Photodynamic Therapy: New Indications

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Abstract. Photodynamic therapy (PDT) is approved for the treatment of actinic keratoses, superficial and nodular basal cell carcinomas, and recently, Bowehs disease. In the last decade the advances experienced in the study of the photodynamic reaction have expanded the spectrum of application to other cutaneous diseases, neoplastic as well as inflammatory and infectious ones. The experience in psoriasis, acne, common warts and cutaneous T cell lymphoma starts to be broad and interesting, which permits to define its use in these entities. Photodynamic therapy is also been tested for a great variety of dermatoses with different photosensitizers and light sources with variable results. In this paper we review the treatment of Bowehs disease and other indications different from non melanoma skin cancer with PDT, providing our experience.

Key words: photodynamic therapy, photosensitizers, non melanoma skin cancer.

TERAPIA FOTODINÁMICA: NUEVAS INDICACIONES

Resumen. Las indicaciones aprobadas de la terapia fotodinámica (TFD) son las queratosis actínicas, carcinomas basocelulares superficiales y nodulares y recientemente la enfermedad de Bowen. En la última década el estudio de la reacción fotodinámica ha experimentado un avance, ampliándose su espectro de actuación a otras enfermedades cutáneas tanto tumorales como inflamatorias e infecciosas. La experiencia en psoriasis, acné, verrugas vulgares y linfoma cutáneo de células T comienza a ser amplia e interesante, lo que permite definir su uso en estos procesos. Otra gran variedad de dermatosis se está ensayando, con diferentes fotosensibilizantes y fuentes de luz, con resultados variables. En este artículo revisamos el tratamiento con TFD de la enfermedad de Bowen y de otras indicaciones diferentes de cáncer cutáneo no melanoma, añadiendo nuestra experiencia.

Palabras clave: terapia fotodinámica, fotosensibilizantes, cáncer cutáneo no melanoma.

Introduction

The last decade has seen advances in the understanding of photodynamic reactions that have led to clinical trials to assess new dermatologic indications for the use of photodynamic therapy (PDT). However, studies carried out over longer periods of time in larger patient groups will be required in order to reach a consensus for the development of practice guidelines.

The new indications for PDT include various types of inflammatory skin disease, skin tumors, infectious skin disease, depilation, photorejuvenation, and vascular lesions.[1,2]

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PDT may be useful in the treatment of these conditions given the advantages offered by the technique[3]: it is noninvasive, specific to the target tissue, well-tolerated, allows treatment of multiple lesions in the same session, and is not associated with cumulative toxicity, allowing multiple treatments to be provided with good cosmetic results.

PDT depends on the presence of 3 essential elements to generate the photodynamic reaction: a photosensitizer and sources of light and oxygen.

Various photosensitizers have been developed since 1900, when Raab, a German medical student, discovered that exposure of *Paramecium caudatum* to acridine orange and light in vitro led to the death of the microorganism. Subsequently, hematoporphyrin was the most widely used early photosensitizer.[3,4]

The ideal photosensitizer should have the following characteristics: low toxicity, target tissue selectivity, more rapid clearance in healthy than diseased tissue, ability to penetrate the target tissue, activation at a wavelength that can penetrate the target tissues, and the capacity to produce sufficiently large quantities of cytotoxic molecules to eliminate the target tissue.

The most commonly used photosensitizers in dermatology are 5-aminolevulinic acid (5-ALA) and the methyl ester of 5-ALA.[5,6]

The light source necessary to achieve the photodynamic reaction must have 2 important characteristics: a wavelength that coincides with the peak absorbance of the photosensitizer and that is capable of penetrating deep into the target tissue and distributing evenly so that a high ratio is obtained between the concentration in the target tissue and that in the healthy tissue.

PDT represents another option for the treatment of patients with skin diseases that are resistant to multiple treatments or as an alternative to treatments that are not tolerated. Nevertheless, much remains to be investigated and studies are required involving a larger number of patients assessed over longer periods, as well as meta-analyses to establish the methodology. In addition, new photosensitizers and treatment regimens need to be explored.

Figure 1. Image of a plaque caused by cutaneous T-cell lymphoma that did not respond to standard treatments.
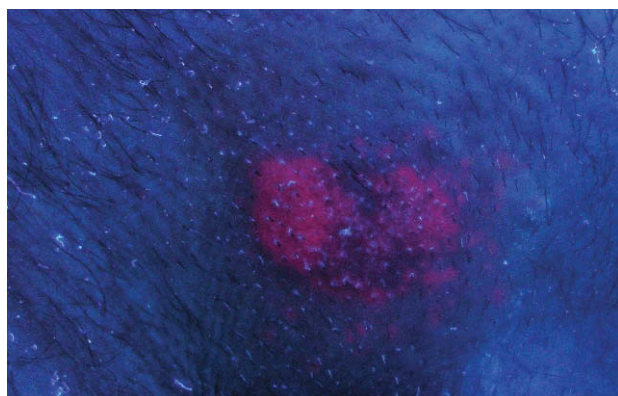
Figure 2. Selective fluorescence of the plaque lesions in cutaneous T-cell lymphoma.

Tumors

Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) is a malignant tumor derived from T-helper lymphocytes. It passes through different phases including macula, plaque, and tumor. Many patients present localized disease; in those patients the best approach is to use topical treatment and monitor the patients. A variety of treatment options are available in this situation: topical corticosteroids, topical nitrogen mustard, psoralen plus UV-A (PUVA), radiation therapy, excision, carbon dioxide laser, and in some cases, photodynamic therapy.

Boehncke et al[7,8] showed, using various photosensitizers with red light, that the photosensitizer is mainly taken up by the lymphocytes in the plaque and that they are inactivated upon application of the light. Orenstein et al[9] found that the malignant cells in the plaques of CTCL have a greater capacity to convert ALA into protoporphyrin IX than peripheral blood lymphocytes. It has been suggested that the greater susceptibility of malignant lymphocytes to photosensitizers is caused by the activated lymphocytes expressing higher levels of CD71 (transferrin receptor), rendering them able to take up more iron and, therefore, produce more protoporphyrin IX.[10] CTCL plaques exhibit fluorescence that is restricted to the affected areas (Figures 1 and 2).

Small case series of patients with CTCL treated with PDT have been published (Table 1).[9,11-17] All of them used long wavelengths (red light or visible light) to penetrate as far as the deep dermis. Based on the studies published to date, it can be concluded that the treatment is of benefit in most but not all patients. Variable periods of remission, between 4 months and 4 years, are obtained. Complete remission requires at least 4 or 5 sessions (Figure 3). The lesions that are in remission have a peculiar histologic appearance, since atypical lymphocytes continue to be visible in the dermis.

PDT seems a valid option for the treatment of CTCL and could be of benefit in patients with localized lesions that are resistant to standard treatments. Further studies will be necessary to optimize the parameters of this treatment. Given that it inactivates but does not eliminate the lymphocytes in the plaque and that the periods of remission are highly variable, follow-up is necessary to monitor possible recurrence.

