Photodynamic therapy in dermatology: A review

Article *in* Lasers in Medical Science · September 2009

DOI: 10.1007/s10103-009-0716-x · Source: PubMed

3 authors:

Sonal Choudhary
University of Miami
54 PUBLICATIONS **954** CITATIONS
SEE PROFILE

Keyvan Nouri
University of Miami
401 PUBLICATIONS **4,933** CITATIONS
SEE PROFILE

Mohamed L Elsaie
National Research Center, Egypt
125 PUBLICATIONS **1,467** CITATIONS
SEE PROFILE

Lasers Med Sci (2009) 24:971–980
DOI 10.1007/s10103-009-0716-x

REVIEW ARTICLE

Photodynamic therapy in dermatology: a review

Sonal Choudhary · Keyvan Nouri · Mohamed L. Elsaie

Received: 30 June 2009 / Accepted: 11 July 2009 / Published online: 5 August 2009

Abstract Photodynamic therapy (PDT) is used for the prevention and treatment of non-melanoma skin cancer. Until recently, clinically approved indications have been restricted to actinic keratoses, nodular and superficial basal cell carcinoma, and, since 2006, Bowen disease. However, the range of indications has been expanding continuously. PDT is also used for the treatment of non-malignant conditions such as acne vulgaris and leishmaniasis, as well as for treating premature skin aging due to sun exposure. The production of reactive oxygen intermediates like singlet oxygen depends on the light dose applied as well as the concentration and localization of the photosensitizer in the diseased tissue. Either cytotoxic effects resulting in tumor destruction or immunomodulatory effects improving inflammatory skin conditions are induced. Treating superficial non-melanoma skin cancer, PDT has been shown to be highly efficient, despite the low level of invasiveness. The excellent cosmetic results after treatment are beneficial, too.

Keywords Photodynamic therapy (PDT) · Porphyrins · Actinic keratosis (AK) · Light emitting diode (LED)

S. Choudhary · K. Nouri · M. L. Elsaie
Department of Dermatology and Cutaneous Surgery,
University of Miami,
Miami, FL, USA

M. L. Elsaie (✉)
Department of Dermatology and Venereology,
National Research Centre (NRC),
Cairo, Egypt
e-mail: Egydoc77@yahoo.com

History

The concept of photodynamic therapy (PDT), a modality being increasingly used to treat a number of diseases and disorders involving different body systems, can be traced back over 4,000 years to the ancient Egyptians, who used a combination of orally administered *Amni majus* plant and sunlight for vitiligo therapy [1–4]. Greeks and Indians are also known to have used this knowledge, with the help of the seeds of *Psoralea corylifolia*, for the treatment of psoriasis and vitiligo, but it was lost for unknown reasons for centuries after that, only to be rediscovered by Western civilization at the advent of the 20th century by Danish investigator Niels Finsen and the Germans Oscar Raab and Herman von Tappeiner. The latter two discovered the photosensitizing properties of acridine while studying the effects of this dye on protozoa [5]. Finsen was awarded the Nobel Prize for this work in phototherapy in 1903. The tumor-localizing ability of hematoporphyrin, along with its phototoxic effect on tumor cells, led to the development of photodynamic therapy as a promising tool in modern cancer treatment. 5-aminolevulinic acid was used in 1990 by Kennedy and colleagues and marked a major advancement in photodynamic therapy.

Definition of PDT

Photodynamic therapy involves the activation of a photosensitizer by visible light to create cytotoxic oxygen species and free radicals, which selectively destroy rapidly proliferating cells [6, 7]. PDT may prove advantageous where size, site or number of lesions limits the efficacy and/or acceptability of conventional therapies.

Mechanism of action

The principle of photodynamic therapy is based on a multistage process. The first stage comprises the administration of a photosensitizer, which possesses negligible dark toxicity; either systemically or topically, in the absence of light. After the optimum ratio of photosensitizer in the target disease vs healthy cells has been achieved, a carefully regulated dose of light is shone directly onto the diseased tissue for a specified length of time that corresponds to the amount of energy sufficient to activate the photosensitizer. Care should be taken to keep the energy at a level safe for the surrounding healthy tissues. The activation of the photosensitizer evokes photochemical reactions that produce lethal toxic agents, such as the reactive oxygen species. These toxic radicals result in cell death and tissue destruction. The successful utilization of PDT is based on the prolonged accumulation of photosensitizer in diseased cells and the rapid clearance from normal tissue cells.

