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Seminars in Cutaneous Medicine and Surgery

# Photodynamic Therapy: Current Evidence and Applications in Dermatology

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**Photodynamic therapy (PDT) involves the activation of a photosensitizing drug, which preferentially localizes to diseased skin, by irradiation with light to cause selective cytotoxic damage. Since its discovery in the early 20th century and the development of topical photosensitizers 2 decades ago, PDT is increasingly being used in dermatology for a wide range of neoplastic, inflammatory, and infectious cutaneous conditions. Topical 5-aminolevulinic acid and methyl aminolevulinic acid, the most commonly used agents in PDT, have received Food and Drug Administration approval for the treatment of actinic keratoses, and many second-generation photosensitizers are under investigation. Compared with conventional therapies, PDT has the advantage of being noninvasive and capable of field treatment. It is also associated with quicker recovery periods and excellent cosmetic results. Because of these benefits, PDT is being evaluated as a potential treatment option for many dermatologic conditions and has been shown to be effective for certain nonmelanoma skin cancers. Although research is still limited, PDT might also have a therapeutic benefit for cutaneous T-cell lymphoma, acne, psoriasis, leishmaniasis, and warts, among others. This article is a review of the clinical applications of PDT in dermatology and summarizes the current evidence in literature describing its efficacy, safety, and cosmetic outcome.**
**Semin Cutan Med Surg 30:199-209 Published by Elsevier Inc.**

**KEYWORDS** photodynamic therapy, photosensitizer, aminolevulinic acid

Photodynamic therapy (PDT) is a promising noninvasive treatment for malignant and nonmalignant diseases in dermatology. It uses a photosensitizing agent, light energy, and oxygen to generate a chemical reaction that results in selective cell killing. With the development of topical photosensitizing agents in the 1990s, there has been a growing interest in the use of PDT. In its early applications, PDT was primarily used for the treatment of oncological conditions, and since then it has become an established treatment modality for actinic keratoses in the United States, as well as for basal cell carcinoma and Bowen disease in Europe. During recent years, PDT has been recognized as a much more versatile therapy with a wide range of so-called off-label uses. It has been used for non-oncological dermatologic conditions such as acne, photoaging, psoriasis, warts, and leishmaniasis with promising results. In this article, we review evidence in literature for the currently approved and off-label applications of PDT, including its efficacy, safety, and cosmetic outcome.

## History, Mechanism, and Photosensitizers

PDT is a treatment modality that uses light, oxygen, and a light-activated chemical called a photosensitizer for selective cell killing. It was first developed at the beginning of the 20th century in Munich, when Oscar Raab and his professor Hermann von Tappeiner observed that acridine orange had a toxic effect on the protozoa paramecia in the presence of light. In 1903, this discovery eventually led to the first clinical application of PDT by von Tappeiner, who in cooperation with a dermatologist named Jesionek used eosin and light to treat conditions such as lupus vulgaris, syphilis, psoriasis, and superficial skin cancer. Von Tappeiner subsequently

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*Conflict of Interest Disclosures:* The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.
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1085-5629/11/$-see front matter Published by Elsevier Inc.
doi:10.1016/j.sder.2011.08.001

went on to publish a textbook with Jodlbauer, which described this phenomenon as an oxygen-requiring process called "photodynamic reaction."[1,2]

The basic mechanism behind PDT involves the activation of a photosensitizing agent by light, resulting in the generation of reactive oxygen species (ROS), primarily singlet oxygen.[3,4] Studies have shown that ROS subsequently cause oxidative damage to cellular components and initiate a cascade of cellular events, resulting in cell death by necrosis, autophagy, and apoptosis, with apoptosis being the primary mechanism.[5-9] Apoptosis in response to PDT was first reported by Agarwal et al[10] in 1991. For sensitizers that localize in mitochondria, like 5-aminolevulinic acid (ALA) (Fig. 1), disruption of mitochondrial function is a key event in PDT-induced apoptosis.[8,11,12] Although the predominant mechanism of action of PDT is thought to be direct cell killing, vascular damage and indirect stimulation of inflammatory mediators also contribute to its effects.[4,7,13,14]

Most photosensitizers used in PDT are derivatives of hematoporphyrin, an endogenous porphyrin first synthesized from heme in the mid-19th century. In 1911, Hausmann reported the photodynamic effects of hematoporphyrin and light on paramecia as well as in the skin of mice exposed to light after systemic hematoporphyrin administration. The localization of hematoporphyin in cancerous tissue was first described by Policard in France in 1924 and then by German researchers Auler and Banzer, who reported similar findings in 1942. However, hematoporphyrin required large doses for photosensitization, resulting in severe phototoxicity, and was thus replaced by a purified hematoporphyrin derivative (HpD) developed by Schwartz in the mid-20th century. A more purified HpD porfimer sodium, now commercially available as Photofrin® (Axcan Pharma, Birmingham, AL) was the first systemic photosensitizer to be approved by the Food and Drug Administration (FDA). Although HpD was more effective in tumor localization and required smaller doses compared with crude hematoporphyrin, the prolonged and pronounced photosensitivity associated with systemic photosensitizing agents continued to be a major drawback.[1]