Squamous Cell Carcinoma

PDT is not a preferred option for the treatment of squamous cell carcinoma. It should be taken into account

Table 1. Cases and Series Published on Cutaneous T-Cell Lymphoma Treated With Photodynamic Therapy

Author	Number of Lesions	Duration of Occlusion	Light	Photosensitizer	Fluence, J/cm^2	Type of Lesion	Response	Relapse
Oseroff 1996[11]	80	Overnight	630 nm	δ-ALA	10-200	NS	Variable	NR
Wang et al 1999[12]	3	4-6 hours	635 nm	δ-ALA	60	Periocular	CR	None in 33 months
Orenstein et al 2000[9]	6	16 hours	580-720 nm	δ-ALA	170-130	1 macula 2 tumors	CR	None in 24 months
Markham et al 2001[13]	1	4 hours	580-740 nm	δ-ALA	20	Tumor	CR	None in 1 year
Edstrom et al 2001[14]	12	5-18 hours	600-730 nm	δ-ALA	80-180	10 maculae 2 tumors	1/10 plaques NR 2/2 tumors NR Remainder PR or CR	In lesions with CR from 4 to 19 months
Leman et al 2002[15]	2	6-24 hours	630 nm	ALA	100	Maculae	CR	None in 12 months
Coors et al 2004[16]	7	6 hours	60-160 nm	δ-ALA	72-144	5 maculae 2 tumors	CR	None in 12-18 months
Zane et al 2006[17]	5	3 hours	635 nm	MAL	37.5	Maculae	4 CR 1 PR	In CR, none in 12-34 months

Abbreviations: δ-ALA, δ-aminolevulinate; CR, complete response; MAL, methyl aminolevulinate; NR, no response; NS, not specified; PR, partial response.

that this tumor has metastatic potential and that the depth of penetration with PDT is limited. The main advantage of PDT is the excellent cosmetic result, and it can be considered in very superficial carcinomas that present contraindications for standard treatment options (surgery, cryotherapy) or in inoperable forms. Curettage of the lesion or application of keratolytic drugs is important in these cases to facilitate the action of PDT.

Various case series have been published with reported cure rates of 40% to 100% using different light sources (red, blue, and visible).[18]

Prevention of Skin Cancer

Skin cancer prevention is defined as the treatment of areas of skin without visible malignant or premalignant lesions to prevent their appearance. Its use is currently considered experimental.

It has been shown in mice that the use of multiple sessions of ALA-PDT in large areas delays the appearance of actinic keratosis, squamous cell carcinoma, and basal cell carcinoma.[19,20] Unfortunately, no extensive human studies are available. A recent study assessed the prevention of squamous cell carcinoma and actinic keratosis with ALA-PDT in 40 transplant patients.[21] After 2 years of follow-up, the investigators concluded that treatment is effective

Figure 3. Appearance following 4 sessions of photodynamic therapy (methyl aminolevulinate, red light, 35 J/cm², 3 hours). Induration is visibly reduced, although hyperpigmentation persists.

for prevention of actinic keratosis but not squamous cell carcinoma.

In practice, some dermatologists use it in patients with multiple poorly defined subclinical actinic keratoses or in patients at high risk of skin cancer (Gorlin syndrome, xeroderma pigmentosa, transplant patients) with or without concomitant use of standard treatments. Prior to treatment, the fluorescence image allows us to localize the subclinical

lesions. A recent study found incubation with the photosensitizer for just 1 hour to be effective.[22] Different light sources, including short-wavelength ones, can be used since deep penetration is not necessary.[23] Lower fluences or shorter exposure times are required than for the treatment of basal cell carcinoma. The main problem is the poor tolerance, given that extensive areas are treated. This can be minimized by moistening the area with water, stopping the treatment so that the patient can take a rest, or using a pulsed dye laser and doses below the purpura threshold (7-8 J/cm²; spot size, 7 mm; pulse duration, 40 milliseconds). Intense pulsed light sources have also been used since they include red light, and good results have been obtained.[24-26]

The appearance of erythema and edema in the treated areas is intentional and indicates that PDT is functioning correctly. The patient should avoid exposure of the treated area to the sun in the 24 to 48 hours following treatment. This is especially important if the incubation time is reduced. Under these conditions, penetration of the topical photosensitizer through the stratum corneum is reduced and phototoxic reactions can occur on exposure to visible light due to penetration after the treatment.[27]

Skin Metastases

PDT has been used as a palliative treatment for skin metastases of breast cancer. Two studies have been published. Both used systemic photosensitizers. The results are variable, with rates of cure between 33% and 88%, and with 55% partial response. The size of the treated lesions seems to be a determining factor.[28,29] This makes sense given the limited penetration of PDT.

Paget Disease

Cases have been reported of inoperable vulvar Paget disease treated with ALA-PDT and blue light (achieving a reduction of 60% in the tumor mass)[30] and another case in which diagnosis by fluorescence was used prior to treatment with a carbon dioxide laser.[31] Paget disease lesions apparently display selective fluorescence in the affected areas.[30,31]

Kaposi Sarcoma

Kaposi sarcoma (KS) has also been treated by PDT. Various studies have been performed, all using systemic photosensitizers and long wavelengths. In one of those studies, a photosensitizer was used in an effort to potentiate the effect of a pulsed dye laser, which is itself already an option for the treatment of KS. The response rates are moderate and the majority of the treated patients display partial responses. As would be expected with this treatment, smaller and more superficial lesions respond better. Thus, PDT could be considered as adjuvant therapy in KS. However, notable adverse effects have been reported (edema, pain, blistering) along with a poor cosmetic result, with formation of scars and hyperpigmentation in the long-term; consequently, it should generally be used with caution.[32,33]

Keratoacanthoma

Calzavara-Pinton[34] reported the successful treatment of 4 keratoacanthomas with 20% ALA and pulsed dye laser.

Alster and Tanzi[35] studied 10 patients with sebaceous hyperplasia treated with methyl aminolevulinate (MAL) and pulsed dye laser at a wavelength of 595 nm. A single treatment was performed and resolution of the lesions was achieved with a good cosmetic result.

Cutaneous B-Cell Lymphoma

Based on the extensive experience and good results obtained with the treatment of CTCL, a recent study used ALA-PDT and red light at 37 J/cm² (standard dose for basal cell carcinoma) to treat 3 patients with single early cutaneous B-cell lymphomas. Following a single session, complete remission was achieved in all of the patients, with a follow-up of between 8 and 17 months.[36]

Melanoma

Cases also exist of melanoma or melanoma metastases treated with PDT. The nature of this tumor demands cure, and in addition, melanin absorbs energy and displaces it from the photosensitizer. Consequently, PDT would not be indicated.

