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Photodynamic Therapy in Dermatology: **History and Horizons**

Large Surface Photodynamic Therapy with Aminolevulinic Acid: Treatment of **Actinic Keratoses and Beyond**

ALA-PDT and Blue Light Therapy for Treatment of Hidradentis Supperativa

Effectiveness and Safety of ALA-IPL in Treating Actinic Keratoses and **Photodamage**

SUPPLEMENT

• VITILIGO • MELANOMA • PSORIASIS

ACNE • LASE • IMPLANTS • NAILS • IMMUNOMODULATORS

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Journal of
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S1 - S39 Original Articles

FOREWORD

Photodynamic Therapy Comes of Age

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Photodynamic therapy (PDT), utilizing the topical administration of 20% 5-aminolevulinic acid (ALA), has generated widespread interest in the past several years among dermatologists. Numerous dermatologic conditions ranging from actinic keratosis to acne vulgaris have been successfully treated with the combination of ALA-PDT and newer applications with this therapy are emerging making ALA-PDT an exciting therapeutic modality for dermatologists.

This special supplement to the Journal of Drugs in Dermatology contains four important articles on photodynamic therapy. The review article, "Photodynamic Therapy in Dermatology: History and Horizons" by Amy Taub, MD examines the historical roots of PDT from the early 1900's to the introduction of less sensitizing 5-ALA in the 1970's and the cutaneous form of 5-ALA introduced recently by DUSA (Levulan Kerastick). Dr. Taub's exhaustive review details the various cutaneous diseases that have benefited from the use of topical 5-ALA. She then reviews the pros and cons of various light sources (laser and non-laser) in activating 5-ALA and concludes her review with an evaluation of recent applications of PDT in acne and photorejuvenation, and new uses of PDT in dermatology and other areas of medicine.

Bissonnette, Bergeron and Liu present their experience in, "Large Surface Photodynamic Therapy with Aminolevulinic Acid: Treatment of Actinic Keratoses and Beyond." Their article reviews the safety and efficacy of large surface ALA-PDT for the treatment of actinic keratoses and photodamage. They review most of the present literature in this regard with the exception of Goldman and Atkin[1] who studied 32 patients with moderate photodamage and multiple actinic keratoses utilizing short contact, full face ALA and blue light therapy. At the end of the clinical trial, lesion counts revealed a 90% clearance of the actinic keratoses. There was also an improvement in skin texture in 72% and skin pigmentation in 59%. Of note, 62.5% of his patients found this therapy less painful than cryotherapy.

Bissonnette et al. treated nude hairless mice with weekly topical ALA-PDT and demonstrated no episodes of skin tumor formation after 10 weeks. Their hypothesis, based on previous animal studies[2,3] is that large surface ALA-PDT for patients with multiple actinic keratoses and photodamage could theoretically prevent skin cancer appearance by inducing a phototoxic reaction in non-visible lesions. These animal studies suggest that large surface ALA-PDT could be used in patients at high risk of developing skin cancer in order to prevent the development of AKs and SCCs.

Avram and Goldman present the first paper on the use of the Lumenis Intense Pulse Light (IPL) with Levulan™, "Effectiveness and Safety of ALA-IPL in Treating Actinic Keratoses and Photodamage." They performed a retrospective trial on 17 patients treated with ALA-IPL. Patients were evaluated for improvement of telangiectasias, blotchy pigment, fine wrinkles, coarseness of skin, and number of actinic keratoses. All side effects were recorded. Sixty-eight percent of actinic keratoses resolved after one treatment. There was a 55% improvement in telangiectasias, a 48% improvement in pigmentary irregularities, and a 25% improvement in coarseness of skin texture. There was minimal change in fine wrinkle appearance. Side effects were minimal including almost no pain, mild erythema, and edema for 3-5 days on average. Of interest was that one treatment with a 1 hour application of 5-ALA followed by standard IPL treat-

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ment produced clinical "photorejuvenation" results similar to 3-5 monthly treatments with IPL alone. In addition to photorejuvenation, with the IPL, the combined use of 5-ALA also treated a substantial number of actinic keratoses which do not resolve with IPL treatment alone.

The final article in this issue by Michael Gold, one of the most active dermatologist's researching new and improved uses for photodynamic therapy, describes "ALA-PDT and Blue Light Therapy for Hidradenitis Suppurativa." Gold identified four individuals with chronic hidradenitis suppurativa who had not responded to traditional therapy with a variety of topical and systemic agents, as well as intralesional corticosteroid therapy. These patients elected to use ALA-PDT therapy as a last resort prior to contemplating a major surgical procedure or CO_2 laser therapy. All of the patients tolerated the treatments well. There were no adverse effects noted during these treatments. These therapies were pain-free and not associated with any downtime for these patients. While the exact mechanism of action on how this process works in hidradenitis suppurativa still needs to be determined, patients described in this report achieved clearance rates from 75-100% which were able to be maintained at a three month follow-up period.

The future of ALA-PDT appears bright. For many years, dermatologists have hoped that ALA-PDT would leave the laboratory setting and become part of our everyday practices. Cosmetic improvements have been shown in a variety of cutaneous concerns including photorejuvenation and acne vulgaris. Short-contact, full face/broad area ALA-PDT treatments make this therapy more appropriate for the dermatologic community; trials have shown it is safe, efficacious, relatively pain-free, and without significant adverse effects. Clinicians should be ready for these new therapeutic approaches to common skin concerns and may rethink how dermatologists treat photodamage, sebaceous hyperplasia, and acne vulgaris, bridging closer the worlds of medical dermatology and cosmetic dermatologic surgery.

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Photodynamic Therapy in Dermatology: History and Horizons

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Abstract

Photodynamic therapy (PDT) uses a photosensitizer, light, and molecular oxygen to selectively kill cells. When localized in the target tissue, the photosensitizer is activated by light to produce oxygen intermediates that destroy target tissue cells. The easy access of skin to light-based therapy has led dermatologists to apply PDT to cutaneous disorders. In dermatology, PDT has been most successful in treating actinic keratoses, basal cell carcinoma, and Bowen's disease. The introduction of aminolevulinic acid, which does not make patients susceptible to phototoxicity for extended periods, has reduced morbidity associated with PDT. This has led to new interest in PDT not only for nonmelanoma skin cancer and premalignant lesions but also in the treatment of acne and as an adjuvant to photorejuvenation procedures. This review examines the historical roots of PDT and the research evaluating different light and laser sources as well as reports on new horizons for PDT in dermatology.

History

Photodynamic therapy (PDT) is a treatment modality that uses a photosensitizer, light, and molecular oxygen to selectively kill cells[1-3]. When localized in the target tissue, the photosensitizer is activated by light to produce oxygen intermediates[2,4-6] that destroy target tissue cells. The photosensitizer, which may be given exogenously or formed endogenously, is retained more by the target tissue (e.g., a tumor) than by normal surrounding tissue. For light to activate the photosensitizer, the wavelength must be within the absorption spectrum of the photosensitizer[6]. The wavelength determines how deeply the light penetrates into the tissue[6,7].

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The first clinical application of PDT occurred in 1900 when Raab noted that *Paramecium caudatum* cells died quickly when exposed to light in the presence of acridine orange[6]. In 1903, Jesionek and Tappeiner treated skin cancer with light and eosin[7]. In these instances, acridine orange and eosin acted as photosensitizers. Interest in photosensitizers later centered on hematoporphyrin[6] which, when irradiated, fluoresced red to reveal the location of tumors. A more purified hematoporphyrin derivative (HPD, Photofrin)[7] was later used in combination with ultraviolet light to locate tumors, then in combination with visible light to treat tumors[4]. Dolmans and colleagues[2] have presented a simple and informative diagram of PDT history.

The use of PDT in cutaneous and non-cutaneous malignancies was extensively explored by Dougherty, et al.[8-12] Applications of PDT in oncology[2,7,12,13], ophthalmology[13], and dermatology[4,5,13-15] have since been reviewed.

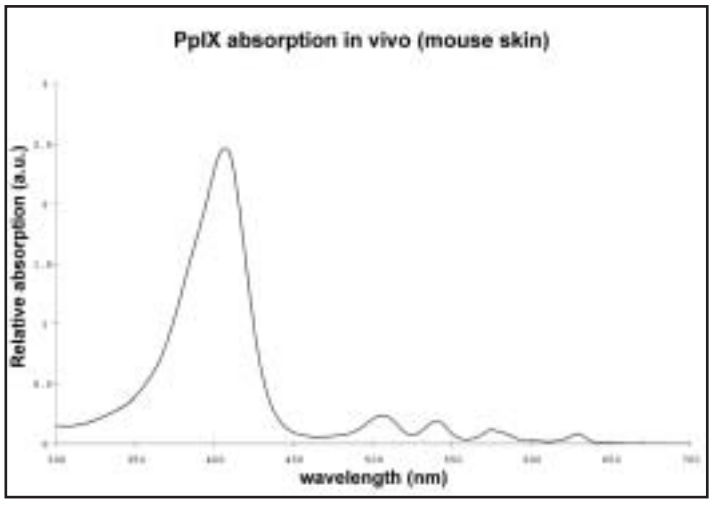
In dermatology, PDT has been most successful in treating actinic (solar) keratoses (AKs), basal cell carcinoma (BCC), and Bowen's disease. This review examines the research culminating in: (1) the 1999 U.S. Food and Drug Administration (FDA) clearance of Levulan® Kerastick® 5-aminolevulinic acid HCl, ALA) for the treatment of multiple AKs on the scalp and head[17], (2) the 2000 FDA clearance of the BLU-U® Blue Light Photodynamic Therapy Illuminator for the AK indication, and (3) the 2001 European approval of topical PDT for the treatment of AK and BCC[18]. The review also describes the pros and cons of light sources (laser and non-laser), recent applications of PDT in acne and photorejuvenation, and new uses of PDT in dermatology and other areas of medicine.

Cutaneous Applications

The easy access of skin to light-based therapy has led dermatologists to apply PDT to cutaneous disorders[6]. Although HPD has been used extensively as a photosensitizing agent, this drug accumulates in skin and clears slowly, resulting in cutaneous photosensitivity that may last several months. During this time, patients are at risk of phototoxic reactions[19].

To avoid prolonged photosensitivity, Kennedy, et al. introduced ALA[19,20], a natural precursor to the protoporphyrin IX (PpIX) formed when ALA enters the tissue. PpIX from the exogenous ALA clears the skin much more rapidly than HPD, thus reducing the time at which patients are at risk for phototoxic reactions. In addition, aqueous ALA passes through abnormal but not normal keratin, thus confining PpIX synthesis to abnormal tissue for subsequent destruction by photoactivating light[19]. This is convenient because the physician need not restrict ALA to the lesion, except perhaps in a patient with sun-damaged or very fair skin[20].