In 1990, Kennedy et al[15] introduced a topical photosensitizer, which represented a significant achievement toward overcoming many of the early limitations of PDT. Kennedy et al described that the topical application of ALA, a precursor of endogenous protoporphyrin IX (PpIX) in the heme biosynthetic pathway, led to intracellular accumulation of photosensitizing concentrations of PpIX preferentially in the abnormal epithelium. The shorter duration of photosensitization, typically resolving within 24 hours after application, was a major advantage of ALA over HpD.[16] ALA (Levulan®; DUSA Pharmaceuticals, Wilmington, MA) was FDA-approved for the treatment of actinic keratoses in 1999. With the development of topically applied ALA in PDT, it was hypothesized that ALA esters, which have greater lipophilicity than ALA, might provide more effective penetration of skin lesions. In a study by Fritsch et al,[17] methyl aminolevulinic acid (MAL) (Fig. 2), a methyl ester of ALA, was found to accumulate in lesional skin with greater specificity compared with ALA. In 2004, MAL (Metvix®; Photocure ASA, Oslo, Norway) was approved by the FDA for the treatment of actinic keratoses in the U.S. However, these FDA-approved PDT agents are not without adverse effects, and there is still a need for photosensitizers with a better safety and efficacy profile. Among the many additional photosensitizers that have been synthesized, silicon phthalocyanine Pc 4 is a promising second-generation photosensitizer developed at Case Western Reserve University.[18] It is a compound structurally related to porphyrins and has been shown to induce cell death via apotosis in vitro.[19] In a phase I trial, Pc 4-PDT was demonstrated to be a safe treatment modality for cutaneous neoplasms.[20] As PDT secures its place as an established treatment in dermatology, the search for improved novel photosensitizers continues.

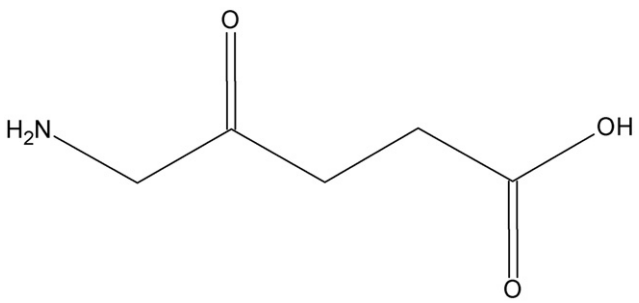


**Figure 1** Structure of 5-ALA.

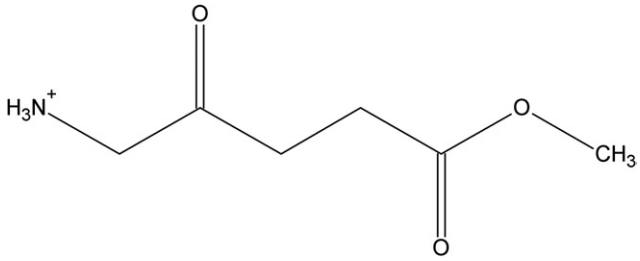


**Figure 2** Structure of MAL.

# PDT for Cutaneous Neoplasms

## Actinic Keratosis

Actinic keratosis (AK) is the most common precancerous lesion of the skin. The lesions develop on areas of chronic ultraviolet exposure and often occur in multiples at these sites, leading to what is termed *field cancerization*. Annual transformation rate for an individual lesion has been reported to vary widely from 0.025%-16% per year.[21] In a longitudinal study by Marks et al,[22] the investigators found that 60% of squamous cell carcinoma (SCC) occurred from progression of AKs. In another report, 97% of SCC cases reviewed were found to be associated with contiguous AKs.[23] Although some studies suggest that the overall risk of malignancy associated with AKs might be low,[22] these lesions represent a dilemma for the clinician who must decide to pursue treatment because there is no reliable way to predict which individual lesion will progress to malignancy. The histologic and

clinical features of AKs and SCC fall on a continuum, and one evolves into the other without any clear distinguishing features.[24] Thus, treatment of all AKs is generally recommended. Treatment options commonly used are cryosurgery, 5-fluorouracil, and curettage.[25]

Several studies have provided strong evidence that MAL and ALA-PDT are effective for nonhyperkeratotic face and scalp AKs, with cure rates ranging from 69%-100%.[26] ALA was the first topical PDT agent to be approved by the FDA for this purpose in December 1999.[27] In 2001, Jeffes et al[28] published an investigator-blinded, randomized clinical trial demonstrating the efficacy of ALA-PDT in treating multiple AKs. The results showed that ALA application followed by irradiation with blue light resulted in complete response in 85% of AKs on the face and scalp compared with 6% in the placebo-PDT group. In a larger multicenter study, Piacquadio et al[29] demonstrated that >75% of AKs cleared in 89% of patients at 12-week follow-up and reported that ALA-PDT is a safe and effective therapeutic option for AKs.

These clearance rates are consistent with those reported for conventional forms of therapy. A European study by Kurwa et al[30] found that there was no statistically significant difference in the reduction of lesional area between patients who received a one-time treatment of ALA-PDT and those who had 3 weeks of 5-fluorouracil. Smith et al[31] further confirmed that ALA-PDT and 5-fluorouracil have similar efficacies in the treatment of AK and also concluded in their study that ALA-PDT was better tolerated and cosmetically superior. More recent studies attempted to characterize the long-term effects of ALA-PDT on AKs. A multicenter study by Tschen et al[32] that reexamined patients 12 months after ALA-PDT reported that the overall recurrence rate was 24% for all lesions that were noted to be cleared at some point during the 12-month period. Seven percent of recurrent lesions were histopathologically diagnosed as SCC. However, there was little difference between the incidences of SCC after PDT compared with baseline, indicating that PDT does not have any cancer-promoting effects.