Bowen Disease

Bowen disease is the most recent indication approved for PDT.[37] The main options for the treatment of Bowen disease include cryotherapy, curettage, surgical excision, local radiation therapy, topical 5-fluorouracil, laser ablation, and PDT. The evidence level for PDT is comparable to that of any of the other therapeutic options available and is better than that for 5-fluorouracil and laser ablation. In the most recent guidelines of the British Association of Dermatologists it is described as a good or very good option to be considered especially in multiple or large lesions or lesions situated in areas that are prone to scarring, given

that the main advantage offered by the technique is an excellent cosmetic result.[38] Its use in the perianal region is not recommended due to the lack of studies in that area.

The studies performed to date using PDT in Bowen disease are summarized in Table 2.[39-53]

Deep penetration of ALA is unnecessary because Bowen disease affects the epidermis. However, care should be taken since invasive foci may be present that are less susceptible to PDT. ALA is usually left in contact for 3 to 6 hours under occlusion. Two sessions are usually employed a week or 15 days apart. The overall rate of cure is between 90% and 100% with 2 sessions, with rates of recurrence at 12 months of between 0% and 11%. Laser and incoherent light are effective in treatment of Bowen disease, although better rates of cure are generally obtained at longer wavelengths. Figures 4 and 5 show examples of Bowen disease treated with PDT.

Adverse effects include pain during treatment, edema, erythema, formation of crusts, and hypo/hyperpigmentation. All of these side effects resolve spontaneously.

Follow-up every 3 to 6 months is obligatory due to the possibility of focal areas of deep invasion and recurrence.

Erythroplasia of Queyrat

Erythroplasia of Queyrat has also been successfully treated with PDT. In a study of 4 patients treated with 20% ALA and red light at 125 J/cm², a good response was obtained in all patients, although 2 patients had recurrence, one at 18 months and the other at 36 months.[54]

Actinic Cheilitis

Treatment of actinic cheilitis with PDT offers cure rates of between 68% and 100%. In a study of 19 patients, 20% ALA was applied for 2 to 3 hours followed by pulsed dye laser at fluences below the purpura threshold.[55] After a mean of 1.8 treatments per month, a cure rate of 68% was obtained. The treatment was well tolerated and the cosmetic result very good. In another study of 3 patients treated with ALA and red light, all were treated successfully and recurrence was not observed during a follow-up period of 13 months.[56]

It can be concluded that PDT is not the treatment of choice for patients with malignant tumors. Its limited capacity to penetrate the skin makes it ineffective in the treatment of invasive tumors. However, it may be an option for palliative treatment in inoperable tumors, cutaneous metastases, or noninvasive (in situ) tumors. The experience accumulated over 10 years of treatment of CTCL, with a large number of patients treated with good results, makes it an alternative for those patients with localized disease.

Figure 4. Bowen disease.

Figure 5. The lesion is visibly cured with a good cosmetic result following 2 sessions of photodynamic therapy a week apart (methyl aminolevulinate, red light, 35 J/cm², 3 hours). No recurrence had occurred at 1-year follow-up.

The studies published to date on treatment of squamous cell carcinoma, KS, Paget disease, and cutaneous B-cell lymphoma reveal poor results from small case series or isolated cases that prevent reliable conclusions from being drawn.

Inflammatory Disease

Acne

The mechanisms of action of PDT in acne are as follows: bacteriocidal (acting on *Propionibacterium acnes*), damage to the sebaceous gland, and reduced follicular obstruction (by improving keratinocyte turnover); recent studies have also shown participation of the immune response. However, the exact mechanism through which PDT acts is still unknown. The results of various studies, such as those of Hongcharu et al, suggest that alteration of sebum production is correlated with clinical improvement of acne. Histologically, following the photodynamic reaction, it has been observed that there is a reduction in the size of the sebaceous glands and vacuolation of the sebocytes.[2,4,57]

The endogenous production of porphyrins by *P acnes* (coporphyrin III, protoporphyrin, and uroporphyrin) is

Table 2. Studies Published in the Literature on Bowen Disease Treated With Photodynamic Therapy

Author and y	Light	Photosensitizer	Number of Sites	Fluence, J/cm²	Response	Other Observations
Svanberg et al 1994[39]	Laser 630 nm	δ-ALA	10	60	9/10 CR	None in 6-14 months
Cairnduff et al 1994[40]	Laser 630 nm	5-ALA	36	125-150	35/36 CR	Recurrence in 3 cases at 18 months (overall success, 89%)
Morton et al 1996[41]	630 nm	5-ALA	20	125	20/20 CR at 12 months 75% cured with 1 session 25% cured with 2 sessions	Probability of cure with a single session greater with PDT than cryotherapy 2/20 with cryotherapy showed ulceration (none with PDT)
Stables et al 1997[42]	Visible light	ALA	3	100	CR in all patients (2 sessions)	Treatment of large lesions that do not respond to standard treatment
Stables et al 1998[43]	Slide projector	ALA	77	100	73/77 CR at 12 months 71/77 CR at 24 months	
Varma et al 1998[44]	Red light	ALA	38	30	95% CR in 2 sessions	No recurrence in 12 months
Morton et al 2000[45]	Red 630 nm Green 540 nm	ALA	32 29	125 62.5	30/32 CR (94%) 21/29 CR (72%)	2 recurrences at 12 months (overall cure rate, 88%) 7 recurrences at 12 months (overall cure rate, 48%)
Morton et al 2001[46]	630 nm	Δ-ALA	40		Lesions >2 cm in diameter 35/40 (88%) CR in 1-3 sessions	PDT first choice treatment in large lesions of Bowen disease Cure rate (88%) similar to superficial BCC of a comparable size
Varma et al 2001[47]	640 nm	δ-ALA	88	105	88% CR	69% CR at 12 months
Wong et al 2001[48]	630 nm	ALA	4	250	3/4 CR (follow-up to 16 months)	All were of the digits (to avoid the need for surgery)
Dijistra et al 2001[49]	400 nm	ALA	1	10-20	90%-100%	Treatment of Bowen disease affecting more than 50% of the scalp
Salim et al 2003[50]	630 nm	ALA	40	100	88% CR, 82% CR at 12 months 2 treatments separated by 6 weeks	Comparison of 5-fluorouracil 4 weeks with 2 treatments 6 weeks apart: 67% CR and 48% CR at 12 months (superiority of PDT)
Dragrieva et al 2004[51]	Visible light	ALA	4	75	2/4 CR at 48 weeks 1/4 recurrence at 48 weeks 1/4 recurrence at 12 weeks	Study undertaken in transplant patients
Britton et al 2005[52]	PDL 585 nm	ALA	17		14/17 (82%) cure at 1 year	Study showed that PDL is an effective light source for the treatment of Bowen disease (parameters: 7 mm, 10 J/cm²)
Baptista et al 2006[53]	630 nm	ALA	13	100	84.6% CR 15% PR	Mean number of sessions for cure, 3.2 Mean follow-up, 38 months
Morton 2006 (cited in Goldman[27])	Red light	MAL	96	75	80% CR at 12 months	Compared with cryotherapy (n=82, 67% CR at 12 months) and 5-fluorouracil (n=30, 69% CR at 12 months) Good or excellent cosmetic result in 94% of patients treated with PDT (66% with cryotherapy and 76% with 5-fluorouracil)