The penetration of topically applied ALA into skin is well established[19,20]. Fortunately, ALA penetrates the skin of BCC tumors more rapidly than healthy skin[21,22] and results in the accumulation of endogenous PpIX,



both by mechanisms not fully understood[23]. The rates of PpIX accumulation and distribution in skin tumors vary with the type of lesion[24-27].

In their dosimetry model for PDT, Svaasand, et al.[28] divide the cytotoxic process with topical ALA into three stages: (1) ALA diffusion through the stratum corneum and into the epidermis and dermis, (2) synthesis of photosensitive PpIX from the exogenous ALA, and (3) production of cytotoxic singlet oxygen when PpIX is irradiated. The time for ALA to penetrate 2.5 to 3.0 mm has been estimated at 3 to 15 hours, depending on the tissue[28].

Using Wood's lamp (ultraviolet light in a dark room), physicians can verify that ALA has penetrated the skin and been converted to PpIX by observing the development of PpIX fluorescence. When ALA-treated lesions are exposed to light for more than 13 hours, patients experience irritation that lasts several minutes before subsiding, leaving the treated tissue edematous. Erythema is also present[20]. Other photosensitizers have been reviewed[2,3,6] but have not yet found extensive use in dermatology.

Traditional Uses in Dermatology

Actinic Keratoses

Prevention of Squamous Cell Carcinoma. Most frequently caused by long-term exposure to ultraviolet rays of the sun, AKs are probably a beginning stage

of a biologic continuum leading to invasive squamous cell carcinoma (SCC)[29,30]. The malignant potential of AKs is supported by studies showing that AKs have the same genetic tumor markers and mutations of tumor-suppressing p53 genes as SCCs of the dermis[31-34]. Which AKs will progress to SCC is not known, and conversion rates range from 0.1% to 20%[35-37]. One study showed that 97% of SCCs were associated with nearby AKs[38] and another showed that nearby AKs were found in 44% of cutaneous lesions that had metastasized[39]. The rate of death from nonmelanoma skin cancer is approximately one-fourth that of melanoma, and 60% of these are due to metastatic SCC[40]. In 2002, 7,000 people died of melanoma in the United States[41]. One could then extrapolate that 1,050 people died from metastatic SCC. AKs should therefore be treated early to avoid malignancy and more extensive treatment[42].

Treatment. AKs have traditionally been treated with cryotherapy, curettage, and 5-fluorouracil (5-FU)[43,44]. Choice of which modality depends on the number of lesions, tolerance, patient satisfaction, and compliance[44]. Standard procedures have some risk of pain, unsightliness, hypopigmentation, hyperpigmentation, and scarring[13]. With its 98% cure rate[45], cryosurgery is considered the standard of care for AK[43] when lesions are few in number[44]. When diffuse actinic damage and/or numerous AKs have been present topical therapies are more appropriate. Although 5-FU has been the gold standard of treatment for diffuse AKs, it is poorly tolerated by many patients due to significant crusting and discomfort that occurs over a period of weeks during and after treatment. Newer topical chemotherapeutic agents include imiquod[46] and diclofenac[47]. Imiquod can also cause significant crusting. Diclofenac has the advantage of being well tolerated by most patients but requires a longer therapeutic window. However, it is not clear if diclofenac is as effective as 5-FU.

The use of PDT and its place among conventional treatments of AK have been reviewed[37,48]. However, past methods of PDT often limited the application of ALA to individual lesions rather than entire skin surface areas. Applying ALA to diffuse areas and capitalizing on its selective uptake by abnormally keratinized cells not only makes it more effective at treating diffuse diseases but also paves the way for PDT to be used for prevention of AK. ALA-PDT utilized in this way could eradicate populations of abnormal cells before they become confluent and manifest as visible AK. In addition, when AKs are extensive, as commonly occurs in the scalps of elderly bald men, standard treatments with topical 5 FU, cryotherapy, curettage, and cautery have limited benefit[49]. Markham et al., using broadband visible light (580-740 nm) at a low dose (20 J/cm^2) and dose rate (20 mW/cm^2), obtained complete responses (CRs) in 3 of 4 elderly men with diffuse, palpable scalp keratoses[49]. The fourth patient showed significant improvement. All patients were of skin type 1 and remission lasted 6 months. Pain during treatment, though significant, did not discourage patients from repeat treatments after 6 months.

In the early 1990s reports appeared on the use of PDT with topically applied ALA for the treatment of both malignant and precancerous skin tumors, including AK[19,50-52] (Table 1) Kennedy, et al. obtained a CR (no clinical evidence of tumor) with 9 of 10 AK lesions[19]. Wolf et al.[50], using 20% ALA, later reported a response in 9 of 9 AK lesions of 3 patients after PDT. Later reports[51,52] led to a prospective clinical study to evaluate the effectiveness and tolerability of PDT in treating AK[16].

In this clinical study, Szeimies, et al., using 10% ALA, applied ALA-PDT once (under occlusion for 6 hours) to 36 AK lesions on the hands, arms, and heads of 10 patients. They irradiated the sites with red light (580-740 nm, 150 J/cm^2) from a nonlaser light source and monitored the patients for 3 months. Twenty-eight days later, complete remission had occurred in 71% of the head lesions. None of the lesions on the hands and arms showed complete remission. Patients reported slight to moderate pain and itching during and after irradiation and the treated areas showed mild to moderate erythema. Cosmetic results were favorable in most cases. The authors concluded that although their results were encouraging, further studies were needed.

Subsequent studies (Table 1) explored different concentrations of topical ALA[53]; primary clinical response, long-term follow-up, and irradiation with different wave bands[54]; the use of laser[53] and non-laser[55] light sources; substitution of green light for red light[56]; low doses (20 J/cm^2) and dose rates (20 mW/cm^2) of light for extensive AKs[49]; and blue light rather than red light[60] for photoactivation. Mild stinging and burning during irradiation and localized edema and erythema were common adverse effects. Hypertrophic lesions did not respond well to treatment[53].

Topical ALA and Blue Light. In 2001, Jeffes, et al.[60] reported the results of a phase II, 36-patient clinical trial of the safety and efficacy of PDT using a new topical ALA (20%, 14 to 18 hours without occlusive dressings) and blue light to treat AKs on the scalp and face. The investigators used a non-laser source whose blue light more strongly activated PpIX than red light (632 nm)[58]. Although blue light penetrates less deeply into skin than red light, it has a much higher absorption peak for ALA than red light (Figure 1). The treatment was effective against superficial AKs[58] with a light dose of 10 J/cm^2 and the investigators achieved complete clearance of 66% of AKs 8 weeks after a single treatment. One retreatment of 16 AK lesions at 8 weeks increased the CR rate to 85% at 16 weeks. Although patients experienced burning and stinging during treatment, these effects resolved within 1 week. Erythema appeared immediately after treatment in 96% of patients and disappeared within 4 weeks.

In phase III trials[58] of 243 patients with non-hypertrophic AK, 83% of patients had CR after 8 weeks. Burning and stinging as well as erythema and edema occurred as in earlier studies. Cosmetic results were good to excellent in 92% of lesions. In a phase III study of four-year efficacy and recurrence, Fowler, et al.[44] reported that 69% of 32 AK lesions in 4 patients were still cleared, 9% were recurrent, and 22% were "uncertain." These results supported the FDA clearance of Levulan® Kerastick® and the BLU-U® Blue Light Photodynamic Therapy Illuminator for the AK indication. The BLU-U® emits blue light at 417 nm ± 5 nm and its power output is fixed at 10 mW/cm^2 at the recommended distance from skin.

Methylaminolevulinate Photosensitizer. In 2003, Freeman, et al., in a prospective randomized study, compared the efficacy, safety, cosmetic outcome, and patient satisfaction of PDT using topical methylaminolevulinate (Metvix®, Photocure ASA, Norway) cream with cryotherapy in the treatment of AKs in 204 patients[59]. Response rates and cosmetic outcomes were statistically superior in the Metvix® PDT group compared to cryotherapy and placebo PDT. In a smaller prospective, randomized, multicenter, placebo-controlled trial, Pariser, et al. (2003) reported similar results in 80 patients with AK[60]. Metvix® has an approvability letter from the FDA for the treatment of AK, but his not yet been cleared for marketing for this indication in the United States.

Basal Cell Carcinoma

Early attempts to treat BCC with PDT and non-ALA photosensitizers had limited success due to high lesion recurrence rates[61,62].

In 1990, Kennedy et al. introduced ALA-induced PpIX PDT in the topical treatment of BCC, SCC (in situ or early invasive), AK, and other conditions[19]. This report led to a series of studies (Tables 2, 3) in which (1) 20% ALA was topically applied for 3 to 8 hours to allow ALA to penetrate skin and be converted to PpIX, (2) lesions were verified by biopsy, and (3) results were evaluated after a single ALA-PDT treatment unless stated otherwise.

Investigators used ALA with non-laser unfiltered visible light[50,63], non-laser filtered light[18-20,50,52,63-69] and lasers[51,70-72]. Light doses ranged from 18 to 300 J/cm^2 and dose rates from 15 to 250 mW/cm^2.