Like ALA, MAL has been demonstrated in multiple clinical trials to be effective in the treatment of AK.[26,33,34] MAL was approved by the FDA for the treatment of AK in 2004; in Europe, MAL has been approved for AK and basal cell carcinoma since 2001. According to Pariser et al,[34,35] 86%-89% of AK lesions displayed complete lesional response after 2 treatments of MAL-PDT with red light. In a follow-up study by Tarstedt et al,[33] a single treatment of MAL-PDT was as effective as a two-treatment schedule, resulting in 93% and 89% complete response, respectively. However, the two-treatment schedule yielded better efficacy in treating thicker lesions. These response rates indicate that MAL-PDT is at least as effective as cryotherapy and ALA-PDT in the treatment of AKs.[34] Szeimies et al[36] published the first study comparing MAL-PDT with cryotherapy in the treatment of AK, reporting similar response rates with either two sessions of MAL-PDT or treatment with cryotherapy (67% vs 75%, respectively) at 3-month follow-up. In another trial by Freeman et al,[37] however, the data suggested that two sessions of MAL-PDT yielded significantly greater efficacy than cryotherapy in the treatment of AKs (91% vs 68%). When compared with ALA, MAL has been shown to have better penetration into AK lesions, suggesting that MAL might be more effective in achieving higher lesional concentrations.[17] Yet, a small double-blind, randomized prospective study by Monoley et al[38] found that both ALA-PDT and MAL-PDT achieved high clearance rates with no demonstrable difference in efficacy between the two.

In conclusion, AKs are highly responsive to PDT by using topical ALA or MAL. It might be the preferred treatment for widespread AKs, because PDT can easily treat multiple lesions simultaneously. It is also particularly beneficial for patients with AKs in cosmetically sensitive areas such as the face because it has been shown to provide a significantly better cosmetic outcome compared with cryotherapy[36,37] as well as an improvement in symptoms of photoaging.[31] PDT has consistently shown to be a safe, highly efficacious mode of therapy for AK, providing greater patient satisfaction, rapid healing, and excellent cosmetic results.[28-31,33,34,36,37]

## Bowen Disease/SCC In Situ

Bowen disease, which is a form of SCC in situ occurring mainly in elderly people, most often appears as a scaly, crusted, erythematous, well-demarcated plaque on sun-exposed surfaces including the face, scalp, and hands.[39] It might also frequently occur on the lower legs.[40] Bowen disease has the potential for malignant invasion into the underlying dermis, which occurs in at least 3% to as high as 20% of cases.[41,42] Once it has invaded into the dermis, metastasis develops in more than one third of the patients.[42] Surgical excision is the gold standard for treatment, but electrodessication and curettage are most commonly performed.[43]

Studies on ALA and MAL-PDT for Bowen disease have reported high efficacy that rivals or exceeds that of conventional therapies. In these studies, the initial clearance rates ranged from 80%-100%, mostly around 90%, and recurrence rate at 12 months was between 0% and 10%.[44] A randomized clinical trial by Morton et al[45] was the first to demonstrate that ALA-PDT is as effective as cryotherapy, clearing 100% of lesions after only two treatment sessions, whereas cryotherapy required three sessions for 100% lesion clearance. Complications such as ulceration, infection, and disease recurrence were reported in the cryotherapy group but not in the PDT group. ALA-PDT was also significantly superior to 5-fluorouracil in both immediate and long-term efficacy. Eighty-eight percent of the lesions had initial complete response after treatment with ALA-PDT versus 67% with 5-fluorouracil. At 12-month follow-up, recurrence was noted in 7% versus 27%, respectively. Moreover, patients treated with 5-fluorouracil experienced more adverse reactions.[46] Of note, in transplant recipients who have an increased risk of skin malignancies because of immunosuppression, ALA-PDT resulted in high initial cure rates but less than satisfactory long-term clearance, possibly because of a greater prevalence of thick, hard-to-treat hyperkeratotic lesions in this group.[47]

More recently, a large multicenter trial involving 40 European medical centers investigated the efficacy, toler-

ability, and cosmetic outcome of MAL-PDT for Bowen disease.[48] In this study, Morton et al[48] observed a 3-month complete response rate of 86%, which was similar to the efficacy of cryotherapy and 5-fluorouracil. At 12 months, the sustained response rate remained high at 80% for MAL-PDT, which was significantly superior to the other 2 modalities. Cosmetic outcome was also significantly better after MAL-PDT. In contrast to ALA-PDT, MAL-PDT did not result in increased recurrence when used in transplant patients. A small randomized trial involving transplant patients with Bowen disease found that both short-term and long-term clearance rates were high, with a response rate of 89% remaining unchanged at 1-month, 3-month, and 6-month follow-up.[49]

Important features of topical PDT for Bowen disease are the rapid healing time and capacity to treat more than 1 lesion at a time. Bowen disease has a predilection for occurrence on the lower legs, where wound healing is more challenging, and in elderly people who often have vascular compromise, which could further delay healing. Unlike surgical excision that can be complicated by wound dehiscence or necrosis, PDT is a noninvasive option that is better tolerated by patients, spares the tissue, and results in less morbidity.[50] The tissue-sparing nature of PDT makes it an attractive option for widespread Bowen disease that cannot be treated by surgery. Studies indicate that PDT is highly effective in clearing large patches of Bowen disease and propose that PDT should be considered as a first-line therapy for such large lesions.[51,52] In summary, PDT is a reliable treatment for Bowen disease, with high efficacy, rapid healing, and excellent cosmesis.