Abbreviations: ALA, aminolevulinic acid; BCC, basal cell carcinoma; CR, complete response; MAL, methyl aminolevulinate; PDL, pulsed dye laser; PDT, photodynamic therapy; PR, partial response.

increased by exposure to a light source or with the administration of exogenous porphyrins. Application of a light source initiates a photodynamic reaction involving photoactivation of the porphyrins leading to production of singlet oxygen and free radicals, which destroy *P acnes*. Death of the bacteria occurs through destruction of the lipids in the bacterial cell wall.[58] Various studies have demonstrated that 5-ALA is metabolized in the pilosebaceous unit to protoporphyrin IX via the heme synthesis pathway, with ALA preferentially accumulating in the sebaceous glands.[59]

Most of the studies undertaken to date on the use of PDT in acne have employed ALA as the photosensitizer and incoherent light sources. The first trials used 5-ALA with long incubation periods followed by application of red light. This protocol improved the acne but the doses used were associated with various adverse effects such as pain during treatment, erythema, flaking, and pigmentation changes. In addition, seborrhea appeared frequently and recurrence of acne lesions occurred relatively early. Subsequently, the use of blue light sources was accompanied by a reduction in pain and the number of adverse effects; however, the associated disadvantage was the reduced penetration capacity.

Papageorgiou et al[60] demonstrated improved efficacy using a combination of red and blue light, since they acted synergistically to produce a combined antibacterial and antiinflammatory effect. The blue light covered the peak absorbance and the red light allowed greater penetration.

PDT in acne is mainly indicated in mild or moderate cases, offering greater benefit in those patients in whom the main bacteria involved is *P acnes*. This can be determined by fluorescence diagnosis based on the endogenous coporphyrin produced by *P acnes*. A greater number of sessions is required to eradicate other types of bacteria.[61] There is no reduction in the number of *P acnes* bacteria following PDT, since rather than destroying the bacteria, what it does is alter their functionality. Thus, 3 weeks after PDT, the sebaceous glands are recolonized by the bacteria.[62] However, reduction of the number of *P acnes* appears not to be necessary to obtain a therapeutic effect with PDT for acne. Instead, what is more important in the long term is the reduced follicular obstruction generated by increasing keratinocyte turnover and reducing hyperkeratosis, as proposed by Hongcharu.[62]

In some patients, acne lesions reappear in the week following PDT. Histologically, this reappearance coincides with the development of acute inflammation followed by partial or incomplete necrosis of the sebaceous glands. The mechanism of this monomorphous acneiform eruption is unknown, but it has been confirmed that the absence of this reactive acne is associated with better prognosis.

Various protocols have been used for treatment of acne involving varying periods of incubation with the photosensitizer and the use of different light sources (Table 3).

To date, most studies of PDT in acne have been undertaken with 5-ALA. We are currently carrying out a research project on PDT in mild-to-moderate acne using methyl-ALA and a coherent light source. The results are promising but a longer period of observation is still required.

Psoriasis

Psoriasis is one of the most extensively studied diseases. Psoriasis plaques can be treated in a number of ways, both topically and systemically; nevertheless, complete remission is not achieved in all patients. PUVA and UV-B phototherapy have proven efficacy, but carry a risk of malignancy. Since PDT does not act on cell nuclei, it could be a safe alternative to those treatments.

ALA is selectively taken up in the plaques (Figures 6 and 7) and converted into protoporphyrin IX. Photobleaching is observed following light treatment, although, curiously, the fluorescence lasts a week.[63] A recent study assessed the fluorescence in psoriasis plaques and concluded that it is not homogeneous due to changes in the thickness of the stratum corneum.[64] The authors proposed that this could also explain the heterogeneity of the response.

In psoriasis, PDT causes apoptosis of lymphocytes in the plaque[65] and also leads to a reduction in the number of CD4 lymphocytes compared with untreated plaques. As in PUVA therapy, it inhibits production of tumor necrosis factor (TNF) α, interleukin (IL)-1, and IL-6.[66,67] Normalization of epidermal keratinization is observed in biopsies along with a reduction in the marker Ki67, which acts as an indicator of epidermal proliferation.[67] Fransson and Ros[68] showed that PDT in psoriasis also reduces inflammatory infiltration and increases neovascularization of the dermis.

Various case series have been reported using different photosensitizers and wavelengths of light (Table 4).[63,64,66-73] In an attempt to summarize the results of all of the studies, it can be concluded that better results are obtained when ALA is used at higher concentrations, although very high concentrations are not required to obtain a response. However, this makes the procedure more painful. Weinstein et al,[69] in a study performed in 24 patients using green light, concluded that the ideal concentration of ALA is between 1% and 5%.

The thickness of the lesion is a determining factor, since penetration is limited; thus, better results are obtained in more superficial lesions. Also for this reason, red light is more appropriate than green or blue light. The use of keratolytics in the weeks prior to treatment improves the penetration of topical photosensitizers. Better responses are obtained in lesions smaller than 8 cm and those located on the trunk. Lesions on the dorsum of the hands show a worse response. A recent study assessed PDT in recalcitrant