- *Photosensitizers:* the first photosensitizer to gain regulatory approval for clinical PDT was Photofrin, but, due to its several disadvantages, particularly prolonged patient photosensitivity, second and third generation photosensitizers were investigated. The second generation photosensitizers are generally single substances and not necessarily porphyrins, and have improved selectivity and activity. The third generation photosensitizers have an additional targeting mechanism, for example, by covalent attachment to monoclonal antibodies.

Currently, in the USA, an alcohol-containing 5-aminolevulinic acid (ALA) solution is the only approved photosensitizer and is available in prepackaged plastic tubes that each contain two glass ampoules, one holding the ALA powder and the other the hydro-alcohol solution (Levulan). The carrier ampoule has a mixture solution containing ethanol, water, laureth-4, isopropyl alcohol and polyethylene glycol. Methyl ester of ALA (MAL) is approved for use only in Europe, in combination with red light, is available in cream form containing 168 mg/g of MAL, glyceryl monostearate, cetostearyl alcohol, polyoxyl stearate, methylparaben, propylparaben, disodium edetate, glycerine, white petrolatum, cholesterol, isopropyl myristate, refined almond oil, olelyl alcohol and purified water.

Christiansen and colleagues [8] published in 2007 a study with the purpose of optimizing a treatment regime based on normal skin fluorescence measurements. The ALA that used the liposomal vehicle achieved maximum fluorescence in 2 h at 0.5% and 1 % concentrations, while the ALA in the cream vehicle took approximately 8 h to do the same and at the much higher concentration of 20%, indicating the superiority of the liposomal vehicle.

- *Light sources:* both laser and non-laser light sources are available for PDT [9]. The older lasers, including the argon laser, the neodymium:yttrium–aluminum–garnet (Nd:YAG) laser and the gold vapor laser, are now being superseded by more compact and less expensive solid state diode lasers. Non-laser lights, including filtered halogen or xenon arc lamps, blue light fluorescent tubes and light emitting diode (LED) arrays are useful for treating large areas of skin.

Non-coherent light sources

Advantages

- Due to large illumination fields, useful in the treatment of large skin lesions
- Low cost and easy availability
- Different photosensitizers with varying absorption maxima can be used

Lasers in PDT

Combinations of light and chemicals are widely used to treat skin diseases. The concept of PDT was introduced for the main branch of this use. PDT is a promising modality for management of tumors and non-malignant skin diseases. It is based on the administration of a photosensitizer that selectively localizes in the target tissue. Exposure of the lesion to visible light in the presence of oxygen results in photodamage and subsequent tissue destruction [10].

Shortly after the invention of lasers in 1960, they were brought into medical use. Fundamental features, such as coherence and monochromaticity of laser light, made them excellent tools for a number of applications: in surgery, treatment of hemangiomas, skin rejuvenation, hair removal, etc. [11]. Since coherence is lost within a few tenths of a millimeter of penetration into human tissue, this property is not necessary for PDT. Non-coherent light is, therefore, frequently used for irradiation of neoplasms. Non-coherent light sources differ fundamentally from lasers in output characteristics. Lasers and non-coherent light sources have been used for PDT and usually show similar efficacies [12]. Non-coherent light sources are relatively inexpensive, stable and easy to operate, and require little maintenance. Non-coherent, filtered, light sources often emit light with a larger bandwidth than that of lasers and LEDs. A comparison of two such light sources is, therefore, not straightforward. Careful dosimetric considerations are required [13].

Photodynamic therapy using a pulsed laser is becoming popular, but its cytotoxic effect is still not clear. In the case of PDT using a continuous wave (CW) light, oxygen

consumption may become a key factor in the determination of PDT effects. Many researchers have shown that oxygen depletion by PDT using CW light is substantially changed by fluence rate. CW light with a high fluence rate causes significant oxygen depletion, resulting in reduction of PDT effects [14]. On the other hand, enhanced PDT effects have been demonstrated when either CW light with a lower fluence rate or fractionated light is used. In addition, oxygen level in the cells exposed to CW light significantly affects the degree of photobleaching of a photosensitizer [15].