In treating superficial BCC, reported CR rates with ALA PDT have generally been high, ranging from 86% to 100% with follow-up times up to 45 months. Reported recurrence rates often were higher when follow-up time was longer. In their 1990 report, Kenne-

Table 1. ALA-PDT in the treatment of AKs

Reference	Light source	Light Dose (J/cm^2)	Dose rate (mW/cm^2)	No. of lesions treated	CR rate (%) (Follow-Up Time)
Kennedy et al.[19]	slide projector (filtered light) >600 nm	150-300	15-150 (3.5-30 min)	10	90 (18 mo)
Wolf et al.[50]	slide projector (unfiltered & filtered to remove <570 nm)	30-100	50-100 (5-20 min)	9	100 (3-12 mo)
Morton et al.[79]	xenon lamp (615-645 nm)	94-156	55-158	4	100 (12 mo) (one AK lesion required retreatment after 2 mo.)
Calzavara-Pinton [51]	argon-pumped dye laser (630 nm)	60-80	100	50	100 (treatment every other day until lesion cleared)
Fijan et al.[52]	halogen lamp, red filter	up to 300	150-250 (20 min)	43	81.4 (up to 20 months)
Szeimies et al.[16] **(10% ALA)**	Waldmann halogen, red light (580-740 nm)	150	160	36	71 (28 days)
Fink-Puches et al.[54]	slide projector, unfiltered and filtered (eliminate <515, 530, 570, 610 nm), UVA	5.4-120 (760 UVA)	50 - 100 (38 for UVA)	251	64
Jeffes et al.[53] **(0%-30% ALA)**	Argon pumped dye laser (630 nm)	10-150	up to 150	218	91% (8 weeks, face and scalp; 45% trunk and extremities) with 30% ALA
Kurwa et al.[55]	Halogen lamp, filtered (580-740 nm)	150	53-100	not stated	73 (mean reduction in lesional area)
Markham et al.[49]	Waldmann halogen, visible light (580-740 nm)	20	20	4 (cases, scalp only; diffuse)	75 (6 mo.)
Jeffes et al.[57]	non-laser fluorescent blue light (417 nm)	2-10	3-10	70	66 (8 weeks)

ALA = 5-aminolevulinic acid; PDT=photodynamic therapy; CR = complete response, the complete removal of tumor at the treatment site.

dy, et al. reported a 90% response rate which decreased to 79% in a later report[20]. Wolf et al.[50], after 7 months (median) had only one recurrence among 37 sBCC lesions cleared with ALA PDT. In contrast, Cairnduff et al.[70] reported that half of 16 cleared lesions had returned within 17 months and suggested that the ALA may not have penetrated deep enough into the tumors to prevent recurrence. Using desferrioxamine (an iron chelator) to stimulate ALA-driven photosensitization in deep regions, Fijan et al.[52] cleared 30 of 34 lesions with a single treatment and 3 more lesions with a second treatment. Only one lesion required surgical excision in this study.

Lui et al.[64] found by histologic studies that tumor tissue persisted in 4 of 8 sites cleared of sBCC lesions 9 to 12 weeks earlier. Wennberg et al.[65] reported no recurrences of sBCC lesions among 144 that had cleared, whereas Fink-Puches et al.[63] reported a 44% recurrence rate 19 months after treatment. Soler et al.[72] used dimethylsulfoxide (DMSO) to enhance skin penetration of ALA in a study comparing CR rates with broadband light (570-740 nm continuous spectrum) and laser (630 nm). Two years after treatment, recurrence rates were 4% with laser and 5% with broadband light. Leman et al.[69] reported recurrence of 5 of 42 cleared sBCC lesions within 36 months after treatment. Morton et al.[67] reported 4 recurrences among 35 lesions cleared by 1 to 3 treatments and followed for 34 months.

In numerous studies, clearance rates for nodular BCC lesions (nBCC) were consistently lower than rates for sBCC[50-52,65], possibly due to limited penetration of ALA[50], increasing thickness and pigmentation of lesions[51], or a combination of insufficient penetration of ALA and light[65]. Fijan et al.[52] obtained higher CR rates for nBCC when using desferrioxamine.

In September 2003, the Dermatologic and Ophthalmic Drugs Advisory Committee to the US Food and Drug Administration did not recommend FDA approval of Metvix® for the treatment of primary nodular BCC.

Bowen's Disease

Traditional treatments for Bowen's disease—cryotherapy, electrodessication, curettage, surgical excision, 5-FU, radiotherapy, topical chemotherapy—may be impractical when lesions are multiple, large, or located in anatomically difficult areas[73]. With cryotherapy, healing may be slow, scars may form, and nerve damage may occur[74,75]. PDT with early photosensitizers (e.g., Photofrin) has been shown to be effective[73,76,77], but these agents remain in the body for up to 30 days, requiring patients to avoid sun exposure for 4 to 6 weeks[73].

ALA PDT does not require patients to avoid sun exposure for more than 48 hours. Kennedy et al.[19], using PDT with ALA-induced PpIX, obtained CRs in six lesions with a diagnosis of either in situ SCC or early invasive SCC, although elevated lesions responded only partially. Cairnduff et al.[70] obtained a 97% CR 2 months after treatment, but three CRs were followed by relapse, reducing the single-treatment CR rate to 89% at 18 months (median). Lui et al.[64] noted 3 cleared lesions of in situ SCC; one was histologically positive for tumor after 12 weeks. Calzavara-Pinton et al.[51] treated nonmelanoma skin cancer lesions on alternate days until they cleared. Two treatments were typically required for clearance of 6 Bowen's lesions. After 29 months (median), no histologically apparent lesions had returned. Using desferrioxamine, Fijan et al.[52] obtained a only a 30% CR rate after 20 months. Two lesions required retreatment at 1 and 4 months due to recurrence and 5 lesions failed to respond with repeated treatments.

Morton et al.[75], in a randomized trial comparing ALA PDT with cryotherapy in the treatment of Bowen's lesions, showed that ALA PDT with a non-laser light source was more effective (75% CR) than cryotherapy (50% CR), the current treatment of choice. Ulceration, infection, and recurrent disease were reported in some lesions treated by cryotherapy, but not in ALA PDT-treated lesions. Wennberg et al.[65], irradiating with a filtered gas discharge lamp, obtained a 78% CR 3 and 6 months after treating 18 Bowen's lesions. No recurrences occurred. Stables et al.[79], using intraepi-

dermal injection of ALA before non-laser irradiation, treated three very large patches of Bowen's disease with >90% CR 3 months after single treatment and 100% CR after a second treatment.

Morton et al.[66] compared the CR rates of red light (615-645 nm) and green light (525-555 nm) in the ALA PDT treatment of Bowen's disease. Initial clearance rates were 94% for red light and 72% for green light. Recurrence rates at 12 months lowered CR rates to 88% for red light and to 48% for green light. The authors attributed the superiority of red light to its deeper penetration into tissue. Morton et al.[67] later showed high response rates for large and multiple patches of Bowen's disease after 1 to 3 treatments. Only 4 of 40 large patches and 4 of 45 (multiple) patches returned within 12 months of treatment.

Salim et al.[18] reported a 40-patient, randomized, two-center study comparing efficacy and adverse effects of ALA PDT and topical 5-FU for the treatment of Bowen's disease. With use of a xenon lamp (615-645 nm), the CR rate for PDT was 88% initially and 82% after 12 months compared to 67% and 48%, respectively, for 5-FU. The difference in effectiveness was statistically significant. Although pain during treatment occurred with both modalities, severe eczematous reactions, ulceration, and erosions occurred only in lesions of patients treated with 5-FU. The authors concluded that ALA PDT is superior to 5-FU in the treatment of Bowen's disease.

Other Cutaneous Conditions

Studies using PDT in treating SCC, Kaposi's sarcoma, Mycosis fungoides, malignant melanoma, skin metastases, and non-malignant cutaneous diseases are limited and have been reviewed[1,6].

Light Sources

Because skin is so accessible to light, any source providing light of wavelengths in the absorption spectrum of the photosensitizer can be used to treat dermatologic conditions by PDT[5-7]. For porphyrins, absorption peaks occur at 505, 540, 580, and 630 nm[5] with a maximum at 410 nm (Soret band) (Figure 1)[50]. One advantage of a longer wavelength of light (630 nm and higher) is that it can penetrate more deeply into tissue whereas shorter wavelengths (400-500 nm) penetrate only 1 to 2 mm[50]. Deeper penetration may not be necessary if dealing with intraepidermal lesions. Pain occurs during treatment with visible light, but can be reduced by using filters to eliminate wavelengths below 515, 530, 570, and 610 nm[54].

A more recently discovered method to reduce pain is to reduce the incubation time of the ALA. Both lasers and non-lasers have been used successfully to deliver light to the skin in PDT. Some investigators have concluded that incoherent sources—from slide projectors[19,50,54,64] to halogen[49,52,55,68,72,78], xenon[18,65,67,69,79] and fluorescent[54] lamps—are more practical and economical than lasers and may be more effective [1,15]. One study[54] demonstrated that treatment of AK lesions with full-spectrum visible light resulted in longer periods without lesion recurrence than treatment with filtered light.

For treating large lesions, some investigators have found that incoherent light is more effective than laser light[5], resulting in the development of incoherent light sources dedicated to PDT[5,6]. One limitation is that radiation density of incoherent light at the edges of a large lesion is less than at the center of the lesion, raising the possibility of nonuniform radiation density. The same is true for areas of uneven contour[6,80]. Nevertheless for treating lesions in which penetration depth is not important (e.g., intraepithelial lesions of superficial skin cancers), white light remains both practical and effective[78]. In a study comparing a broadband lamp with a copper vapor laser pumping a dye laser for the treatment of sBCC by ALA PDT, Soler at al[72] showed that cure rates and cosmetic outcomes were comparable with both sources. The authors used DMSO to increase ALA penetration into the skin[81] and EDTA to enhance the temporary accumulation of endogenous PpIX[81]. Although the broadband lamp was only 43% as efficient as the laser, Soler et al. cited the reduced cost, increased safety (no safety glasses needed, as in lasers) and potential general use by dermatologists

as advantages of the halogen lamp. As disadvantages, the authors indicated that light dosimetry may be less accurate than with a laser, and that unwanted infrared radiation may be present, resulting in heating of the skin.

The most frequently used laser sources in the past for dermatologic PDT have been the continuous-wave argon pumped dye[6,7,51,53] and pulsed gold vapor lasers[5,6]. Copper vapor [70,72] and pulsed Nd:YAG[71] dye lasers have also been used. With lasers the user can (1) select specific wavelengths, (2) minimize exposure times due to the high energy outputs available at these wavelengths and (3) target specific areas more easily[51].One disadvantage of lasers is that a physician or technician has to perform the treatment and this will take longer if there are larger areas.

The past three years has seen a resurgence of interest in PDT and experimentation with a great number of new laser and light sources. Blue light and vascular wavelength lasers have been the principal sources studied. The latter would include pulsed dye lasers in the 585-595 nm range, intense pulsed light (IPL), IPL with radiofrequency (Aurora ELOS™, Syneron Medical Ltd.) and any others in the 532-630 nm range.

The BLU-U® PDT Illuminator, which accommodates a patient's entire scalp or face for a single treatment, has been cleared by the FDA for the treatment of AK[13]. The device takes advantage of the efficient activation of PpIX by blue light with a fluorescent tube. For simultaneous skin rejuvenation and treatment of AK by ALA PDT, Ruiz-Rodriguez et al.[82] reported success with noncoherent (filtered) IPL (590-1200 nm). Acne of 13 patients has been improved by PDT, using a halogen light source (600-700 nm) after applying ALA[84]. The authors concluded that the polychromatic light source was more cost effective, provided more uniform illumination, and took less time to treat large areas of acne than a pulsed excimer-dye laser used in a previous study[84]. The most recent study of ALA PDT for the treatment of AKs utilized a 595nm wavelength long-pulsed pulsed dye laser[85]. These investigators found over 90% clearance of head lesions at 6 months after a single treatment, with somewhat less efficacy on extremities and trunk.