Table 3. Summary of Studies Involving Photodynamic Therapy for Treatment of Acne

Author	Number of Patients	Photosensitizer and Incubation Time	Light Source and Fluence	Number of Sessions	Clinical Response
Hongcharu 2000[62]	22 patients with mild–moderate acne on the back	4 areas of treatment: 20% ALA for 3 hours + red light; ALA alone; red light alone; control	Broad-band red light (550-700 nm) 150 J/cm^2	Half of the patients were treated in a single session and the other half in 4 sessions	Statistically significant clinical improvement on the side treated with PDT without recurrence after 20 weeks in the group treated with 4 sessions and after 10 weeks in the group that received 1 session
Itoh et al 2001[116]	13 patients with intractable acne	20% ALA for 4 hours	Polychromatic visible light (600-700 nm) with a halogen light source at total doses of 13 J/cm^2	Single session	Excellent results with improvement in all patients at 1, 3, and 6 months after treatment
Pollock et al 2004[57]	10 patients with mild–moderate acne	4 areas of treatment: ALA + red light; ALA alone; red light alone; control. Incubation 3 hours	Red diode light (635 nm) at 15 J/cm^2	3 sessions per week	Statistically significant reduction in the number of lesions on the side treated with ALA-PDT following the second session
Arianee et al 2005[117]	13 patients with varying degrees of acne	20% ALA incubated for 3 hours	IPL with 560 nm filter at 26 J/cm^2	2 sessions separated by 2 weeks	No improvement until the fourth week of assessment. All patients showed reduction of the acne on the side treated with ALA, lasting to 8 weeks
Hörfelt 2006 (cited in Goldman[27])	30 patients with moderate–severe acne	Treatment area divided into 2 zones: MAL and placebo. Incubation 3 hours	Incoherent red light at 635 nm (Aktilite), 37 J/cm^2	2 sessions separated by 2 weeks	Statistically significant increase in the reduction of inflammatory lesions on the side treated with MAL (54% on the treated side compared with 20% on the placebo side)
Wiegell and Wulf 2006[118]	36 patients with moderate–severe facial acne	21 patients with MAL incubated for 3 hours 15 patients in control group	Red light at 635 nm (Aktilite), 37 J/cm^2	2 sessions separated by 2 weeks	68% reduction in acne compared with the control group
Alexiades-Armenakas 2006[4]	19 patients with moderate–severe facial acne	15 patients received ALA-PDT and 4 were used as controls Incubation 45 minutes	Pulsed dye laser, 595 nm at 7-7.5 J/cm^2, 10 ms, and 10 mm spot size	1-6 sessions per month	Complete resolution of acne in the group treated with PDT at 13 months of follow-up A mean of 3 treatments were required
Wiegell and Wulf 2006[119]	15 patients with at least 12 inflammatory lesions on the face	Half the face received 20% ALA and the other half MAL. Incubation 3 hours	Red light at 635 nm, 37 J/cm^2 (Aktilite)	Single session with assessment at 6 and 12 weeks	Clinical improvement without statistically significant differences between the treatments. More prolonged adverse effects on the side treated with ALA
Rojanamatin and Choawawanich 2006[120]	4 patients with at least 10 inflammatory lesions	Half of the treatment area received IPL alone and the other half IPL after ALA incubated for 30 minutes	IPL with 560-590 nm filter at 25-30 J/cm^2 and 20-40 ms delay	3 sessions separated by 3-4 weeks	Improvement was seen in both treatment areas but was greater and more prolonged on the ALA side
Yeung et al 2007[121]	30 Chinese patients of phototype IV-V with moderate acne	Half of the face was treated with IPL alone and the other half with IPL and PDT. Incubation with MAL for 30 minutes	IPL 530-750 nm. Single Pass with a double pulse of 2.5 ms with a delay of 10 ms. Fluence, 7-9 J/cm^2	4 sessions separated by 3 weeks	In Asian patients, PDT with MAL was not associated with improvement of acne compared with IPL alone. A reduction in the number of noninflammatory lesions was observed in both groups.

Abbreviations: ALA, aminolevulinic acid; IPL, intense pulsed light; MAL, methyl aminolevulinate; PDT, photodynamic therapy.
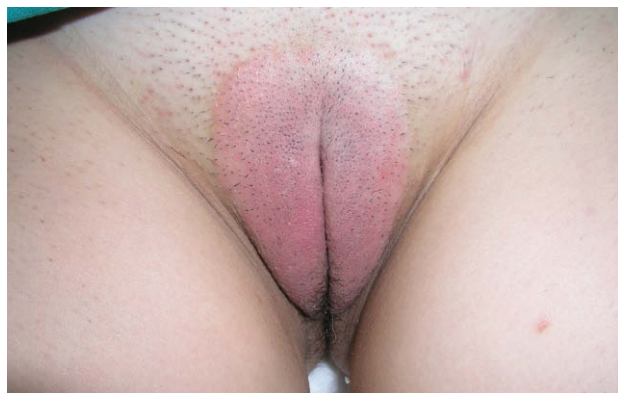
Figure 6. Clinical appearance of a psoriasis plaque in the vulva diagnosed by biopsy. Since the plaque did not respond to standard treatments, photodynamic therapy was attempted. The treatment was not tolerated with either red light or pulsed dye laser.

Figure 7. Image showing selective fluorescence of the psoriasis plaque.

palmoplantar psoriasis and good results were obtained.[74]

In terms of the number of treatments, approximately 50% clearing is obtained after 2 sessions (1 or 2 per week) and a maximal response is obtained after 4 weeks. Regimens involving multiple sessions are the most effective.

Smits et al[67] attempted to improve the efficacy of PDT for psoriasis by fractionating the treatment. Treatment was performed in 2 sessions separated by a period of 2 hours in the dark to allow resynthesis of protoporphyrin IX and reoxygenation of the treated tissues. This way of improving the efficacy of PDT has been demonstrated in animals[75] and recently in basal cell carcinoma.[76]

Use of this treatment in psoriasis has major limitations since it is very painful. When patients are assessed on a visual analogue pain scale from 0 to 10, the mean score is 7. In all studies, patients have withdrawn due to discomfort during treatment. In our experience, no patients have been able to cope with the treatment, even when red light was replaced with a pulsed dye laser, which tends to be much better tolerated. In addition, it can only be applied in localized areas, meaning that it would only be an option in plaque psoriasis affecting a small number of sites. Finally, a phenomenon known as koebnerization has been described in which clinical improvement occurs after treatment (reduced erythema, flaking, and infiltration) although the plaque size increases.

More studies involving a larger number of patients and addressing new photosensitizers and light sources will be required in order for PDT to be considered a therapeutic option in psoriasis.

Lichen Sclerosus et Atrophicus

Various studies have assessed the use of PDT in the anal and genital area. Hillemans et al[77] treated 12 patients with lichen sclerosus et atrophicus (LSA) of the vulva with 20%

ALA and an argon laser at a wavelength of 635 nm (80 J/cm²). The treatment was well tolerated, although 3 patients needed analgesia with opiates. Improvement of pruritus was observed in 10 patients and clinical improvement of the lesions was observed in 2 patients.

In our experience, treatment of vulvar LSA by PDT requires injection of anesthetic in the areas to be treated, and even with anesthesia, treatment with incoherent light is not tolerated. This may be due to widespread uptake in the vulva (the fluorescence is not selective). As an alternative, a pulsed dye laser can be used at 595 nm in the affected areas in an attempt to minimize exposure of unaffected areas. Using this approach, treatment is well tolerated and a marked improvement of the lesions is obtained. However, the results that we have obtained to date in LSA outside the genital area have been quite poor.

Morphea

Localized forms of morphea that do not respond to standard treatments can be treated with PDT. Karrer et al[78] treated 23 lesions in 5 patients using 20% ALA and exposure to an incoherent light source (Waldman 607-657 nm lamp) at 10 J/cm². They applied 25 to 43 sessions and all patients showed improvement that was maintained 2 years later.

Our experience in the treatment of localized morphea is limited; to date, we have obtained partial responses and delay of lesion progression.

Alopecia Areata

Conflicting data have been obtained in the case series published on alopecia areata treated with PDT.