## Basal Cell Carcinoma

Initially termed *ulcus rodens* by Hermann Lebert in 1851 because of its resemblance to something a rat had gnawed on,[53] basal cell carcinoma (BCC) is the most common skin cancer. Between 1979 and 1993, there was an 80% increase in the incidence of BCC.[54] Although BCC only rarely metastasizes, it can grow aggressively, causing extensive tissue destruction and significant morbidity.[55] Most BCCs occur on the head and neck, with the nose as the most common site (25%-30%). Most frequent histologic subtypes of BCCs are nodular (50%-54%) or superficial (9%-11%).[56]

Although the mainstay of BCC therapy has been surgery or other forms of ablation, the cosmetically sensitive location of BCCs makes a noninvasive form of treatment like PDT an attractive choice. There exists now a large body of evidence supporting PDT as an effective alternative treatment for BCC, and guidelines have been developed to help direct treatment choice.[26,57-59] In a review by Peng et al,[60] complete clearance rates of 87% and 53%, respectively, for 826 superficial and 208 nodular PDT-treated BCCs at follow-up periods of 3-36 months were reported. Since then, other studies have followed that further support that ALA-PDT is a highly effective therapy for superficial BCC.[57,58]

Nodular BCCs showed a less favorable response, with clearance rates lower than 50% after a single treatment.[61] Partial debulking in combination with PDT raises remission rates to as high as 92%.[61] By contrast, a more recent study by Berroeta et al[62] found that prior curettage of nodular BCCs before treatment with ALA-PDT did not show an advantage in improving PDT efficacy. Compared with surgical excision, ALA-PDT with debulking was still inferior, with a failure rate of 30%, versus 2% for surgery. Because tumor thickness is a factor that limits responsiveness to PDT, Morton et al[59] concluded that ALA-PDT is effective for superficial BCCs $<2$ mm thick and particularly for larger or multiple lesions, but less than optimal for nodular lesions.

Interestingly, MAL-PDT has achieved far better results than ALA-PDT in the treatment of BCCs, especially for nodular BCCs. Greater efficacy of MAL might be due to its higher lipophilicity, faster skin penetration, and higher selectivity. Soler et al[63] demonstrated that MAL-PDT resulted in an overall cure rate of 79%, with 89% remaining in complete response at 2-4 years after PDT. They also reported improved efficacy of MAL-PDT when preceded by curettage. Hence, prior curettage is now routinely used in combination with MAL-PDT. MAL-PDT for superficial BCC has also been reported efficacious, with cure rates of 80%-100%.[64] A large multicenter study by Horn et al[65] demonstrated a 92% response rate for superficial BCCs. This was supported by Vinciullo et al,[66] who found an 89% response rate at 3-month follow-up for "difficult-to-treat" BCCs, defined as a large lesion or a lesion occurring in the H-zone of the face. Indeed, more recent studies provide evidence that MAL-PDT results in long-term response rates that are comparable to conventional forms of therapy. In a 5-year randomized trial by Basset-Seguin et al,[67] there was no difference in 5-year recurrence rates with either MAL-PDT or cryotherapy (22% vs 20%, respectively), whereas a significantly greater proportion of patients in the PDT group reported excellent cosmetic outcome.

In contrast to ALA-PDT, multiple phase III studies have also consistently demonstrated the high efficacy and reliability of MAL-PDT in the treatment of nodular BCCs. Horn et al[65] and Vinciullo et al[66] reported clearance rates of 87% and 82%, respectively, of nodular BCCs at 3-month follow-up after 1-2 sessions of MAL-PDT. Although the lesional clearance rates after MAL-PDT of nodular BCC were slightly lower than the rates seen with superficial lesions, the response remains excellent and in no way inferior to rates seen with surgical excision, the gold standard of BCC therapy. Rhodes et al[68] reported that complete response rates between groups treated with surgery versus MAL-PDT did not differ significantly (98% vs 91%). Results at 24-month follow-up, however, suggested higher recurrence after MAL-PDT than surgery, with 9.4% of lesions recurring in the PDT group compared with only 1.9% after surgery. In a 5-year follow-up study executed by the authors, the higher trend of recurrence with PDT continued, with recurrence occurring in 14% of lesions treated with MAL-PDT versus 4% in the surgery group.[69]

Although surgery remains the first-line therapy for BCCs, PDT is also a potent treatment modality for BCCs and has repeatedly shown significantly superior cosmetic

outcome. PDT might be considered a first-line therapy for patients who are not appropriate for surgery such as patients with bleeding disorders or those at high risk of scarring.

### Cutaneous T-Cell Lymphoma

Mycosis fungoides (MF) is the most common and indolent form of cutaneous T-cell lymphoma (CTCL), accounting for about 70% of cases.[70] There is no curative treatment for MF. Current skin-directed options include topical steroids, topical chemotherapy, and phototherapy. However, the response to these traditional forms of treatment has been disappointingly transient, and patients with advanced CTCL continue to have poor prognosis.[71] Advances in treatments that are low in toxicity while providing lasting results are warranted. Because of the rarity of CTCL, very few randomized trials have been conducted that compare the conventional therapies. Studies involving PDT are scarce, consisting mainly of case reports and clinical trials involving a small number of patients.