For the treatment of non-hypertrophic AKs or superficial actinic damage, a superficial wavelength should theoretically be sufficient to penetrate to the basal level of the epidermis and upper dermis where the lesion or defects reside. Due to the variable thickness of hypertrophic AKs, superficial BCC and Bowen's disease, studies may find that longer wavelengths may be necessary to achieve effective penetration depths. Blue light is ideal for acne because endogenous PDT occurs due to the specificity of the porphyrins in the acne bacteria which should be greatly magnified by adding ALA, although it is possible that longer wavelengths may be necessary to achieve enough depth to reach glandular tissue. To treat dermal lesions like nodular BCC, presumably deeper penetrating wavelengths, enhanced penetration of ALA or both will be necessary to achieve significant clearing.

New Applications

Acne

The appropriate therapy for acne depends on the extent, severity, and duration of the condition; the nature of the lesions; and psychological factors[86]. The complex pathogenesis of acne has been reviewed[87-89]and updated treatment modalities—topical[90], systemic[91], hormonal[92], radiofrequency[93], pulsed-dye laser[94], combinations[95,96], and less common methods[97] have been described. The Global Alliance to Improve Outcomes in Acne has developed consensus recommendations for the management of acne[98].

Topical formulations may irritate skin and acne bacteria often resist oral antibiotics. Isotretinoin, though the gold standard for the treatment of acne[99], is expensive, may not be available in some countries[84], and has a high risk for teratogenicity[100]. These drawbacks have led researchers to develop treatment alternatives.

The use of visible light to activate either ALA-induced porphyrin or endogenous porphyrin produced

Table 2. ALA-PDT in the treatment of sBCC

Reference	Light source	Light Dose (J/cm^2)	Dose rate (mW/cm^2)	No. of lesions treated	CR rate (%) (Follow-Up Time)
Kennedy et al.[19]	Slide projector, filtered light >600 nm	150-300	15-150 (3.5-30 min)	80	90 (2-3 mo.)
Wolf et al.[50]	slide projector (unfiltered & filtered to remove <570 nm)	30-100	50-100 (5-20 min)	37	97 (4-8 weeks)
Cairnduff et al.[70]	Copper vapor dye laser (630 nm)	125-250	<150	16	88% (2 mo.) and 50% (17 mo)
Svanberg et al.[71]	Nd:YAG laser pumping a dye laser (630 nm)	60 (10-20 min)	<110	55	100 (3 weeks)
Lui et al.[64]	filtered light, slide projector	100	19-44	8	88 (4-8 weeks)
Fijan et al.[52]	halogen lamp, red filter	up to 300	150-250 (20 min)	34	88.2 (up to 20 months)
Calzavara-Pinton[51]	argon-pumped dye laser (630 nm)	60-80	100	23	100 (treatment every other day until lesion cleared)
Wennberg et al.[65]	filtered broadband xenon lamp 620-670 nm	75-100 (10 min)	125-166	157	92 (3 and 6 mo)
Fink-Puches et al.[63]	full-spectrum or filtered visible light or UV-A	18-131 (vis), 1.1 (UV-A)	50-100 37 (UV-A)	95	86 (full-spectrum), 87 (filtered), 90 (UV-A)
Soler et al.[72]	Copper vapor laser pumping a dye laser (630 nm), broadband halogen (570-740 nm, filtered)	100-150 (laser) 150-200 (broadband)	120-150 (laser) 100-180 (broadband)	245	86 (laser), 82 (broadband) (6 mo.)
Leman et al.[69]	filtered (630 nm) xenon	100-150	18-122	42 (multiple patients); 45 (1 patient)	88 (45 mo., multiple patients); 93% (1 patient)
Morton et al.[67]	xenon short arc (615-645 nm, filtered)	100-150	20-86	40 (large), 58 (multiple)	88 (large patches, 1-3 treatments), 90 (multiple)

ALA = 5-aminolevulinic acid; PDT=photodynamic therapy; CR = complete response, the complete removal of tumor at the treatment site.

by *P. acnes* has shown promise in the treatment of acne in some patients[101]. This photodynamic approach has evolved as a result of the following observations: (1) sun exposure and phototherapy with visible light improve acne in many patients[100,102]; (2) *Propionibacterium acnes* produces coproporphyrin III[103] that absorbs radiation at 415 nm[104]; (3) irradiation of *P. acnes* colonies with blue light results in photoexcitation of endogenous bacterial porphyrins, generation of singlet oxygen, and destruction of bacteria[104,105]; (4) ALA is taken up by pilosebaceous units and metabolized to PpIX[20,104,106]; and (5) phototherapy with blue light, red light, and mixed blue-red light is effective against mild-to-moderate acne[104,107].

In their open-label, prospective study, Hongcharu et al.[108] showed that acne lesions respond to PDT in adult patients. They hypothesized that destruction of *P. acnes*, sebaceous glands, or both by PDT would improve acne vulgaris. Each of 22 patients (age 18 to 44 years) with mild to moderate acne (on their back) received four different treatments, each at a different site of the back: (1) ALA (Levulan® Kerastick®), (2) red light, (3) ALA and red light, and (4) no treatment. In patients receiving ALA-red light, ALA was applied, kept in contact with lesions for 3 hours under occlusion, and irradiated with broadband light (550-700 nm, 150 J/ cm^2). Half of the patients were treated one time and half received four treatments (once per week for 4 consecutive weeks).

The authors reported (1) significant clearance for up to 10 weeks with a single ALA-red light treatment and for up to 20 weeks after four ALA-red light treatments; (2) marked damage to pilosebaceous glands in ALA-red light-treated sites; and (3) erythema, exfoliation, and hyperpigmentation after ALA-red light treatment. These effects caused some patients to postpone treatments. (Improvements in acne were not apparent in lesions treated with ALA alone, red light alone, or nothing.) The authors concluded that ALA-red light may improve acne in some patients and that additional studies were needed to establish dosimetry parameters that would minimize adverse effects.

Itoh et al.[84] treated a patient with intractable facial acne by ALA PDT, using a pulsed excimer-dye laser, 635 nm and 5 J/cm^2 dose. A single treatment prevented new acne lesions for up to 8 months and the treatment was well tolerated. Edematous erythema appeared after treatment and healing was complete in 10 days. After healing, the authors treated the patient's full face with glycolic acid chemical peeling every 3 to 4 weeks and applied 1% nadifloxacin cream to diminish acne scars.

A year later these authors reported single treatments to 13 similar patients, this time using polychromatic visible light (600-700 nm, 17 mW/ cm^2, 13 J/ cm^2) from a halogen light source[83]. This less expensive incoherent light source illuminated the larger areas of skin surface more uniformly than the laser in the previous study. The goal was to prevent new lesions. Patients experienced burning and stinging during treatment, followed by edematous erythema, epidermal exfoliation, irritation and hypersensitivity to physical stimulation, and pigmentation or erythema after epidermal exfoliation. Treated lesions appeared as normal skin within 1 month after PDT. Facial appearance improved and new acne was reduced in all patients 1, 3, and 6 months after PDT treatment. Seborrhea returned and more acne lesions appeared during the next 6 months in most patients.

Lloyd et al.[99] preloaded enlarged sebaceous glands with indocyanine green chromophore, then selectively treated the loaded glands with a long pulse diode laser at 810 nm. Indocyanine green, with its 800-nm absorption peak, absorbs the laser light to cause localized heating and destruction of only the loaded glands. The authors theorized that destroying the enlarged glands by photothermolysis would eliminate overproduction of sebum, the growth medium for bacteria. Acne was decreased in treatment areas for 3, 6, and 10 months after treatment.

Goldman and Boyce[109], using BLU-U® light with and without ALA (Levulan® Kerastick®), treated 22 patients with mild to moderate acne. Patients receiving only BLU-U® light were treated once a week for 2 weeks and evaluated 2 weeks later. Patients given ALA and BLU-U® light were treated twice, with 2

weeks between treatments, and evaluated 2 weeks later. Acne severity improved 32% in the ALA-BLU-U® patients compared to 25% in the BLU-U® light patients. Papule counts decreased 68% vs. 40%, and pustule counts were 61% vs. 65% in ALA-BLU-U® and BLU-U® patients, respectively. Serious adverse events did not occur in either group and treatment was not painful by either procedure.

The ClearLight™ System (Lumenis), a narrow-band, high-intensity blue light (407-420 nm) has been FDA cleared for the treatment of moderate inflammatory acne[110]. In a single-center open study[111], Kawada, et al. achieved 64% reduction in mild to moderate acne lesions when patients were treated with the ClearLight™ System twice weekly for up to 5 weeks. In a multicenter uncontrolled study, researchers achieved a 70% median reduction of inflammatory lesions in 175 patients with mild to severe acne[110].

Elman et al.[112] used the ClearLight system to treat patients with papulo-pustular acne according to three 4-week protocols: (1) a split face dose-response study of 10 patients whose left side of the face received 8 minutes and the right side received 12 minutes exposure twice a week, (2) a full-face open trial (n = 13) in which patients received 15 minutes exposure twice a week, and (3) a split face, double-blinded, self-controlled study in which one side of the faces of 23 patients was randomly chosen for 15 minutes exposure and the other side was shielded with black cloth.

No adverse effects of the treatment were observed. The split face dose response study showed mean reductions of 65.9% and 67.6% in the number of lesions on the left and right sides of the face, respectively, indicating that the difference in treatment time had no effect. In the full-face open trial, 10 of 13 patients showed a 59% mean reduction at the end of 4 weeks. Four weeks later, 12 of the 13 patients showed a mean reduction of 81%. In the split face, double-blinded, self-controlled study, 20 of the 23 patients showed a median reduction of 60% in the number of lesions on the treated side. Reductions were 59%, 61%, and 53% for 2, 4, and 8 weeks after therapy. The untreated sides showed a median reduction of 30%. The authors concluded that high-intensity, narrow band 405-420 nm light was an effective alternative to topical and parenteral treatments for acne.

Endogenous and ALA-assisted PDT for acne is in its infancy: many leading dermatologic surgeons are experimenting with light sources and various protocols. The next 2 years are likely to yield an explosion of new information with regards to light and laser assisted PDT of acne.