Table 4. Studies Published in the Literature on Psoriasis Treated With Photodynamic Therapy

Author and y	Light	Photosensitizer and Concentration	Incubation Time	Number of Sites	Sessions per Week	Fluence, J/cm²
Boehncke 1994 (cited in Goldman[27])	600-700 nm	10% topical ALA	5 hours	3	3	25
Weinstein et al 1994[69]	UV-A	Topical ALA	3 hours	84	4	2.5-3
Collins et al 1997[70]	400-650 nm	20% topical ALA	4 hours	36	Multiple (NS)	2-16
Robinson et al 1999[63]	Visible	20% topical ALA	4 hours	19	3	2-8
Bisonette 2002 (cited in Goldman[27])	417 nm	Oral ALA	1, 3, 6 hours	180	NS	1-20
Beattie et al 2004[71]	Laser 630 nm	20% topical ALA	4 hours	3	1	10
Radakovic-Fijan et al 2005[72]	740 nm	1% topical ALA	4-6 hours	29	2	5, 10, 20
Fransson and Ros 2005[68]	630 nm	20% topical ALA	4-5 hours	8	1	10-30
Smits et al 2006[67]	600-750 nm	10% topical ALA	4 hours	8	1	Fractionated 2 and 8
Scheyler 2006 (cited in Goldman[27])	600-740 nm	Topical ALA	4-6 hours	12	2	20
Kleinpenning 2006 (cited in Goldman[27])[a]		20% topical ALA	3 and 6 hours	14	-	
Kim et al 2007[74]	630 nm	20% topical ALA	3 hours	3	1	15

Abbreviations: ALA, aminolevulinic acid; NS, not specified; PASI, Psoriasis Area Severity Index; SEI, Scale, Erythema, Induration index (from 0 to 12); VAS, visual analogue scale (from 0 to 10).
[a]Fluorescence was studied but patients were not treated with photodynamic therapy.

A study involving a topical porphyrin derivative and ultraviolet radiation (4 J/cm²) 3 times per week for 8 to 10 weeks showed good results in 2 patients.[79]

A more recent study used ALA at 5%, 10%, and 20% in 6 patients with a red light source (5 and 10 J/cm²).[80] Up to 20 sessions were performed twice weekly, with no signs of regrowth.

In the first study the light source used had a shorter wavelength to achieve significant penetration in the dermis and act on the hair follicle. However, the unpredictable and fluctuating character of alopecia areata makes it difficult to assess the results. In the patients we have treated with red light and methyl-ALA, signs of regrowth were apparent following multiple sessions (at least 6), but the hair that appeared was white and fine. Further studies using appropriate light sources will be necessary to determine the true effect of PDT in alopecia areata.

Lichen Planus

One case has been published of lichen planus on the penis treated successfully with PDT. ALA was used at a concentration of 20% with a light source at a wavelength of 607-657 nm. Treatment was provided for 6 weeks and the remission obtained lasted 6 months.[81] A recent study reported the treatment of 13 patients with 26 oral lichen

Response	Other Observations
Partial response	Compared with dithranol: similar efficacy observed
Various concentrations of ALA used (2%, 10%, and 20%) Best results obtained with 20% ALA (greater than 50% improvement on SEI)	
10/36 eliminated 4/36 reduced by more than 50% (SEI)	Recurrence at 2 weeks Fluorescence lasted 14 days
4/19 lesions cleared 10/19 partial response 5/19 no change	Biopsy confirmed that fluorescence was limited to the epidermis Fluorescence was observed in other lesions in which ALA was not applied Serious discomfort during treatment
From 0% to 42% (SEI)	Selective accumulation of ALA observed in the plaques along with apoptosis of T lymphocytes Excellent treatment tolerance
2/3 showed 50% improvement (SEI) 1/3 showed 17% improvement (SEI)	Narrow-band UV-B was superior in the other plaques (3 sessions per week) Relapse at 4 months Very poorly tolerated
20 J/cm^2, improvement of 59% on PASI 5 and 10 J/cm^2, improvement of 46%	Painful treatment 8 patients withdrew
SEI from 7 to 1.5 (statistically significant) Highly variable response	4 patients withdrew 3 used Eutectic Mixture of Lidocaine and Prilocaine VAS (0-10): 7
Statistically significant reduction in SEI compared with placebo	Fractionated treatment (2 hours in the dark) Fluorescence not homogeneous
Various concentrations of ALA used (0.1%, 1%, and 5%) Improvement in PASI of 37.5%, 45.6%, and 51.2%, respectively	Substantial pain during treatment (required constant interruptions)
	Fluorescence not homogeneous (lower in lesions with a thick stratum corneum) Incubation for 6 hours reduced the selectivity of fluorescence, which extended to tissue adjacent to the plaque
Moderate improvement in the 3 patients	Three types of palmoplantar pustular psoriasis were treated that were resistant to standard treatments

planus lesions.[82] An aqueous solution of 5% methylene blue was applied and irradiated with a laser at a wavelength of 632 nm. Treatment was performed once a week for 12 weeks. An overall improvement of 44.3% was observed and the keratotic lesions disappeared completely.

Others

Isolated cases have also been published showing a good response to PDT for sarcoidosis (multiple cutaneous nodules),[83] granuloma annulare,[84] Hailey–Hailey disease,[85] keloids,[86] actinic porokeratosis,[87] lymphadenosis benigna cutis,[88] and rosacea.[37]

Infectious Disease

Human Papilloma Virus Infection

Verruca Vulgaris

There is scientific evidence supported by numerous publications that PDT is of use in the treatment of verruca vulgaris (common warts). Three studies of an appropriate size and design have been published that show PDT to be superior to cryotherapy or placebo in the treatment of recalcitrant warts. It also represents the first nonmalignant skin disease that has yet to be approved in which the treatment is beginning to be standardized. More studies are required in immunosuppressed patients. The results

available to date suggest that the treatment is less effective in this group of patients.[89,90]

The rationale for the use of PDT in warts is based on its anti-inflammatory and antiproliferative properties. It has been demonstrated that protoporphyrin IX accumulates in warts following topical administration of ALA.[89] PDT acts by destroying infected keratinocytes and disrupting free virus particles. Consequently, it inhibits the early phases of the infection. The keratinocytes that contain the virus are located in a similar position to superficial basal cell carcinomas that are treated successfully with PDT (in the upper part of the epidermis, within or close to the stratum granulosum). Thus, although warts are thick lesions, following curettage or application of keratolytics, the light and ALA or methyl-ALA can reach the infected keratinocytes.[89-91]

PDT can be offered to those patients in whom warts persist after 3 months of standard treatment monitored by

Figure 8. Patient with a common wart that appeared 3 years earlier. Treatment had been unsuccessful with multiple sessions of cryotherapy, keratolytics, topical imiquimod, and intralesional bleomycin.