The suggested mechanism of PDT using pulsed light is basically similar to that using CW laser, dependent on the present light conditions. This is because, regardless of laser source, the cytotoxic effect had a direct relationship to both the oxygen consumption during PDT and the resultant photobleaching after PDT. Thus, common mechanisms are suspected; however, cytotoxic efficiency appeared to be different, depending on the laser source [16].

Another plausible reason for the difference between cytotoxic efficiency in PDT using a pulsed laser and a CW laser has been reported. Miyamoto et al. have shown that PDT using pulsed light induces a particular type of cell death, which is different from that induced by PDT using CW light [17]. Nevertheless, further investigation is required to elucidate the mechanistic details of the decreased effect of PDT using a pulsed laser.

Commonly used lasers for PDT are pulsed dye laser and diode lasers. In a study assessing the safety and efficacy of the long-pulsed pulsed dye laser (LP PDL) (595 nm) with PDT for the treatment of actinic cheilitis (AC), 21 patients were treated with a 20% ALA solution followed by activation with LP PDL [18]. Of these, the condition in 37% cleared with a single treatment, 68% cleared after 1.8 treatments, and 21% cleared after three treatments. In three patients with erosive AC, postoperative impetiginization occurred.

Two pulsed light sources available for the treatment of some aspects of cutaneous photodamage are the flashlamp-pumped pulsed dye laser and the filtered flashlamp/intense pulsed light (IPL). These have recently been used in conjunction with ALA for photodamage. Strasswimmer and Grande [19] demonstrated that IPL and PDL had a faint dose–response effect on PDT activation but were less potent than a smaller fluence of CW blue light.

Karrer et al. [20] studied the efficacy of PDT with ALA using a long-pulse (1.5 ms) tunable flashlamp-pumped pulsed dye laser (LPDL) in vitro and in vivo. HaCaT human keratinocytes were incubated with ALA and irradiated with LPDL at 585 nm, 595 nm and 600 nm compared with an incoherent light source (580–740 nm). Also, 24 patients were treated topically with 20% ALA PDT emulsion irradiated by either an incoherent light source or 585 nm LPDL. Maximal cytotoxic effects in vitro were achieved with the LPDL at 585 nm or the incoherent lamp (50 J/cm^2). Complete remission was achieved in 79% of 100 patients with actinic keratosis (AK) treated by ALA and LPDL and in 84% of 100 patients with AK treated by ALA and the incoherent lamp. Pain during light treatment was significantly reduced by with the LPDL. Control lesions (LPDL without ALA) did not clear.

Advantages of using lasers as a light source for PDT:

- Maximum effectiveness can be achieved if the wavelength of the laser matches the peak absorption of the photosensitizer, due to the monochromatic quality possessed by the lasers.
- High irradiance produced by lasers helps minimize therapeutic exposure time.
- Lasers can be delivered to internal organs such as gastrointestinal tract and lungs, when conjugated with fiberoptics.

Disadvantages:

- Expensive modality
- High maintenance
- Coupling with fiberoptics renders lasers useful only to small lesions on the skin

The choice of light source may be influenced by the intended applications. For dermatologic purposes, where the light has to penetrate the skin, the scatter is high and so the effective depth of ALA PDT is 1–3 mm at 630 nm. Number and size of lesions, need for a portable compact source with a smaller field source, flexibility, treatment times and cost are the other important factors taken into consideration in the choice of a light source.

Uses/indications in dermatology

Currently, the only Food and Drug Administration (FDA) approved indication of ALA PDT and MAL PDT is treatment of actinic keratoses. The off-label and alternative uses include treatment of basal cell carcinoma (BCC), photo-aging, acne vulgaris, Bowen's disease and hidradenitis suppurativa.

In 2001 Zeitouni et al. [10] showed a complete response rate of 92% for superficial BCCs and 71% for nodular BCCs with ALA PDT. There have been numerous studies for testing effectiveness and safety of PDT use for various indications.

Contraindications

For ALA and MAL use in patients with:

- Cutaneous sensitivity at 400–450 nm
- Porphyria

- Known allergies to porphyrins
- Known sensitivity to any components of the ALA solution.
- Caution to be exercised in patients with sensitivity to other wavelengths

Both ALA and MAL are classified as FDA pregnancy category C and are not approved for use in children.

The topical use of PDT has limited depth of treatment due to restricted depth of penetration of the photosensitizer. This can be enhanced by increasing the uptake of the product using penetration enhancers and modalities such as iontophoresis and electroporation.