Other Sebaceous Disorders

The first case of nevus sebaceous of Jadassohn (NSJ) treated with ALA-PDT was reported by Dierickx, et al.[113]. Concerned with cosmetic outcome, a 38-year-old woman with extensive NSJ on the right side of her face and scalp had refused surgery. The researchers treated the patient with ALA-PDT 13 times at 4- to 8-week intervals. The lesion flattened and became smaller with successive treatments. Two unresolved nodules were curetted immediately prior to ALA application at the last two treatments. The NSJ was clinically resolved with excellent cosmetic results and the patient had no serious adverse effects. The lesion had not returned 16 months after the last treatment.

Horio, et al.[114] used ALA-PDT with a slide projector to treat senile sebaceous hyperplasia in a 61-year-old Japanese man. The treatment was repeated three times at 1-week intervals. Lesions became smaller with successive treatments, although large papules never completely resolved. The treatment was well tolerated, with edema and hyperpigmentation subsiding within days after the final treatment. No treated lesion had returned 1 year after the treatment.

Photorejuvenation

Manifestations of skin damage by sun exposure—wrinkling, rough skin texture, changes in pigmentation, and telangiectases—have been improved by photorejuvenation with IPL[115,116]. Photodamaged skin may also have AKs whose removal has traditionally required cryotherapy or topical 5-FU as a separate procedure.

Ruiz-Rodriguez, et al.[82] have reported their use of ALA PDT with IPL to remove AKs on the face and scalp as part of a single photorejuvenation procedure. In their study, ALA (20%) topically applied for 4 hours followed by IPL treatment for photorejuvenation—two treatments spaced 1 month apart—cleared 34 of 38 AK lesions in 17 patients for at least 3 months. The cosmetic outcome was favorable and the technique well tolerated. The researchers used incoherent light (590-1200 nm) with a 615-nm cutoff filter, allowing for inclusion of the 630- and 690-nm absorption peaks of PpIX and deeper penetration. The total fluence was 40 J/cm^2 with a 4.0 msec double pulse mode and 40 msec delay time between pulses.

In a pilot study reported[117] and later reviewed[101], 18 patients with moderate diffuse facial photodamage and four or more nonhypertrophic AKs were randomized to receive 1 hour, 2 hour, or 3 hour exposure to 5-ALA (20%) followed by blue light (10 J/cm^2). Ten patients were observed at baseline, 1 month, and 5 months after a single ALA (Levulan® Kerastick®)-PDT treatment. The treatment resulted in statistically significant improvement in skin quality, fine wrinkling, and sallowness; borderline improvement in mottled pigmentation; and no improvement in coarse wrinkling. Satisfaction was good to excellent as reported by more than 80% of patients. The authors recommended microdermabrasion immediately before treatment to remove stratum corneum and allow more uniform and rapid penetration of 5-ALA.

Gold has reported improved skin elasticity and reduced skin thickening in the regions of multiple nonhyperkeratoric facial AKs cleared by ALA PDT (blue light) in two patients with moderately photodamaged skin[118].

The area of adjuvant PDT photorejuvenation is in experimental stages. Current investigators are hoping that adding ALA to photorejuvenation may make treatments more effective, make it possible to achieve similar results to traditional photorejuvenation with fewer treatments, and prevent the development of AKs and non-melanoma skin cancer.

Other Cutaneous Disorders

In dermatology, PDT has recently been used to treat cutaneous leishmaniasis[119,120] and localized scleroderma[121]. In other areas of medicine, the technique has been applied to malignancies in the lung[122], bladder[123,124], rectum[125], prostate[126,127], esophagus[128,129], head and neck[130], as well as glioma spheroids[131], cervical intraepithelial neoplasia[132], mesothelioma[133], obstructive endobronchial Hodgkin lymphoma[134], endobronchial metastases[135], and hilar cholangiocarcinoma[136]. PDT in the treatment of Barrett's esophagus has received considerable attention[137,138,139]. In addition, PDT has recently been used to improve wound healing[140], treat choroidal melanoma[141], choroidal neovascularization[142,143], neovascular age-related macular degeneration[144], viral disease[145], periodontal disease[146], and rheumatoid arthritis[147]. PDT may also have applications in regenerative medicine[148].

The use of PDT in combination with surgery, chemotherapy, anti-angiogenic therapy[149], and other treatment modalities has been reviewed[2,6]. Fractionation of light[150] and photosensitizer dosing[151] to optimize PDT protocols as well as conjugating tumor-associated antibodies to improve tissue specificity[152,153] have been described. Advanced delivery systems to improve photosensitizer selectivity have been reviewed[2,3].

Conclusion

During the 1970s and 1980s, Dougherty, et al. described the use of HPD-based PDT in the treatment of various malignancies. In the early 1990s, Kennedy, et al. introduced ALA, a photosensitizer which, unlike HPD, did not make patients susceptible to phototoxicity for extended periods. ALA-PDT has since been used to treat AKs, BCC, and Bowen's disease, acne, and other cutaneous diseases. Current studies are underway to evaluate ALA-PDT as an adjuvant for aesthetically oriented treatments such as photorejuvenation. Pain during treatment which had previously limited the practical use of PDT has been virtually eliminated by using shorter incubation times. Post-treatment erythema, edema, and crusting are being tamed by

Table 3. ALA-PDT in the treatment of Bowen's disease

Reference	Light source	Light Dose (J/cm^2)	Dose rate (mW/cm^2)	No. of lesions treated	CR rate (%) (Follow-Up Time)
Cairnduff et al.[70]	Copper vapor dye laser (630 nm)	125-250	<150	36	97% (2 mo) 89% (18 mo)
Svanberg et al.[71]	Nd:YAG laser pumping a dye laser (630 nm)	60 (10-20 min)	<110	10	90 (3 weeks)
Lui et al.[64]	filtered light, slide projector	100	19-44	3	67 (12 weeks)
Calzavara-Pinton [51]	argon-pumped dye laser (630 nm)	60-80	100	6	100 (treatment every other day until lesion cleared)
Fijan et al.[52]	halogen lamp, red filter	up to 300	150-250 (20 min)	10	30 (up to 20 months)
Morton et al.[75]	xenon short arc, entire visible spectrum	125	70	20	75 (2 mo)
Wennberg et al.[65]	filtered broadband xenon lamp (620-670 nm)	75-100 (10 min)	125-166	18	78 (3 and 6 mo)
Stables et al.[78]	quartz-tungsten-halogen lamp (400-700 nm)	125	150	3	>90 (3 mo)
Morton et al.[66]	xenon short arc; visible (615-645nm [red], 525-555 nm [green])	125 (red), 62.5 (green)	86	32 (red), 29 (green)	94% (red), 72% (green)
Morton et al.[67]	xenon short arc (615-645 nm)	125	20-86	40 (large), 45 (multiple)	88 (large patches, 1-3 treatments), 98 (multiple)
Salim et al.[18]	xenon lamp filtered to 615-645 nm	100	50-90 (12-40 min)	33	88 (82% in 12 mo)

ALA = 5-aminolevulinic acid; PDT=photodynamic therapy; CR = complete response, the complete removal of tumor at the treatment site.

identifying more optimal parameters resulting in less downtime for patients. The FDA clearances of Levulan® Kerastick® for the treatment of multiple AKs on the scalp and head, the BLU-U Blue Light Photodynamic Therapy Illuminator in addition to many other blue light sources, and the renewed interest in utilizing ALA with lasers that have wavelengths in the visible spectrum allow investigators to explore off-label uses of ALA, assuring a bright and exciting future for PDT in dermatology.

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Large Surface Photodynamic Therapy with Aminolevulinic Acid: Treatment of Actinic Keratoses and Beyond

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Abstract

Photodynamic therapy (PDT) with topical aminolevulinic acid (ALA) is currently approved in the US and Canada for the spot treatment of non-hypertrophic actinic keratoses of the face and scalp. Dermatologists are currently using ALA-PDT on larger skin surfaces for the treatment of extensive actinic keratoses, sun damage and acne. This article reviews the safety and efficacy of large surface ALA-PDT for the treatment of actinic keratoses and photodamage. New data on the carcinogenic potential of weekly topical ALA-PDT in mice is also presented. Groups of hairless mice were treated weekly with either ALA alone, blue light alone or ALA-PDT using blue light for a total of 10 months followed by an additional 2 months or observation. Mice were examined weekly for the presence of skin tumors. Skin tumors were not observed in mice treated weekly with blue light alone, with topical application of ALA alone or with ALA-PDT.

KEYWORDS:
Skin Cancer
Ultraviolet Radiation
Protoporphyrin IX
Photodynamic Therapy

Introduction

Actinic keratoses (AK) are premalignant lesions mostly found on sun exposed areas of fair skin individuals. The prevalence of AKs in the US has been reported to be as high as 55% in Caucasians 65 years and older with a history of high sun exposure[1]. AKs can progress to invasive squamous cell carcinoma over time. As the exact risk of transformation of individual lesions cannot be accurately predicted, it is current practice to treat all visible AKs. This can be performed with various techniques such as cryotherapy, surgical excision, topical application of 5-fluorouracil or photodynamic therapy (PDT) with aminolevulinic acid (ALA).

Photodynamic therapy is a two step process that requires the administration of a photosensitizer, or photosensitizer precursor, followed by light exposure to treat a disease [2]. Following light exposure the photosensitizer is excited to a higher energy state which generates free radicals and singlet oxygen. Topical aminolevulinic acid (ALA) is a photosensitizer precursor currently approved in the US and Canada for the treatment of non-hypertrophic actinic keratoses of the

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face and scalp. Following topical application, ALA is taken up by keratinocytes and transformed into the photosensitizer protoporphyrin IX (PpIX) [3]. There is preferential accumulation of PpIX in actinic keratoses as compared to adjacent skin [4,5]. In the FDA-approved protocol, 20% aminolevulinic acid in hydroalcoholic vehicle (Levulan, DUSA Pharmaceuticals, Valhalla, NY) is applied on individual AKs followed one day later by 10 J/cm^2 of blue light from a panel of blue fluorescent tubes (Blue-U, DUSA Pharmaceuticals, Valhalla, NY). This treatment has been shown to result in a high complete clearance rate of 83 to 88% for AKs [6,7].

Since the approval of ALA-PDT for the treatment of AK, the use of ALA-PDT on larger skin surfaces has been reported for the treatment of patients several diseases such as extensive actinic keratoses, photoaging and acne. The purpose of the present article is to review the use of large surface ALA-PDT in patients with actinic keratoses and photodamage as well as to present results of a study performed on mice to assess the carcinogenic potential of multiple ALA-PDT sessions.