Figure 9. Result following 6 weekly sessions of photodynamic therapy (methyl aminolevulinate, 7 mm pulsed dye laser, 7 J/cm², 6 milliseconds).

a dermatologist. A series of 6 treatments over the course of 9 weeks has been shown to be effective in recalcitrant warts. The response is assessed after 3 sessions and if it is complete the treatment is considered finalized; if the response is incomplete the treatment is continued for another 3 sessions. If after 18 weeks from the beginning of treatment the warts are still not resolved, treatment is considered to have failed.[27]

In a double-blind study comparing ALA-PDT with placebo, a total of 232 warts on the hands and feet were randomly assigned to treatment and placebo groups.[89] Occlusion with 20% ALA was performed for 3 hours followed by irradiation with a narrow-band light source. Three sessions (1 per week) were applied and repeated in warts that persisted. The response was evaluated at 14 and 18 weeks. The number of resolved warts and the difference in relative wart area were significantly improved at 14 and 18 weeks in the group treated with ALA-PDT.

In another study undertaken by the same group, the efficacy of PDT was compared with that of cryotherapy in 250 recalcitrant warts.[92] Application of 20% ALA was performed with occlusion for 4 hours followed by irradiation with a slide projector using red or blue light to provide a total dose of 40 J/cm². It was compared with a double cycle of cryotherapy applied 4 times over 2 months. The overall results at 12 months were 73% complete response with white light, 42% with red light, 28% with blue light, and 20% with cryotherapy.

In a recent study, 121 warts were treated (20% ALA, 5 hours; lamp, 400-700 nm) in 3 weekly sessions.[93] A cure rate of 75% was obtained compared with 28% in control individuals.

Pain is a limiting factor for treatment of warts with ALA-PDT. Most patients experience moderate to intense pain, and as a result, some require anesthesia or abandon the treatment.[92] In a recent study of the pain during this treatment (red light, 20% ALA, n=45, compared with placebo) it was concluded that the pain is very intense in a fifth of the patients and that it lasts for up to 30 hours.[94] Our experience using pulsed dye laser at doses below the purpura threshold is good, with a good therapeutic result and excellent tolerance (it does not produce pain), with the additional advantage that the session is short (Figures 8 and 9).

It is important for curettage of the lesion to be performed or for keratolytics to be used in the weeks prior to treatment (salicylic Vaseline, urea, etc)—the second option being the most effective in our experience—since it reduces the thickness of the lesion and facilitates PDT.

Treatment of warts with PDT does not lead to significant adverse effects, with no appearance of crusts or discomfort following treatment. The cosmetic result is excellent compared with other therapeutic modalities, since the surrounding skin is not damaged. Interestingly, the warts themselves do not fluoresce.

Genital Warts, Vulvar Intraepithelial Neoplasia, and Epidermodysplasia Verruciformis

PDT is also a treatment for genital warts. The fluorescence in this case is selective, explaining its potential therapeutic effect.[95] The rates of cure vary according to the study, both with coherent light or laser and ALA, and ranges from 33% to 95%, with follow-up periods of 2 to 24 months. The rate of recurrence is around 5%.[96-100]

Vulvar intraepithelial neoplasia (VIN) has also been treated by PDT. The cure rates are around 57% to 69%, with periods of follow-up of up to 7 years.[97-101]

A case of epidermodysplasia verruciformis has been published that was well controlled with a single PDT treatment (20% ALA, 160 J/cm^2, 600-700 nm), yielding an excellent cosmetic result.[102]

Our experience has also been good with bowenoid papulosis, which, like genital warts, also displays selective fluorescence.

PDT is a noninvasive therapy that is easy to perform, causes minimal destruction of healthy tissue, is well tolerated, has excellent cosmetic results, and requires a shorter recuperation period than laser treatment.

Fungal Infections

Recent studies have shown that various species of dermatophytes, staphylococcus, streptococcus, and candida are sensitive to treatment with PDT.[61,103] Its mechanism of action is based on the inactivation of various enzymes and lysis of cell membranes, lysosomes, and mitochondria. In the case of dermatophytes, it has been shown in vitro that PDT causes degradation of the hyphae and inactivation of the spores.[104]

Appropriate light sources must penetrate deep into the stratum corneum and hair follicles, and should therefore be in the red region of the spectrum. In the case of infections caused by *Candida* species, a wavelength starting around the blue region would be sufficient.[105]

Although various studies that have been performed in cultured cells, few have been undertaken in animals or humans. In a study of patients with onychomycosis, it was shown that application of ALA followed by irradiation with red light inhibits the growth of *Trichophyton rubrum*.[106] This dermatophyte emits red fluorescence, which when viewed under the microscope, is concentrated in the mycelium.

Calzavara-Pinton et al[107] treated 9 patients with interdigital mycosis (20% ALA, 4 hours, 75 J/cm^2). Three patients were cured with a single treatment, and another 2 were cured with a total of 3 treatments. However, recurrence occurred in 4 of those 5 patients 4 weeks later.

Cutaneous Leishmaniasis

Two articles have been published on cutaneous leishmaniasis treated with PDT.[108,109] In a study performed in 60 patients (20% ALA, 633 nm, 100 J/cm^2, 4 hours), a session was applied once a week for 4 weeks and compared with injection of paromomycin sulfate and placebo. The rates of cure were 93.5%, 41.2%, and 13.3%, respectively. It was concluded that PDT is a simple, effective, and extremely rapid treatment for cutaneous leishmaniasis.[109]

Photodynamic Photorejuvenation

Prolonged exposure to sunlight leads to chronic actinic damage characterized by the appearance of telangiectasis, dyschromias, lentigines, fine wrinkles, and sallow skin with elastosis. These effects are often associated with actinic keratosis. Treatment of this photoaging usually involves topical and systemic retinoids, antioxidants, α-hydroxy acids, and estrogens.

Since Ruiz-Rodríguez and Avram demonstrated good cosmetic results with the use of ALA and subsequent application of intense pulsed light for the treatment of photodamaged skin with actinic keratosis in various studies, a new option appeared for the treatment of cutaneous photoaging referred to as photodynamic photorejuvenation.[110] In the 2006 consensus conference on the use of PDT in dermatology, a series of guidelines was developed in an attempt to create a standard protocol for the use of PDT in photorejuvenation. Photoaging was divided into 3 categories and 3 levels of treatment were defined, establishing the usefulness of PDT in type-C photoaged skin, characterized by intense elastosis associated with multiple actinic keratoses (Table 5).[110] According to the depth of the actinic damage, different light sources are used:

1. Red light penetrates the skin to 6 mm and is therefore more useful in those situations in which the lesions are deeper.

2. Blue light is used in cases of more superficial damage, since its penetration capacity is 1 to 2 mm.

Consequently, the most commonly used light sources are red light, blue light, intense pulsed light, and pulsed dye lasers.

The following histological changes are observed with PDT[111]:

1. One hour after treatment, cells containing an eosinophilic cytoplasm and marked nuclear staining appear in the basal layer of the epidermis. A discrete infiltrate of lymphocytes and neutrophils is seen in the upper dermis.