Uses

Actinic keratosis More than 90% of all neoplasias in patients who have undergone organ transplantation are epithelial skin tumors [21].

Acne vulgaris The rise in antibiotic-resistant strains reduces the future usefulness of current mainstay therapies, and, accordingly, the need for alternative therapies is mandatory. Phototherapy has been shown to be an effective treatment for acne, and there has been a renewed interest in photodynamic therapy as a treatment modality for this condition. The main advantages of PDT in comparison with other treatment modalities are its excellent cosmetic results and its high remission rates despite low invasiveness.

Basal cell carcinoma BCCs having a predilection for head and neck demand a high degree of cosmesis in the therapy chosen for it. Generally, for nodular BCCs, surgical excision remains the treatment of choice. For BCCs > 2–3 mm in thickness, exophytic components of the lesions should be first removed [22]. PDT and carbon dioxide (CO_2) laser when used as monotherapy have been successfully used to treat BCCs, with the greatest success in the superficial histologic subtype. These modalities when used alone have a number of limitations when compared with surgical excision, including the limited depth of penetration of PDT (2 mm absorption), which potentially limits the efficacy of treatment of nodular BCCs greater than this thickness or which are deeply invasive.

Actinic cheilitis Actinic cheilitis is a pathologic condition affecting mainly the lower lip and is caused by long-term exposure of the lips to ultraviolet (UV) radiation in sunlight. Analogous to actinic keratosis of the skin, actinic cheilitis is considered as a precancerous lesion and may develop into squamous cell carcinoma.

Viral infections of the skin The new indications for PDT include many types of viral skin infections that are related to the human papilloma virus (HPV), such as verrucae of the feet and hands, condylomata acuminata, periungueal warts, epidermodysplasia verruciformis, but viral skin lesions not related to HPV, such as molluscum contagiosum and herpes simplex, can be successfully treated. The use of PDT in HPV infections is due to its anti-inflammatory and antiproliferative characteristics: in the lesions treated there is a release of cytotoxic radicals which damage keratinocytes infected by HPV, inducing their selective apoptosis and necrosis [23].

Cutaneous T-cell lymphoma Mycosis fungoides (MF) is the most common primary cutaneous T-cell lymphoma (CTCL). Unilesional MF is characterized by a limited involvement of the skin and a chronic yet indolent course. If lesions are refractory to topical steroids, treatments such as localized chemotherapy, photochemotherapy and radiotherapy are available. However, they have several acute and chronic side-effects, and toxins may accumulate if repeated and protracted treatment cycles are delivered to refractory or relapsing lesions. Photodynamic therapy after topical application of 5-aminolevulinic acid is an effective therapy for nonmelanoma epithelial skin cancers. It has also been tried for cases of cutaneous T-cell lymphoma, and successful results have been seen. More recently, a clinical trial of silicon phthalocyanine Pc 4-PDT at Case Western Reserve University (CWRU, Cleveland, USA) has been initiated. Pc 4 has been shown to possess the advantages of intense absorption at longer wavelengths, relative photostability, and, with topical application, a shorter drug–light interval. In preclinical studies, T-cells were found to be more susceptible than keratinocytes to Pc 4-PDT-induced-apoptosis [24].

Cosmetic applications By combining the photothermal effects of pulsed light with the photochemical effects of PDT, an enhanced cosmetic effect has been demonstrated in a variety of dermatologic conditions. In addition, the use of shorter 5-ALA incubation times allows improved patient tolerance during treatment and subsequently fewer adverse effects in the postoperative period [25] Table 1.

Adverse effects

Patients complain of burning, stinging or prickling sensations, restricted to the area exposed to light. These sensations usually decrease if exposure to the light source is paused or terminated. On AKs, the reaction may be marked by erythema, edema, crusting, vesiculation or