Materials and Methods

Multiple ALA-PDT sessions in hairless mice

A total of 80 four week old SKh1 hairless mice (Charles River Laboratories, St-Constant, Canada) were divided into 4 groups of 20 mice each (Table 1).

Table 1: Treatment groups

Group	ALA	Blue Light
A	Yes	Yes
B	Yes	No
C	No	Yes
D	No	No

ALA (DUSA Pharmaceuticals, Valhalla, NY) was prepared daily at 20 % in hydroalcoholic solution (DUSA Pharmaceuticals, Valhalla, NY). For group A, ALA was applied weekly on the back of mice 3 hours before exposure to 0.2 J/cm^2 (60 % of minimal phototoxic dose) of blue light at 11.7 mW/cm^2. The blue light source was custom made with the same fluorescent tubes present in Blue U units (DUSA Pharmaceuticals, Valhalla, NY) used for the treatment of patients with actinic keratoses. The irradiance was measured weekly with an International Light IL 1700 radiometer (Newburyport, MA) equipped with a SED 240 detector, a UVB-1 filter and a "Wide Eye" Diffuser (W). The measured irradiance was multiplied by a factor of 1.63 following comparison of the International Light radiometer against a UDT S370 radiometer (Graseby Optronics, Orlando, FL). Mice from group B received topical ALA at the same rate and under the same conditions as group A but were not exposed to blue light. Mice from group C were exposed weekly to blue light under the same conditions as mice from group A but did not receive ALA. Group D was a control group that received neither ALA nor blue light. Mice from group A, B and C were treated for a total of 10 months. Mice were examined weekly for the presence of skin tumors. All mice were sacrificed 12 Months after the start of ALA-PDT.

Results

Weekly topical ALA-PDT was well tolerated by mice. Starting at week 16 some mice developed skin erythema on the day following ALA-PDT. At week 24, 25% of mice had erythema on their back following ALA-PDT. Skin tumors were not seen in all mice studied, including the ALA and blue light control groups.

Discussion

Treatment of patients with numerous actinic keratoses can be a challenge. Current options include 5-FU, imiquimod, dermabrasion, cryotherapy and photodynamic therapy. Cryotherapy is used infrequently for numerous and confluent AKs because of the pain and crusting associated with the treatment of large surfaces. 5-FU is used on large surfaces but can give rise to an intense local reaction with erythema, edema an crusting. Erythema often persists for weeks and even months after

treatment with 5-FU, although this has been reduced with the introduction of the 0.5 % concentration [8]. Imiquimod is currently used off-label for the treatment of AKs. It can also generate a severe skin reaction at the application site with erythema, crusting, erosion and purpura [8]. Surgical excision and curettage can be used to treat a few lesions but is difficult to perform if multiple lesions are present. Dermabrasion is rarely used nowadays for multiple AKs. Other modalities that have shown efficacy in the treatment of multiple AKs include retinoinds, diclofenac and colchicine [9].

PDT with methylaminolevulinate, another topical precursor of protoporphyrin IX has also shown good efficacy for the treatment of AKs [10]. In this study lesions were scraped gently with a dermal curette before photosensitizer application. The complete lesion response rate was 89% after two PDT treatments with red light given one week apart. A comparative study of a single cycle of cyrotherapy and two PDT sessions with methylaminolevulinate given 7 days apart showed a superior lesion response rate in the PDT group[11]. Methylaminolevulinate is currently approved in Europe for the treatment of AKs and basal cell carcinoma but has not yet been granted FDA approval.

PDT with aminolevulinic acid is currently approved by the FDA for the spot treatment of multiple AKs. The complete response rate following PDT of AK with ALA in hydroalcoholic solution (Levulan) has been reported to be 83% in phase III studies [6]. In the FDA-approved protocol, ALA is applied on actinic keratoses in the afternoon and exposure to blue light is performed 14-18 hours later. Using this protocol most patients complain of pain at some point during treatment [12]. Post-PDT erythema has been reported to occur in 99% of patients treated with ALA-PDT and 79% of patients treated with vehicle-blue light [12]. Local edema has been reported in 35% of ALA-PDT treated Aks while vehicle-treated patients did not show edema[12]. The overall treatment tolerance of ALA-PDT is very good considering the alternative treatments for extensive AKs.

In the FDA-approved protocol, ALA is only applied on visible AKs. However studies have also been conducted with application of ALA on larger skin surfaces for the treatment of acne, psoriasis, actinic keratoses and photodamage. Markham and Collins presented a series of 4 patients with extensive scalp actinic keratoses that were treated with large surface ALA-PDT [13]. Fields of up to 10 X 7 cm were treated with ALA in a cream base and activated with a Waldmann PDT lamp. The treatment was associated with pain and erosions but the complete response was excellent. Resistant lesions were seen in 2 patients and were shown to be invasive squamous cell carcinoma following histopathological analysis [13]. Touma and Glchrest conducted a study to assess the safety and efficacy of large surface ALA-PDT in 18 patients with mild to moderate photodamge and actinic keratoses[14]. The complete study was still unpublished at the time this review was submitted. Patients received ALA application followed by light exposure 1, 2 or 3 hours later. Mild to moderate erythema, edema and occasional areas of crusting were reported after PDT. The study showed a good efficacy for ALA-PDT in the treatment of actinic keratoses even with a 1 hour incubation as compared to 14-18 h which is recommended on ALA's the package insert. The authors observed improvements in sallowness, fine wrinkling and mottled hyperpigmentation. They also mention that the beneficial effects of ALA-PDT on photodamage can be enhanced when microdermabrasion if performed before PDT [14]. Improvement in photodamage has also been reported in case studies where patients with multiple AKs were treated using the FDA-approved spot treatment [15]. Anecdotal reports have also described the use of large surface ALA-PDT with other light sources such as pulse dye laser and intense pulsed light [16-18]. This suggests that performing ALA-PDT with these light sources may have additive and or synergistic effects on several sun induced lesions such as actinic keratoses, wrinkles, erythema, lentigos and telangiectasias. More studies are needed in this area. Large surface PDT performed with ALA in various vehicles has also been reported for the treatment of acne, nevus sebaceous, psoriasis, lichen sclerosus and scleroderma [19-23]. These studies have been mostly performed with ALA in vehicles other than the FDA-approved hydroalcoholic solution.

Large surface ALA-PDT for patients with multiple AKs and photodamage could theoretically prevent skin cancer appearance by inducing a phototoxic reaction in non-visible lesions. Weekly large surface ALA-PDT performed on hairless mice has been shown to delay the appearance of UV induced actinic keratoses [24]. Our group has extended these observations and showed that weekly systemic (intraperitoneal) ALA-PDT as well as weekly PDT with topical methylaminolevulinate at a sub-erythemogenic fluence can also delay the appearance of UV induced skin cancer [5, 25]. These animal studies suggest that large surface ALA-PDT could be used in patients at high risk of developing skin cancer in order to prevent the development of AKs and SCCs. In view of the current use of large surface ALA-PDT in patients, the promising results obtained for the prevention of AKs with ALA-PDT in mice as well as in view of studies suggesting that ALA-PDT may be genotoxic [26], it was decided to study the carcinogenic potential of multiple ALA-PDT sessions using the hairless mouse as a model. One of the characteristics of ALA-PDT is that PpIX can be activated with visible light without having to use highly carcinogenic UV radiation. UV radiation is filtered out by Blue-U units and it is the blue portion of the visible spectrum that activates PpIX. Blue light is known to be absorbed by endogenous chromophores and has been associated with the development of melanoma in the Xiphophorus fish model [27]. Recently however blue light has been shown to inhibit the growth of TPA-induced skin tumors in mice [28]. In the current study hairless mice were exposed weekly to ALA-PDT with blue light for up to 10 months. Skin tumors were not observed in mice treated weekly with blue light alone, with topical application of ALA alone or with ALA-PDT. The hairless mouse is a highly sensitive model for the development of actinic keratoses and squamous cell carcinoma following various interventions such as exposure to UVB, UVA, PUVA or the application of topical carcinogens [29-31]. The absence of tumors in mice exposed chronically to ALA-PDT with blue light is additional safety evidence for use of ALA-PDT in man.

In our own practice we use large surface ALA-PDT in patients with multiple actinic keratoses and extensive photodamage. In these patients it is often difficult to clearly distinguish between actinic keratoses and uninvolved skin. We first perform a thorough evaluation to rule out the presence of skin malignancies such as basal cell carcinoma or squamous cell carcinoma. In doubt a skin biopsy is performed. This cannot be overemphasized as the inadequate treatment of the superficial aspect of a malignant lesion with PDT can give rise to clinical resolution with subsequent recurrence[32]. We use the commercial formulation of aminolevulinic acid in hydroalcoholic solution (Levulan). The area to be treated is brushed once with the Kerastick (commercial applicator for Levulan). A thin layer of ALA is applied on the complete area and let to dry. This is followed by 2 applications of Levulan on visible actinic keratoses. Each time AKs, as well as a few mm of surrounding skin, are soaked with Levulan and let to dry. We use blue light at one hour after ALA application. Light exposure at 1 hour after ALA application has been reported to be less painful than the FDA approved overnight incubation but this has never been compared in a clinical trial [14]. At 1 hour after ALA application we can see red fluorescence on actinic keratoses but not on adjacent photodamaged skin with a high power UVA lamp (Black-Ray long model B-100, UVP, Upland, CA). Our patients usually complain of a mild and tolerable burning sensation or puritus, some patients report no burning sensation or no pain at all. We have found that the Smart Cool device (Cynosure, Chelmsford, MA) that is sold to be used with the V-Star pulse dye laser (Cynosure, Chelmsford, MA) is very helpful in alleviating pain in patients who find that pain during light exposure is difficult to bear. Twenty-four hours after light exposure erythema is present on areas where ALA is applied with sometimes crusting of AKs. The erythema fades rapidly and is usually absent by one week post light exposure which compares favorably with 5-FU, imiquimod and cryotherapy. This treatment usually clears visible AKs and provides improvement in skin texture. It should be noted that the complete lesion clearance rate of ALA-PDT performed with a 1 hour and 18-24 hours incubation remains to be compared in a clinical trial. Any persistent AK is

treated with either cryotherapy or another PDT session. Any lesion persisting after 2 rounds of PDT is biopsied to rule out invasive squamous cell carcinoma.