Table 5. Clinical Studies of Photodynamic Therapy in Photorejuvenation

Author	Number of Patients and Type of Study	Light Source	Photosensitizer and Incubation Time	Results
Goldman 2005 (cited in Goldman[27])	32 patients Single session	Blue light	ALA 1 hour	90% reduction of AK, 72% improvement in texture, and 59% improvement in dyschromia
Gold et al 2006[122]	3 sessions	IPL	30 minutes to 1 hour of incubation with ALA	85% reduction in AK. Improved elasticity and reduced thickening of the skin
Touma and Gilchrest 2007 (cited in Gold et al[122])	18 patients	Blue light at 10 J/cm²	ALA incubated for 1 to 3 hours	Reduction in AK, disappearance of fine wrinkles and sallow skin. Prior use of microdermabrasion improved the results by achieving a homogeneous distribution of ALA
Szeimies 2007 (cited in Gold et al[122])	Comparative study between cryotherapy with PDT and PDT	Red light at 570-670 nm	MAL	Clinical response similar but cosmetic results better in the treated zone
Parisier 2007 (cited in Gold et al[122])		Red light	MAL	Safe and effective treatment with good cosmetic results
Ruiz-Rodríguez et al 2002[123]	17 patients treated in 2 sessions 1 month apart	IPL	ALA	87% reduction in AK and improvement of fine wrinkles, skin texture, dyschromias, and telangiectasis
Avram and Goldman 2006[26]	Single session	IPL	ALA	69% reduction in AK, 55% reduction in telangiectasis, 48% reduction in dyschromia, and 25% improvement in skin texture
Alster and Surin-Lord 2006[112]	10 patients treated in 2 sessions 1 month apart	IPL at 30 J/cm² in a double pulse of 2.4/4.8 ms and a delay of 10 ms	ALA	Comparison of treatment with IPL alone and PDT with IPL
Marmur et al 2005[113]	7 patients Demonstration of ultrastructural changes	IPL	ALA	Greater increase in collagen I on the side treated with PDT
Dover 2006 (cited in Gold et al[122])	20 patients	IPL	ALA for 30-60 minutes	80% reduction in photoaging on the side treated with PDT compared with 50% on the side treated with IPL. More marked reduction of fine wrinkles and mottled pigmentation on the side treated with PDT.
Gold et al 2006[122]	3 sessions at 1-month intervals	IPL	ALA for 30-60 minutes	Better results on the side treated with PDT
Lowe 2006 (cited in Gold et al[122])	6 patients	IPL	5% ALA in the periorbital region for 30 minutes	Reduction of fine wrinkles along with improved skin tone in 4 patients
Barrer 2006[21]	24 patients Study performed in vivo and in vitro	PDL 585 nm	ALA	Cytotoxic effects in vitro 79% reduction in AK on the scalp
Alexiades-Armenakas 2006[4]		PDL 595 nm	ALA	99% reduction in AK on the scalp Reduction in AK on the trunk and limbs to a lesser extent
Key 2006 (cited in Gold et al[122])	12 patients	PDL 585 nm	ALA for 1 hour	Improvement of skin texture, dyschromias, and telangiectasis. Well tolerated

Abbreviations: AK, actinic keratosis; ALA, aminolevulinic acid; IPL, intense pulsed light; MAL, methyl aminolevulinate; PDL, pulsed dye laser; PDT, photodynamic therapy.

Figure 10. Photodynamic photorejuvenation. Left panel, prior to treatment; right panel, after treatment. There is a visible reduction in the depth of the wrinkles along with more homogeneous pigmentation (images kindly provided by Dr. Jaén).

2. Necrosis of all layers of the epidermis is seen in the tumoral and pretumoral areas between 1 and 3 days after the session.

3. Seven days after PDT, the tumor cells of the epidermis disappear and the thickness of this layer is recovered.

Confocal microscopy reveals mitochondrial dysfunction, along with increased cell adhesion and reorganization of components of the cytoskeleton. These histological findings resulting from the treatment of tumors and precancerous conditions also appear to be implicated in the clinical improvement following photodynamic photorejuvenation.[112]

Various studies have been published on the use of PDT in photorejuvenation, with varying clinical results (Table 5).[5,110-113]

Marmur et al[113] observed a series of ultrastructural changes leading to clinical improvement:

1. Epidermal reorganization: recovery of keratinocyte adhesion (revealed by hematoxylin-eosin staining and confocal microscopy).

2. Recovery of the dermal extracellular matrix: *a)* reappearance of anchoring fibrils and *b)* displacement of elastosis and superficial remodeling of dermal collagen.

Prospective studies are required involving a larger number of patients followed over a longer period in order to optimize the protocols in terms of the incubation time and type of photosensitizer, light source, and appropriate dosage.

Figure 10 shows a patient treated with PDT for photorejuvenation.

Table 6. Summary of Skin Diseases Other than Basal Cell Carcinoma and Actinic Keratosis in Which Photodynamic Therapy Has Been Successfully Used

Large Case Series
CTCL
Bowen disease
Acne
Psoriasis
Common warts
Genital warts

Small Case Series
Squamous cell carcinoma
Skin metastases
Keratoacanthoma
Sebaceous hyperplasia
Cutaneous B-cell lymphoma
Lichen sclerosus et atrophicus
Morphea
Alopecia areata
Oral lichen planus
Hirsutism
Erythroplasia of Queyrat
Actinic cheilitis
Vulvar intraepithelial neoplasia
Dermatophyte infections
Cutaneous leishmaniasis

Isolated Cases
Kaposi sarcoma
Amelanotic melanoma
Keloids
Granuloma annulare
Actinic porokeratosis
Lymphadenosis benigna cutis
Hailey–Hailey disease
Sebaceous nevus
Rosacea
Hidradenitis
Extramammary Paget disease
Epidermodysplasia verruciformis

Abbreviation: CTCL, cutaneous T-cell lymphoma.

Vascular Lesions

PDT could be an option for treatment of capillary malformations. Pulsed dye laser is effective for the treatment of this type of lesion; however, the degree of bleaching is unpredictable and in some patients it is not achieved after multiple sessions. This situation obliges alternatives to be sought.

On the other hand, PDT does not reach the microvessels (diameter less than 20 μm) responsible for capillary malformations. Also, there is a lack of agreement on a standard suitable wavelength and, for the moment, no appropriate photosensitizers are available.[114]

Hirsutism

PDT has proven to be effective in the treatment of hirsutism. The response is dose dependent, such that intensities of 100 J/cm² achieve a response of 50%, while intensities of 200 J/cm² achieve a 90% response after various sessions.[115] The advantage over laser depilation is that it allows elimination of grey hair.

Conclusions

PDT has been an emerging technique in recent years. The use of different light sources and photosensitizers, along with the large number of studies published, makes it difficult to address all the possibilities of this technique. In this article we have attempted to provide a synthesis to generate better understanding of the potential of PDT (Table 6).

Acknowledgments

Conflicts of Interest
The authors declare no conflicts of interest.

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