Among the topical PDT agents, ALA has the most data supporting its potential as an effective treatment for CTCL. The investigation of PDT for CTCL stemmed from earlier reports that PpIX preferentially accumulated in malignant T lymphocytes.[72] In a small prospective study, Edström et al[73] investigated the clinical and histologic effects of ALA-PDT in the treatment of MF. The results demonstrated complete response in 7 of the 9 plaques after 2 or 3 PDT sessions, with no recurrence during the 4-19 months of follow-up. Additional case reports[74,75] of successful treatment of CTCL lesions resulting in both clinical and histologic clearance further suggest that this modality might be a good alternative. Coors et al[76] have also had success in achieving complete remission in persisting lesions of patients who had reached a partial remission with conventional therapies. Thus, the authors suggest the use of PDT as an additional therapeutic option for patients with lesions resistant to traditional therapy.

MAL and silicon phthalocyanine Pc 4, a second-generation photosensitizer, are also being investigated for use in the treatment of CTCL. In a study involving 5 patients with MF, Zane et al[77] observed MAL-PDT resulted in complete remission in 4 patients and partial response in 1 patient after an average of 6 treatment sessions. In a recent in vitro study conducted by our group, Pc4-PDT was observed to preferentially induce apoptosis of malignant T lymphocytes from the blood of patients with diagnoses of Sezary syndrome and to induce photodamage of the antiapoptotic protein Bcl-2 in skin biopsies of MF lesions.[78]

Presently, the role of PDT in the treatment of CTCL is not clearly established, and larger studies assessing clinical as well as histologic clearance are needed to demonstrate efficacy and define optimal treatment protocols. Nevertheless, the limited data available indicate that PDT is a promising new alternative treatment of CTCL that warrants further exploration.

## PDT for Inflammatory Conditions

### Acne Vulgaris

Acne vulgaris is a common, chronic inflammatory skin disorder typically occurring in adolescents, although it can affect people of any age. It is characterized by open and/or closed comedones as well as inflammatory lesions including papules, pustules, and cysts. The mainstay of treatment consists of topical retinoids, benzoyl peroxide, topical or oral antibiotics, and oral isotretinoin for severe cases.[79]

The idea to use light in the treatment of acne vulgaris first arose from the knowledge that *Propionibacterium acnes*, the primary bacterium implicated in the pathogenesis of acne,[79] naturally produces endogenous porphyrins, predominantly coproporphyrin III.[80] It has been theorized that *P acnes* hyperproliferate in the sebaceous glands and that these porphyrins, by their cytotoxic effects, might contribute to the inflammatory reaction seen in acne.[81] In a study to better characterize the role of porphyrins in acne vulgaris, Borelli et al[82] examined the concentration of coproporphyrin III in previously untreated acne patients before and after 2 months of treatment with isotretinoin. The authors noted that clinical improvement corresponded to decreases in porphyrin concentrations.

The knowledge of the relatively large amounts of endogenous porphyrins in acne skin spurred the idea of treating acne patients with phototherapy. Ashkenazi et al[83] found that irradiation of *P acnes* in culture with intense blue light, shown in in vitro studies to be the most sensitive wavelength for this bacterium,[84] resulted in moderately reduced viability of culture. This demonstrated that illumination of coproporphyrin with blue light appears to play a role in *P acnes* photoinactivation. Similarly, a clinical trial performed by Kawada et al[85] in which acne patients were treated with blue light phototherapy showed that phototherapy might be effective in acne treatment, reducing acne lesions by 64% in the participating patient. In addition, Ashkenazi et al noted in their in vitro studies that the addition of ALA to the cultures further led to significantly more decreased viability, suggesting that ALA might be a good treatment for acne.

In 2000, Hongcharu et al[86] conducted the first prospective clinical trial to evaluate the effectiveness of topical ALA-PDT for patients with back acne both clinically and histologically. When ALA was applied to acne for 3 hours and then irradiated with red light, a clinically significant improvement of the inflammatory lesions was observed. On histology, a transient acne-like folliculitis was noted. Clinically, sebum excretion was eliminated, and these effects lasted for at least 20 weeks after multiple treatment sessions and 10 weeks after a single treatment. Thus, it is suggested that the mechanism of PDT in acne includes photodestruction of *P acnes* as well as a reduction in the size and/or function of the sebaceous gland. However, reduction in *P acnes* or sebum excretion in patients with back acne was not seen in a study by Pollock et al,[87] despite clinical improvement and treatment protocol similar to the one used by Honcharu et al. Limiting factors in the use of

PDT for acne vulgaris were commonly reported significant side effects, including pain, edema, hyperpigmentation, and blistering rash.[86,87] Itoh et al[88] examined the effects of ALA-PDT for intractable facial acne and also reported efficacy results and a side effect profile consistent with the findings of the previously mentioned studies.

Although there have been fewer studies published concerning MAL of acne vulgaris, a study by Wiegell and Wulf[89] was the first to demonstrate efficacy of MAL-PDT in treating moderate to severe facial acne. With 68% reduction in the number of inflammatory acne lesions, MAL-PDT was demonstrated to be at least as effective as oral antibiotics. MAL-PDT, however, was not quite as effective as isotretinoin and resulted in severe pain, edema, erythema, and pustular eruptions. The first comparative split-face study of ALA and MAL for acne was conducted by Wiegell and Wulf in 2006.[90] Patients with facial acne were treated with ALA or MAL on each hemiface, followed by irradiation with red light. At the end of the study, both treatments were effective in improving the lesions, and no significant difference in response rates existed between the two. All patients experienced some side effects, which occurred more severely and uniformly on the side of the face treated with ALA-PDT, perhaps because of the greater accumulation of PpIX found in the normal skin of the ALA side.