Additional research on the use of ALA-PDT for the treatment of Aks and photodamage is needed. An important issue is the influence of the time for light exposure after ALA-application on clinical efficacy and tolerability for actinic keratoses and other aspects of photodamage. The influence of the application technique as well as the quantity of ALA applied also deserves to be studied. The influence of single versus multiple PDT sessions performed a few weeks apart also needs to be investigated. The use of ALA-PDT for the treatment of basal cell carcinoma and Bowen's disease also deserves to be studied with ALA in the hydroalcoholic vehicle as most published studies for these tumors used ALA in other vehicles. Finally in view of the promising results of large surface ALA-PDT for the prevention of skin cancer in mice this strategy should be studied in patients at high risk of developing skin cancer.

In conclusion weekly large surface ALA-PDT is not carcinogenic in the hairless mouse model. Large surface ALA-PDT is well tolerated by patients with multiple actinic keratoses and can have the additional benefit of improving photodamage.

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ALA-PDT AND BLUE LIGHT THERAPY FOR HIDRADENITIS SUPPURATIVA

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Abstract

Background: Hidradenitis suppurativa (HS) is a chronic, often suppurative skin condition which affects primarily apocrine glands. A variety of therapies have been used to treat HS, often with unsatisfactory results. Photodynamic therapy (PDT), utilizing topical 20% 5-aminolevulinic acid (ALA) is being used to treat a variety of dermatologic skin concerns, including photorejuvenation and associated actinic keratoses, and acne vulgaris, and other skin tumors.

Objective: The purpose of these case reports is to evaluate the effectiveness of ALA-PDT in treating recalcitrant cases of HS.

Methods: Four patients, not responding to standard HS therapy, underwent short-contact ALA-PDT therapy utilizing a blue light for activation. One to two week intervals between therapies was utilized for 3-4 total treatments and follow-up was for 3 months following the last treatment.

Results: All four of the patients tolerated the therapies well. Clinical improvements from 75-100% were noted n ll of the patients. No adverse effects were seen during the treatments. The treatments were pain free and there was no downtime associated with these ALA-PDT treatments.

Conclusions: HS is a chronic disease which most dermatologists find difficult to treat. The use of ALA-PDT is finding an ever-expanding role in dermatology. These case studies support the use of ALA-PDT in cases of HS. Although all advertising material is expected to conform to ethical and medical standards, inclusion in this publication does not constitute a guarantee or endorsement by the Journal or its staff of the quality or value of such products or of the claims of any manufacturer.

KEYWORDS:
PHOTODYNAMIC THERAPY
HIDRADENTIS SUPPERATIVA
AMINOLEVULINIC ACID
APOCRINE GLANDS

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Introduction

Hidradenitis suppurativa (HS) is a chronic, often suppurative cicatricial skin condition which principally affects apocrine gland-bearing skin.[1, 2] The skin of the axillae and inguinal areas are most commonly involved in those that suffer from HS; reports from other apocrine gland areas are also found including the mammary and perianal areas, buttocks, scrotum, and mons pubis. The etiology of HS includes keratinous plugging of the apocrine duct, dilation of the apocrine duct, and severe inflammation of the apocrine gland.[3] A genetic predisposition may play an important role and hormonal influences may be required for the progression of HS. An association with acne vulgaris exists, although some with HS show no signs of acne vulgaris.[4] A variety of treatments have been reported for HS, often with mixed results. These have included both topical and oral antibiotics; a variety of hormonal therapeutics; intralesional corticosteroids; oral retinoids; and a variety of surgical modalities including incision and drainage, wide surgical excision, and $C0_2$ laser therapies have been used.[5]

Photodynamic therapy (PDT) refers to the therapeutic use of photochemical reactions. It involves the use of photosensitizing drugs, the application of an appropriate light source to activate the sensitizing drug which leads to the production of singlet oxygen for tissue destruction. The most common photosensitizing drug used for PDT is 20% 5-aminolevulinic acid (ALA).[6, 7] The combination of ALA-PDT is currently FDA approved for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp.[8] Other dermatologic indications for ALA-PDT include basal cell carcinomas, squamous cell carcinomas, Bowen's disease, actinic chelitis, cutaneous T-cell lymphoma, Kaposi's sarcoma, verrucae vulgaris, and molluscum contagiosum.[6, 7] Recently, this author and investigators have described the successful use of

ALA-PDT in treating acne vulgaris and success with the use of the intense pulsed light source and vascular lasers in the photorejuvenation process and associated actinic keratoses.[9, 10]

PDT works by having diseased tissue produce and accumulate protoporphyrin IX (PpIX). PpIX is a potent photosensitizer and has been shown to accumulate in dysplastic and neoplastic dermatologic skin lesions and epidermal appendages and hair follicles which can be induced by the topical application of 5-ALA HCL, the biological precursor of porphyrin. The exogenously induced photosensitization targets the tissue for PDT. During PDT, the porphyrin molecule itself is photoactivated by exposure to visible light which will result in the production of a cytotic oxygen product that will destroy abnormal cells where the PpIX has been concentrated. There is minimal damage to the surrounding unaffected skin making PDT an attractive therapy for dermatologic concerns.[6, 7]

With this background, we identified four individuals with chronic HS who had not responded to traditional therapy with a variety of topical and systemic agents, as well as intralesional corticosteroid therapy. These patients elected to use ALA-PDT therapy as a last resort prior to contemplating a major surgical procedure or $C0_2$ laser therapy. All of the patients tolerated the treatments well. There were no adverse effects noted during these treatments. These therapies were pain-free and not associated with any downtime for these patients.

Case #1

The first patient is a 22 year old female with a history of HS involving the axillae and inguinal areas. Previous therapies included systemic and topical antibiotics; systemic, intralesional and topical corticosteroids; and incision and drainage, when appropriate. After receiving full disclosure of the ALA-PDT process and the off-label FDA use of this product for HS, the patient signed an informed consent. Twenty percent 5-ALA, Levulan® (Dusa Pharmaceuticals, Wilmington, MA) was applied to the affected areas and allowed to incubate on the skin for 30 minutes prior to light therapy. The light source used was the ClearLight™ photoclearing system (Lumenis, Santa Clara, CA), a blue light phototherapy system emitting light in the 407 – 420 nm range. Eighteen minutes of blue light in-

cubation was given to each affected area prior to light therapy. The patient received three total treatments at two-week intervals and achieved 75% clearance with this therapeutic modality. The clearance achieved has been maintained at a three month follow-up visit.

Case #2

The second case report involves a 19-year old female with a history of HS involving the axillary areas. Past treatment has included systemic and topical antibiotics, systemic and intralesional corticosteroids, and incision and drainage of several lesions. After signing an informed consent, the patient underwent four ALA-PDT treatments with the blue light photoclearing system. ALA incubation was for 15 minutes prior to each light therapy. The patient received four blue light/ALA-PDT treatments at 1 week intervals. A 75% clearance rate was achieved which was maintained at a three month follow-up (Figures 1, 2).

Case #3

The third case is a 46-year old female with a history of HS involving the inguinal areas. Past therapies have included systemic and topical antibiotics, and systemic and topical corticosteroids. The patient gave and signed an informed consent and received a total of eight blue light/ALA-PDT treatments. The ALA drug incubation was for 30 minutes prior to the blue light therapy. Each therapy was given at 1 week intervals and the patient noted 100% improvement in her HS symptoms. This has remained clear at the three month follow-up visit (Figures 3, 4).

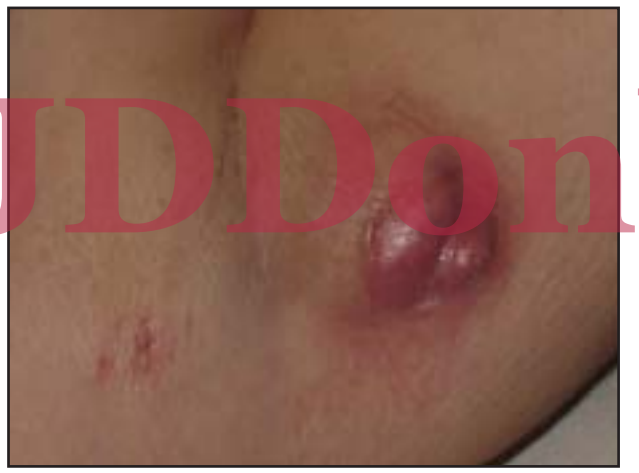

Figure 1. Pre ALA-PDT Axillae.

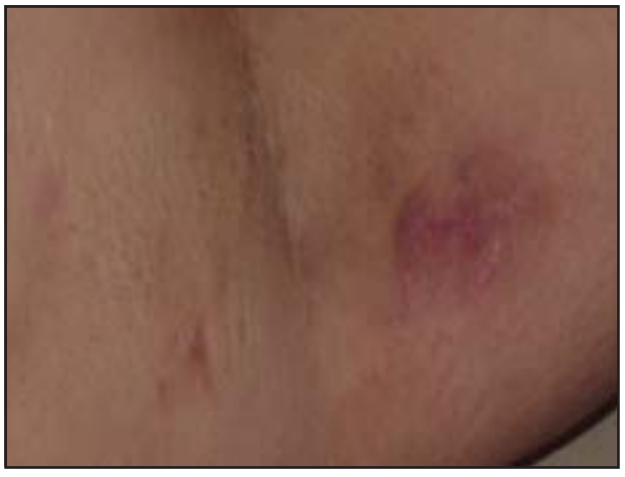

Figure 2. Post ALA-PDT Axillae.

Figure 3. Pre ALA-PDT Inguinal.

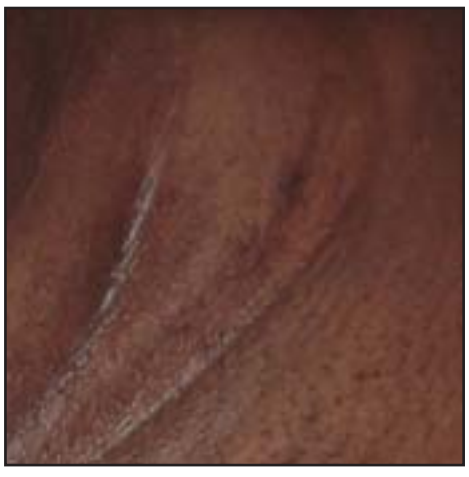

Figure 4. Post ALA-PDT Inguinal.

Case #4

The fourth case is a 24-year old female with a history of HS in the inguinal area. Past therapies have included systemic and topical antibiotics. The patient signed an informed consent and received four blue light/ALA-PDT treatments at one week intervals. Drug incubation with ALA was for 15 minutes prior to light therapy. The patient noted 75% improvement after the four treatments which persisted at a three month follow-up visit.

