatment of AC.

Broad-Area Application of ALA

Another area of interest has been broad-area application of ALA, as with 5-FU. This approach has the potential advantage of clearing subclinical as well as clinical AKs.[59,60] In a 36-patient study, Smith and colleagues[60] compared the efficacy of broad-area ALA PDT with 1-hour ALA incubation to 5-FU treatment of patients with at least 4 nonhyperkeratotic AK lesions. Patients were randomized to receive (1) ALA PDT with blue light activation, (2) ALA PDT with 595-nm pulsed dye laser activation, or (3) 5-FU. Patients received 2 treatments spaced 30 days apart. Four weeks after the second treatment, the individual AK lesion clearance rates were 80%, 50%, and 79%, respectively, showing that broad-area application of ALA with 1-hour incubation and activation by non-coherent blue light resulted in clearance rates comparable to 5-FU, the standard method for multiple AK lesions over broad areas. ALA PDT was also better tolerated.

Encouraged by a report[61] that UV-induced skin tumors were delayed by ALA PDT in hairless mice, Bissonette and colleagues[62] treated skin tumors in hairless mice weekly with ALA alone, blue light alone, or ALA PDT with blue light. They reported that skin tumors did not develop for up to 10 months. Liu and colleagues[63] found that weekly ALA PDT with blue light delayed skin tumor induction in hairless mice exposed daily to UV light. Together, these studies suggested that ALA PDT may be an alternative to 5-FU for the treatment of multiple AKs over broad areas of skin. This was supported by Touma and colleagues,[54] who reported significant AK reduction over broad areas of human skin treated by ALA PDT. These studies also suggest that ALA PDT may delay or prevent skin cancer.

More recently, Gilbert[25] reported that 14 of 15 patients with multiple diffuse AKs maintained 90% lesional clearance 1 year after being treated with 5-FU for 5 days followed by one session of ALA PDT with IPL. The rationale was to substitute ALA PDT for 5-FU before 5-FU-associated skin irritation appeared.

Photodynamic Therapy with Methyl Aminolevulinate

ALA diffuses slowly through cell membranes due to its low lipophilicity. To ensure sufficient accrual of ALA in diseased tissue, a large amount of ALA must be applied to the skin.

To increase diffusion rate, researchers have prepared ALA derivatives of higher lipophilicity, hypothesizing that these ALA prodrugs would enter diseased tissue more rapidly for enzymatic conversion to ALA and formation of PpIX.[64,65] Fritsch and colleagues[66] compared porphyrin accumulation from topical ALA with accumulation from topical methyl aminolevulinate (MAOP). Porphyrin levels were higher in solar keratoses than in the adjacent normal skin for both ALA- and MAOP-treated areas. Results also showed that MAOP was a more specific sensitizer of keratotic cells than ALA.

These studies led to prospective randomized trials of the use of MAOP PDT for the treatment of AK.[67-69] Clinical responses and tolerability with MAOP PDT were comparable to those of cryotherapy in 2 trials[67,69] and cosmetic outcome and patient satisfaction were high in all 3 trials.[67-69]

MAOP PDT has also been used to treat AKs in transplant recipients.[70] Details of MAOP use in other applications have been reviewed.[71,72]

These investigations led to the European approval of MAOP cream (Metvix™, PhotoCure ASA, Norway) for the treatment of AKs of the face and scalp and BCC unsuitable for conventional therapy in 2001, and to the FDA clearance of Metvix for the treatment of AKs in 2004. Metvix is not available in the US at the time of this writing.

Disadvantages of the use of MAOP include having to (1) remove loose crusts, scales, and other debris from lesions to be treated; (2) roughen lesional surfaces to increase access of the cream and red light; and (3) occlude and incubate the MAOP cream for 3 hours before activation by red light.[67-69,73,74] Allergies to ALA[75] and MAOP,[76] though rare, have been reported.

Conclusions

Most AKs are still treated with cryosurgery. 5-FU and imiquimod are effective against multiple AKs, but these treatments are also associated with pain, pruritus, burning, erythema, erosion, and other adverse effects. ALA PDT offers comparable efficacy against multiple AKs without these adverse effects. High rates of complete clearance and cosmetic benefits are additional benefits with ALA PDT.