Table 1 Multi-use trials involving PDT, and their outcomes

Reference	Study objective	Results
Braathen et al. [26]	Evaluation of the effect of incubation time (1 h vs 3 h), MAL concentration (160 mg/g vs 80 mg/g) and lesion preparation in the setting of MAL-PDT for treatment of AK	For the face/scalp, complete response rates were 78% for thin AK lesions and 74% for moderately thick AK lesions after 1 h vs 96% and 87% after 3 h incubation with MAL 160 mg/g. Lesion recurrence rates at 12 months after two treatments were similar [19% (3 of 16) after 1 h vs 17% (3 of 18) after 3 h with 160 mg/kg MAL-PDT] and lower than for 80 mg/g MAL-PDT (44–45%)
Fernández-Guarino et al. [27]	To assess the clinical outcomes of photodynamic therapy in patients with multiple AKs and the correlation of those outcomes with fluorescence imaging	The greatest improvements were obtained for facial lesions; these required fewer sessions, and remission lasted longer than lesions at other sites. The treatment was best tolerated on the dorsum of the hands. The fluorescence area and the reduction in intensity on treatment were found to be strongly and significantly correlated with the extent of clinical response
Tarstedt et al. [28]	An open prospective study comparing the efficacy and safety of MAL-PDT given as a single treatment with two treatments of MAL-PDT 1 week apart	Complete response rate for thin lesions after a single treatment was 93%, which was similar to 89% after repeated treatment. Response rates were lower after single treatment of thicker lesions (70% vs 84%), but improved after repeated treatment (88%)
Szeimies et al. [29]	To evaluate the efficacy and tolerability of PDT using an LED and topical MAL for treatment of multiple AKs	MAL-PDT was superior ($P<0.001$) to placebo-PDT in complete response rates of lesions (83.3%) and patients (all lesions showed complete response, indicating that the topical use of MAL PDT using an LED is an effective treatment for multiple AKs
Piacquadio et al. [30]	To determine the safety and efficacy of PDT using 20% wt/vol aminolevulinic acid hydrochloride (hereinafter ALA) and visible blue light for the treatment of multiple actinic keratoses of the face and scalp	Complete response rates for patients, with 75% or more of the treated lesions clearing at weeks 8 and 12, 77% and 89%, respectively, for the drug group and 18% and 13%,respectively, for the vehicle group
Tschen et al. [31]	In a multicenter phase IV trial, 748 actinic keratoses patients in 110 patients were treated with 20% ALA solution with a 12 month follow-up	The remission rate after 12 months was 78%. The rate of recurrence(confirmed by histology) was 19% after 1 year
Hauschild et al. [32]	In two randomized controlled phase III studies, investigation of efficacy and safety of the patch in comparison with placebo-PDT (superiority design, observer-blinded; study AK 03) and standard therapy, cryosurgery (non-inferiority design, open; study AK 04)	Twelve weeks after treatment, 5-ALA patch-PDT proved to be superior to placebo-PDT ($P<0.001$) and cryosurgery ($P=0.007$). Efficacy rates on a lesion basis were 82% (AK 03) and 89% (AK 04) for PDT, 77% for cryosurgery and 19% (AK 03) and 29% (AK 04) for placebo-PDT
Perrett et al. [33]	To compare topical MAL PDT with topical 5% fluorouracil (5-FU) cream in the treatment of post-transplantation epidermal dysplasia	Two sessions of MAL-PDT were performed a week apart. 5-FU cream was applied twice daily for 3 weeks. After 6 months, 89% of PDT-treated areas showed complete remission compared with 11% of those treated with 5-FU
Sami et al. [34]	To evaluate the effectiveness of PDL, IPL and LED phototherapy for the treatment of moderate to severe acne vulgaris	The reduction in acne lesions treated with the PDL was 90% or more; With IPL and the LED, the reductions were 41.7% and 35.3%, respectively
Taub [35]	A comparison of intense pulsed light, combination radiofrequency and intense pulsed light, and blue light in photodynamic therapy for acne vulgaris	ALA-PDT with activation by IPL appeared to provide greater, longer-lasting, and more consistent improvement than either radio frequency (RF)-IPL or blue light activation in the treatment of moderate to severe acne vulgaris
Morton et al. [36]	An open study to determine the effect of narrowband blue light on the reduction of inflammatory and non-inflammatory lesions in patients with mild to moderate acne and to evaluate patient tolerance of the therapy	With eight 10–20 min sessions, there was a reduction in the number of inflamed lesions in subjects with mild to moderate acne at 4 weeks, and maximal effect was seen between 8 and 12 weeks
Ryou et al. [37]	Evaluation of the efficacy and safety of intralesional injection (ILI)-PDT (PDT with an ILI of ALA) in patients with recalcitrant localized acne. Improvement in the ILI-PDT group was compared with those with conventional PDT (PDT with topical application of ALA)	There was definite superiority of effect in the ILI-PDT group after the first and second PDT sessions ($P<0.05$; spot count performed after 1 month) and a similar overall effect after the third PDT session