Current investigations into PDT for acne vulgaris indicate that it is an effective alternative option for the treatment of this condition. Despite the occurrence of unwanted side effects, PDT did not leave residual scarring.[86-89]

### Psoriasis Vulgaris

Although PDT has been used for psoriasis since the early 1990s, there is a lack of data in the literature of well-conducted trials, and thus the clinical efficacy of PDT in psoriasis remains controversial. In 1990, Kennedy and Pottier[16] were the first to report selective accumulation of ALA-induced PpIX in plaque psoriasis. However, other studies have also found accumulation of PpIX in plaques distant from the application site, possibly indicating a systemic effect of topical ALA.[91,92] When Robinson et al[92] treated chronic plaque psoriasis with multiple sessions of topical ALA-PDT, for up to 12 treatments, 8 of the 10 patients showed clinical improvement. Biopsies of the post-PDT lesions showed PpIX localization in the epidermis and stratum corneum. Although PDT improved the plaque-type psoriasis, the level of fluorescence was not consistent between sections taken from the same biopsy, and patients frequently reported adverse effects. Thus, the authors concluded that ALA-PDT is an unsuitable option for the treatment of psoriasis because of significant patient discomfort and unpredictable response.

A study by Bissonnette et al[93] investigated the effect of oral ALA-PDT on psoriatic plaques. The results demonstrated that, like topical ALA, oral ALA accumulated mostly in the epidermis, and subsequent irradiation with light led to clinical improvement. They also observed that oral ALA-PDT induced apoptosis in the lesional T lymphocytes, which have been suggested to play a key role in the pathogenesis of psoriasis. Apoptosis of T lymphocytes has also been observed after psoralen plus ultraviolet A (PUVA) therapy. Among the therapeutic options that exist for psoriasis, PUVA is associated with one of the longest periods of remission, and thus it has been suggested that the apoptosis of lesional T lymphocytes might indicate longer remission time after treatment of psoriasis. In contrast to the study by Robinson et al,[92] overall tolerability of systemic ALA-PDT in this group was reported to be excellent, especially with the lower doses of ALA administered.

Other clinical trials supported the findings of Robinson et al[92] that ALA-PDT has suboptimal efficacy and a poor adverse event profile. Radakovic-Fijan et al[94] conducted a randomized trial in which 21 patients with generalized chronic plaque-type psoriasis were treated with ALA-PDT. Complete clearance was observed in only 8 lesions, and substantial improvement occurred in 4 of the 63 lesions treated. In addition, patients experienced very painful sensations in a dose-dependent manner during the treatment session and lasting for up to 2 days after treatment. In another study by Schleyer et al,[95] topical ALA-PDT resulted in a mean improvement of 38%-51%, in a dose-dependent manner, in patients with chronic plaque psoriasis. During treatment, irradiation had to be interrupted several times because of severe burning and pain. Thus, in both studies, the authors concluded that ALA-PDT is an inadequate treatment option for psoriasis because of disappointing clinical response and an unfavorable side effect profile. Of note, although topical PDT appears to be an unsatisfactory option for plaque-type psoriasis, recent case reports of patients with palmoplantar pustular psoriasis (PPP) suggest that PDT might be an effective alternative therapy in its treatment. Kim et al[96] describe 3 intractable cases of PPP, all of which resulted in mild to marked improvement after PDT.

Overall, small clinical trials have demonstrated variability in the efficacy of PDT for psoriasis. Perhaps there is a need for other photosensitizers with greater T-cell specificity to elucidate the role of PDT in psoriasis vulgaris.

## Antimicrobial Applications of PDT

### Leishmaniasis

Cutaneous leishmaniasis (CL),[97] caused by protozoa *Leishmania*, was first described back in the 9th century but still continues to be a major health problem, with approximately 1.5 million new cases occurring each year. *Leishmania* are transmitted by sandflies and infect dermal macrophages, which eventually fill with multiplying amastigotes and burst, resulting in further spread of infection. Infection with *Leishmania* results in a variety of clinical conditions ranging from a simple ulcer to fatal disease. There is no single optimal treatment, because therapy is guided by the species of the causal organism, which determines the severity of disease and response to treatment. Cutaneous lesions can also potentially self-heal, resulting in natural resolution over months or

years and leaving an atrophic scar. Standard treatments are often ineffective or result in poor cosmetic results.

Several case reports in literature have documented successful treatment of CL with PDT. In 2003, Enk et al[98] were the first to describe the antiparasitic effect of PDT in their report of 11 Israeli patients with CL. Treatment of 32 lesions with topical ALA-PDT resulted in clinical improvement with significant reduction in lesion size after 1 week. Amastigotes were no longer detectable in all but one of the lesions. Furthermore, Sohl et al[99] reported a patient with leishmaniasis resistant to paromomycin, itraconazole, and pentamidine who responded rapidly to MAL-PDT with good cosmetic result. A study by Gardlo et al[100] investigating the efficacy of PDT in comparison with paromomycin, an established systemic agent for CL, found that PDT showed superior results. All 5 CL lesions treated with PDT were clear of *Leishmania* both clinically and histologically, whereas only 2 lesions cleared by using paromomycin. Moreover, lesions that were nonresponsive to paromomycin improved when they underwent subsequent PDT. Recently, a larger clinical trial by Asilian et al[101] involving 60 patients divided into 3 groups investigated the efficacy of topical PDT, paromomycin, and placebo, respectively. Results confirmed that PDT is a superior treatment modality compared with paromomycin, with a complete response rate of 93% in the PDT group versus 41% in the paromomycin group.