Discussion

HS is a chronic skin disease in which a variety of treatment options have been used in an attempt to control the symptoms of the disease. The use of ALA-PDT and an appropriate light source is a novel/new therapeutic option which is receiving a great deal of interest in dermatology as its potential uses are being defined and explored. These case reports describe the first reported cases on the use of ALA-PDT in this predominantly apocrine gland condition.

The exact mechanism of action on how this process works in HS still needs to be determined. It is felt that there is production of PpIX in the affected glandular areas/follicular units which are amenable to ALA-PDT activation with blue light therapy. The patients described in this report achieved clearance rates from 75-100% during the treatment intervals which were able to be maintained at a three month follow-up period. The patient who received the most treatments had the best response which would indicate that continued therapies in the others might yield an even greater clinical response.

ALA-PDT is finding its place in dermatologic therapy. HS can now be added to the list of entities which can be treated with ALA-PDT and light therapy. Perhaps a more invasive surgical procedure, with associated risks and morbidities, can be avoided in these patients by utilizing ALA-PDT.

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Effectiveness and Safety of ALA-IPL in Treating Actinic Keratoses and Photodamage

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Abstract

Background: Photorejuvenation involves the use of a light source or laser in reversing the signs of aging. The Intense Pulsed Light (IPL) has demonstrated effectiveness in treating signs of photodamage. Photodynamic therapy is a relatively new and promising treatment for actinic keratoses.

Objective: To determine the effectiveness of ALA-IPL in treating actinic keratoses as well as reversing the signs of aging.

Methods: A retrospective trial of 17 patients treated with ALA-IPL. Patients were evaluated for improvement of telangiectasias, blotchy pigment, fine wrinkles, coarseness of skin and number of actinic keratoses. All side effects were recorded.

Results: 68% of actinic keratoses resolved after one treatment. There was a 55% improvement in telangiectasias, a 48% improvement in pigmentary irregularities and a 25% improvement in coarseness of skin texture. There was minimal change in fine wrinkle appearance. Side effects were minimal including mild erythema and edema for 3-5 days on average. No infections were noted.

Conclusions: ALA-IPL treatment is effective in treating both actinic keratoses and signs of photodamage. In this study, we achieved significant improvement after just one treatment. ALA-IPL is a safe, effective way to treat both actinic keratoses and photodamage with little down time.

KEYWORDS:
Photodynamic Therapy
Intense Pulsed Light
Actinic Keratoses
Photodamage

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Background

Photorejuvenation involves the use of a light source or laser to reverse the signs of aging. The Intense Pulsed Light (IPL) is effective in treating several components of photoaging including dyschromia, skin texture and vascular lesions[1,2]. Photodynamic therapy is a relatively new method to treat extensive actinic keratoses, Bowen's disease, and basal cell carcinomas[3,4,5,6]. Photodynamic therapy (PDT) consists of light irradiation after topical application of aminolevalinic acid (ALA),

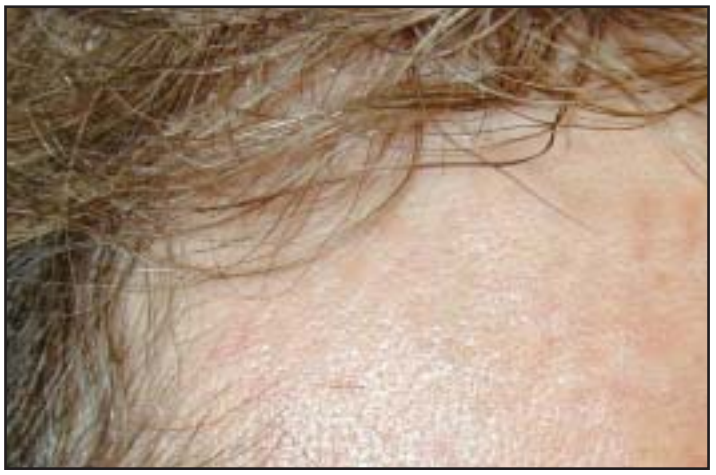

Figure 1. Pre-op.

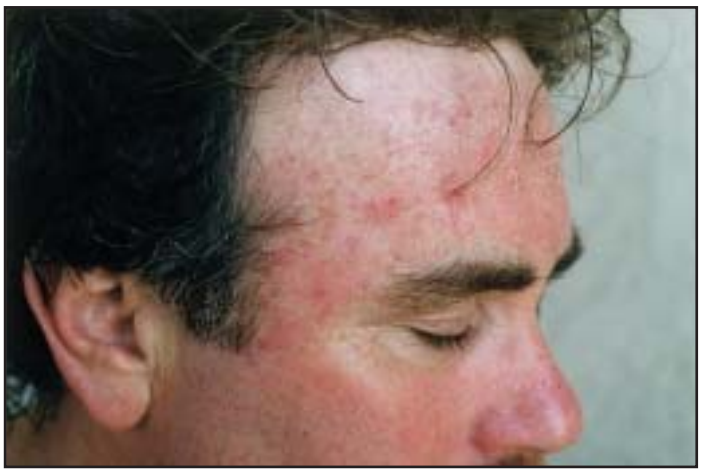

Figure 2. One day post-op.

Figure 3. Four days post-op.

Figure 4. One week post-op.

a porphyrin precursor. The objective of this study is to determine the effectiveness of topical ALA application followed by IPL irradiation (ALA-IPL) in treating actinic keratoses as well as signs of photoaging.

Subjects and Methods

A retrospective trial of 17 patients treated with ALA-IPL over four months (October-February 2003) at one center was performed. Patients with greater than three actinic keratoses on the face as well as signs of photoaging that included fine wrinkles, coarseness of the skin, pigmentary irregularities and telangiectasias were enrolled and treated. The average age of patients treated was 52 with a range from 38 to 78. Twelve patients were women and five were men. Patients had no previous history of photodynamic therapy. All patients were Fitzpatrick skin types I-III.

ALA (Levulan Kerastick, Dusa Pharmaceuticals Inc., Wilmington, MA) was applied to the entire face for one hour. The IPL was then used with a 560nm filter Vasculite Elite (Lumensis Corporation, Santa Clara, CA) at 28-32 J/cm^2 with a double pulse of 3.0 and 6.0 millisecond with a 10msec delay. Post procedure wound care consisted of sun protection and moisturizer. Standard digital photographs were taken prior to the treatment and at follow ups that occurred at 1 week, 1 month and 3 months post procedure. Patients were not treated with any topical anesthetic or

Figure 5. Pre ALA-IPL.

Figure 6. One week post ALA-IPL.

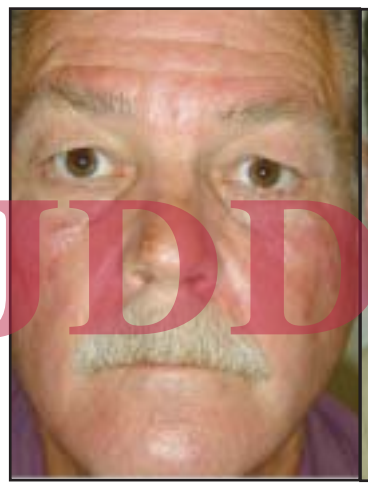

Figure 7. Pre ALA-IPL.

Figure 8. One week post ALA-IPL.

regional nerve block. At initial visit and with each follow up the number of actinic keratoses on the face was recorded for each patient.

On each follow up, patients were evaluated for improvement of pigmentary irregularities, skin texture, fine wrinkles and vascular lesions on a quartile scale from 0%; 1-25%; 26-50%; 51-75%; and 76-100%. The level of improvement of all these parameters was evaluated by a non treating physician by comparing digital images at the end of the trial. All side effects were recorded at each visit. Patients were asked the degree of discomfort during procedures from none, mild, moderate and severe.

Results

68% of actinic keratoses resolved after one treatment. There was a 55% improvement in telangiectasias, a 48% improvement in pigmentary irregularities, a 25% improvement in coarseness of skin texture and no change in fine wrinkle appearance after only one treatment. Side effects were minimal including mild erythema, edema and flaking for 3-5 days. Treatment was mildly discomforting in 78% of patients and moderately discomforting in 22%. No infections were noted. One patient had a BCC at initial visit that did not respond to one treatment. A total of three treatments were performed on this biopsy proven nodular BCC and it did not clear after these treatments. The nodular BCC was subsequently excised.

Discussion

The results of this study demonstrate the efficacy, safety and cosmetic benefit of a single treatment with ALA-IPL. This study confirms the findings of Ruiz-Rodriguez et al. that ALA-IPL is effective in treating AK's[7]. In their study, 33 out of 38 AK's were cleared after two treatments. In this study, 68 percent of AK's were cleared with just one treatment. We did not breakdown the morphology of each actinic keratoses treated but the more hypertrophic lesions were clearly more resistant. Options for treating actinic keratoses including cryosurgery, curettage and topical 5-FU. All of these options have shortcomings such as pain, pigmentary changes, scarring and limited areas to treat at once. 5-FU can treat large areas but patients have to be willing to apply the medication for weeks and then tolerate side effects such as prolonged erythema, edema, flaking and potential infection. Side effects from the ALA-IPL treatment were quite tolerable. Patients typically had mild to moderate erythema and edema for 3-5 days. Flaking was minimal. No prolonged side effects were noted and there were no cases of infection.

Aminolevulinic Acid (ALA) is a precursor in the heme biosynthesis pathway of the endogenous photosynthesizer protoporphyrin (PpIX). ALA penetrates the altered epidermis of actinic keratoses and then is

enzymatically converted to PpIX. Irradiating PpIX with light at appropriate wavelengths releases cytotoxic radicals. ALA has been used with various light sources to treat actinic keratoses. These have included lasers, xenon arc/discharge lamps, incandescent filament lamps and solid-state light emitting diodes. Most of these sources seek to utilize the peak absorption of PpIX in the red spectrum at 630nm wavelength[8]. IPL with a 560 filter targets this peak absorption and also allows for the beneficial cosmetic effects that we found in this study.

Besides the efficacy in treating actinic keratoses, ALA-IPL clearly improved signs of photodamage. There was a 55% improvement in telangiectasias, a 48% improvement in pigmentary irregularities, a 25% improvement in coarseness of skin texture and no change in fine wrinkle appearance after only one treatment. This is the first study to clearly demonstrate the effectiveness of ALA-IPL in treating both actinic keratoses and signs of photodamage.

Conclusion

ALA-IPL treatment is effective in treating both actinic keratoses and signs of photodamage. There was a 68 percent clearance of actinic keratoses after just one treatment. Cosmetic results included improvement in telangiectasias, pigmentary irregularities and skin texture were found as well. Side effects were mild including 3-5 days of erythema, edema and flaking.

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