Disclosure

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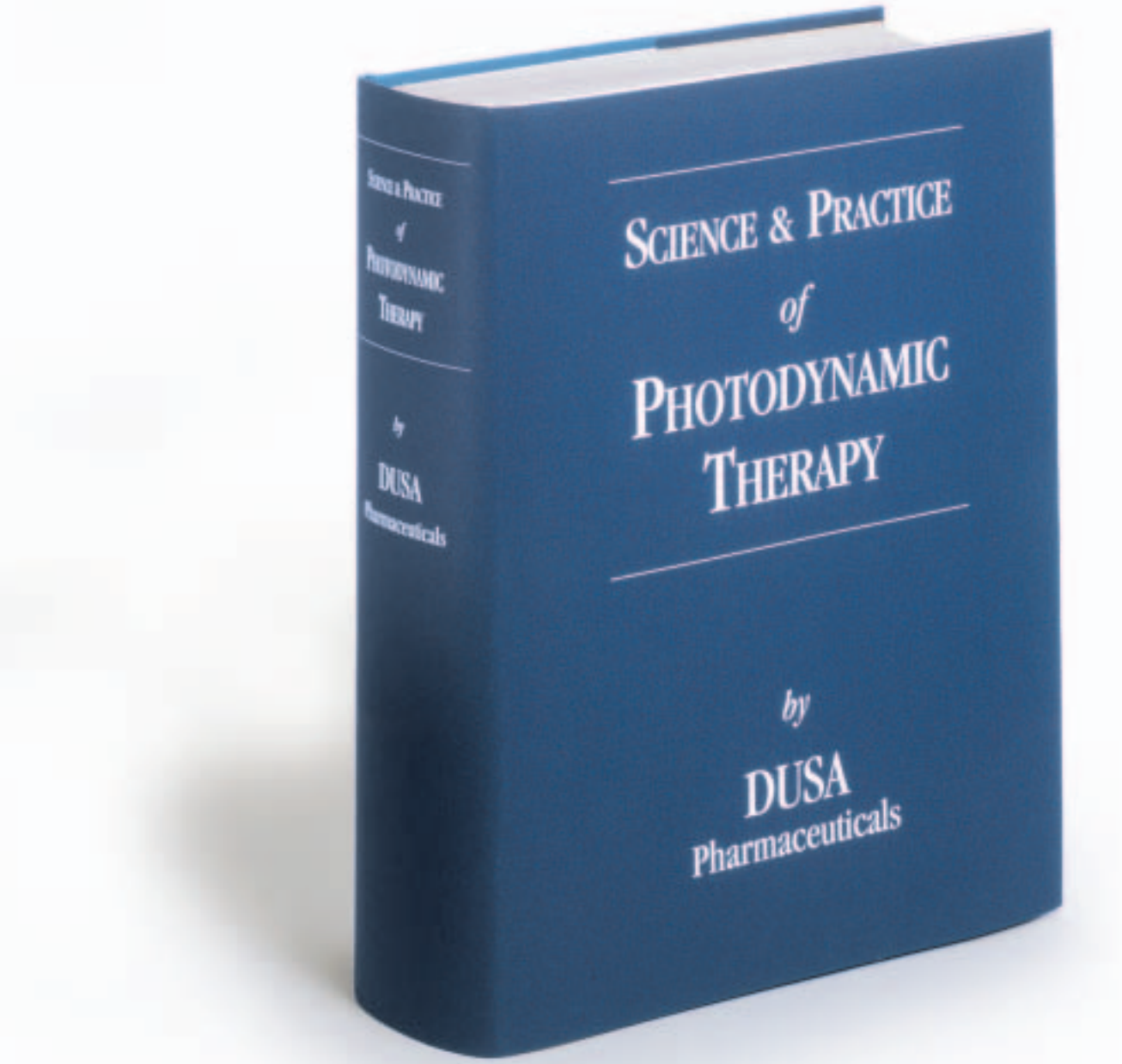

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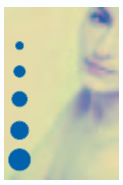

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