The mechanism underlying the effect of PDT on CL is not clearly understood. In an in vitro study by Sah et al,[102] *Leishmania* were found to be deficient in 7 or 8 of the enzymes required for heme synthesis and thus were unable to convert ALA to PpIX. Normally, activation of PpIX by light results in oxidative damage that is responsible for the toxic effect seen with PDT. However, inability to produce PpIX would disrupt this mechanism and makes the efficacy of ALA-PDT against *Leishmania* intriguing. In addition, Kosaka et al[103] observed in their in vitro studies that the uptake of PpIX by *Leishmania* was not enough to kill the parasites and proposed an alternative mechanism for the clinical efficacy of PDT for CL. The authors suggest that the effects of PDT on CL are the result of vascular obstruction resulting in nonspecific tissue destruction and depopulation of macrophages, rather than direct killing of parasites.

In summary, current data indicate that topical PDT is a well-tolerated, safe alternative treatment option for CL, with high efficacy exceeding traditional treatments. Although CL spontaneously heals with time, PDT results in rapid eradication of amastigotes and improvement in the appearance of the lesion.

## Warts

Human papillomaviruses[104] are responsible for the development of a range of common skin diseases including warts on the hands or soles of the feet, genital warts, cervical carcinoma, and anogenital squamous carcinoma. Treatment includes surgical excision, cryotherapy, curettage, or cytotoxic drugs and is generally efficacious. However, some warts remain recalcitrant to therapy, and even those that are successfully removed have a high rate of recurrence.

In earlier studies, PDT was suggested to have antiviral properties. Fehr et al,[105] who were investigating the feasibility of using PDT for vulvar or vaginal condylomas and intraepithelial neoplasia, treated biopsies of condylomata with ALA and visualized selective fluorescence of the condylomata. This indicated that nonselective application of a photosensitizer resulted in selective accumulation in the viral lesion. Ross et al[106] supported this finding, reporting that 17 of 25 condylomata acuminata treated with topical ALA displayed significantly greater fluorescence compared with the normal adjacent skin. The reason for the selectivity was theorized to be due to an alteration in the stratum corneum of the infected cells, resulting in increased drug penetration. The results of these studies suggested that ALA-PDT might be a potential therapy for condylomata and could also be useful as a tool to localize these lesions before treatment.

In a comparative trial by Stender et al,[107] 30 patients with hand and foot warts resistant to other therapy were treated with keratolysis plus ALA-PDT by using various light sources or cryotherapy. They observed that topical ALA with white light resulted in complete remission in 73% of lesions, whereas ALA with red light and blue light had response rates of 42% and 23%, respectively. Twenty percent remission occurred after cryotherapy. At 12-month follow-up no recurrence was noted, and no scars were observed in the ALA-PDT treated areas. In a larger trial conducted by the same group,[108] similar high rates of efficacy were observed after PDT of recalcitrant hand and foot warts, and the investigators found ALA-PDT to be significantly more effective than placebo. Fifty-six percent of warts vanished with ALA-PDT, and no recurrence was noted at week 8. Fabbrocini et al[109] also conducted a trial examining the effect of ALA-PDT on plantar warts and found that ALA-PDT was a highly effective alternative treatment. The warts were keratolysed with urea and salicylic ointment before the application of ALA. At 2-month follow-up 48 of 64 treated lesions (75%) were completely healed. Although there is less research in the treatment of warts with MAL-PDT, some case reports have been described. A case of a recalcitrant thumb wart treated with topical MAL-PDT by Chong et al[110] was the first documented report of successful treatment of a resistant acral wart with MAL-PDT. Yoo et al[111] also reported that the use of a carbon dioxide laser with MAL-PDT can enhance the treatment of periungual warts. In conclusion, current data suggest that ALA-PDT is an effective promising alternative for recalcitrant hand and foot warts, especially when coupled with prior keratolysis. ALA-PDT in combination with white light might deliver the best results.

Likewise for genital warts, current evidence supports the use of ALA-PDT. In a pilot study by Frank and Bos[112] involving 7 patients with anogenital warts, treatment with ALA-PDT resulted in complete remission in 4 of the patients. Pain was the major drawback reported. Furthermore, in a small study involving 9 men with genital condyloma unresponsive to at least 1 conventional therapy, Herzinger et al[113] achieved complete cure in 3 patients and partial response in 3 others

after treatment with ALA. Recurrence occurred in 1 patient 3 weeks after treatment. Compared with established treatments for genital warts, Fehr et al[114] found that ALA-PDT had similar rates of efficacy as $CO_2$ laser ablation and surgery in 38 patients with vulvar intraepithelial neoplasm I/II or vaginal condyloma. At 12-month follow-up, 51% were recurrence-free in the laser group versus 56% in the local excision group and 45% in the PDT group. A recent study by Chen et al[115] observed that condyloma acuminata had equally high complete removal rate in the ALA-PDT group (95%) and in the control group treated with $CO_2$ laser (100%). However, recurrence rate was lower in patients who were treated with ALA-PDT than $CO_2$ laser (6% compared with 19%, respectively) at 12 weeks. In addition, the proportion of patients reporting adverse events was significantly lower in the ALA-PDT group. The authors concluded that topical ALA-PDT is a simpler, more effective, and safer treatment for condylomata compared with $CO_2$ laser therapy. Thus, ALA-PDT appears to be a viable therapeutic option for the treatment of genital warts with the advantage of a faster healing period and excellent cosmetic result. Although it is still unclear whether PDT results in improved recurrence rates, PDT might also provide the advantage of removing subclinical lesions and reducing viral shedding, which might lower the likelihood of recurrence.

## Antifungal Applications

Fungal infections have been increasing in incidence during the last 20 years and represent a significant health burden as a major pathogen in critically ill patients.[116] *Candida* currently represent the third leading cause of bloodstream infections in the U.S., and disseminated candidiasis has an associated mortality rate >25%.[117] It has been suggested that the increase in these infections might be due to increasing use of immunosuppressive drugs, antibiotics, prosthetic devices, and surgeries.[116] Compared with the myriad of antibiotics that exist, antifungal treatment options are limited, and to make matters worse, drug resistance to antifungal agents might be increasing.[118] Hence, there is a critical need for alternative antifungal treatments. Although there is growing interest in exploring the clinical application of PDT as an antifungal therapy, little has been published on this topic aside from preliminary in vitro studies.

Smijs and Schuitmaker[119] published the first study that demonstrated the susceptibility of dermatophytes to PDT by using various photosensitizers. The study found that phthalocyanines and Photofrin had fungistatic effects, whereas porphyrins had a fungicidal effect on *Trichophyton rubrum*. The authors recommended PDT as a promising entity, which should be further investigated as a treatment for tinea infections. Since then, several in vitro findings have demonstrated that dermatophytes and yeasts can be effectively targeted by PDT. In a study conducted by our laboratory at Case Western, Lam et al[120] showed that Pc4-PDT can effectively induce apoptosis of *Candida albicans* grown in culture, indicating that this modality could feasibly be developed as a treatment option for candidiasis.

Despite the significant body of preliminary data that exist regarding antifungal applications of PDT, very few in vivo trials have been conducted up to now.[121] Among the limited clinical data that exist, Sotiriou et al[122] reported 10 cases of tinea cruris caused by *T rubrum* that were treated with ALA-PDT. After 2 treatments at 2-week intervals, 8 of the 10 patients had negative dermatophytes by microscopy. However, at 8-week follow-up, only 4 patients continued to have negative microscopy examinations. Sotiriou et al[123] also treated 10 cases of tinea pedis caused by *T rubrum* with ALA-PDT. Six of the 10 patients had a response to the PDT, with half experiencing recurrence at 8 weeks. Thus, although PDT initially had a good therapeutic effect, long-term efficacy was poor. A report of 9 cases of interdigital mycoses of the foot by Calzavara-Pinton et al[124] further confirmed the high rate of recurrence associated with mycoses treated with PDT. In this study, 6 of 9 patients recovered after treatment with ALA-PDT, but 4 had rapid recurrence noted at 4 weeks. The authors suggested that the temperature, humidity, and other environmental conditions might account for the unsatisfactory long-term response seen in vivo. ALA-PDT has also been applied to the treatment of onchomycosis in a study by Sotiriou et al[125] involving 30 patients infected with *T rubrum*. The treatment was noted to be safe and generally well-tolerated, causing only mild to moderate burning, edema, and erythema. One year after treatment, 43% of patients were cured, and the cure rate dropped to 36% at 18 months. Authors proposed that removal of the nail plate and nail bed hyperkeratosis might be necessary to allow sufficient accumulation of ALA.

With the lack of data from clinical trials, it is uncertain at this point what PDT's place will be in the treatment of mycoses. So far, studies indicate that the initial response to PDT is high; however, the rapid recurrence makes PDT an unacceptable treatment option. Further investigations are warranted to look for protocols that can reduce the rate of recurrent disease, because PDT can be a safe and selective method of treatment that would be advantageous where risk of drug-resistant fungal strains is a serious concern.

## Conclusions

There is abundant evidence in literature demonstrating that PDT is effective for the treatment of nonmelanoma skin cancers as well as non-oncological cutaneous conditions. Topical PDT in dermatology is approved for the treatment of AKs in the U.S., and studies suggest that it can also be recommended as a first-line treatment for Bowen disease and superficial BCC. Because PDT is relatively noninvasive and capable of field treatment, it might be the preferred mode of treatment in patients who are poor surgical candidates or those who have multiple or cosmetically sensitive lesions. PDT is associated with faster recovery periods and has consistently demonstrated superior cosmetic outcome over conventional treatments. In respect to the nonmalignant conditions, currently available evidence supports that PDT can be a safe option for the treatment of acne, psoriasis, warts, and certain cutaneous infections. However, larger clinical trials are

needed to evaluate its effectiveness, especially in comparison with existing treatments. In addition, there is currently a lack of consensus regarding skin preparation, incubation time, the choice of light source, and duration of light exposure. Hence, future advances in the application of PDT for these various conditions should involve the development of standardized treatment protocols. Overall, PDT is a generally well-tolerated treatment modality for a wide range of malignant, inflammatory, and infectious processes, and its use in dermatology is expected to increase in the future.

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