Table 1 (continued)

Reference	Study objective	Results
Haedersdal et al. [38]	To evaluate the efficacy and safety of LPDL alone vs LPDL in photodynamic therapy with MAL-LPDL for acne vulgaris	Inflammatory lesions were reduced more with MAL-LPDL-treated sides than on LPDL-treated sides (week 4 70% vs 50%, P=0.003; week 12: 80% vs 67%, P=0004)
Wiegell and Wulf [39]	Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid vs methyl aminolevulinate	PDT appeared to be an effective treatment for inflammatory acne vulgaris, with no significant differences in the response rate between ALA-PDT and MAL-PDT. ALA-PDT resulted in more prolonged and severe adverse effects after treatment
Rhodes [40]	To compare 5-year lesion recurrence rates in primary nodular basal cell carcinoma treated with topical methyl aminolevulinate PDT or simple excision surgery	More patients treated with methyl aminolevulinate PDT (87%) than surgery (54%) had an excellent or good cosmetic outcome. Long-term follow-up indicates superior efficacy of surgery to methyl aminolevulinate-PDT in nodular basal cell carcinoma
Szeimies et al. [41]	To compare the efficacy and cosmetic outcome (CO) of photodynamic therapy with topical methyl aminolevulinate (MAL-PDT) with simple excision surgery for superficial basal cell carcinoma (sBCC) over a 1-year period	After 12 months, 94.1% lesions treated with MAL-PDT had an excellent or good CO, according to the investigators, compared with 59.8% with surgery
Basset-Seguin et al. [42]	A multicenter, randomized study comparing photodynamic therapy using topical methyl aminolevulinate (MAL PDT), a non-invasive modality, with cryotherapy for treatment of superficial basal cell carcinoma	Cryotherapy (19%) led to remission rates comparable to those with PDT (22%) after 48 months. At a 60-month follow up, the remission rates were almost identical(75% for PDT and 74% for cryotherapy)
de Haas et al. [43]	Comparison of response of sBCC to a single illumination and twofold illumination scheme in which two light fractions of 20 J cm and 80 J cm were given 4 h and 6 h after the application of a single dose of 20% ALA	Twelve months after therapy, complete response(CR) rate to a twofold illumination was 97%, whereas the CR to a single illumination was 89%
Whitaker et al. [44][a]	Combination therapy with both modalities (PDT with CO_2 laser) in 12 patients, with the aim of improving treatment efficacy	All lesions responded to treatment as assessed by clinical evaluation, with regular follow-up on a 3-month basis. There were no recurrences during this time
Morton et al. [45]	To compare the efficacy, tolerability, and cosmetic outcome of PDT using topical methyl aminolevulinate with cryotherapy or topical fluorouracil for treatment of squamous cell carcinoma in situ	At 12 months, the estimated sustained complete response rate fo lesions after treatment with methyl aminolevulinate-PDT was superior to that with cryotherapy and better than that with fluorouracil. Cosmetic outcome after 3 months was good or excellent in 94% of patients treated with methyl aminolevulinate-PDT vs 66% for those treated with cryotherapy and 76% with fluorouracil, and was maintained at 12 months
Varma et al. [46]	To investigate the safety and efficacy of a large field light source, the Waldmann PDT 1200, in the treatment of Bowen's disease (BD), BCCs and solar keratoses (SKs)	Within two treatments, 88% of BD lesions, 95% of BCCs and 99% of SKs showed complete clinical clearance. At 12 months the complete response rates were 69% for BD, 82% for BCC and 72% for SK
Berking et al. [47]	To assess the efficacy of PDT in the treatment of actinic cheilitis of the lower lip	Complete clinical cure was observed in 47% of the patients and partial cure in another 47% of the patients. By histopathologic analysis, residual disease was found in 62%
Smucler and Jatsová [48][a]	Comparative study of aminolevulic acid photodynamic therapy plus pulsed dye laser vs pulsed dye laser alone in treatment of viral warts	All three therapeutic methods were able to cure infectious warts, with high probability (>80%). However, a combination of PDT and PDL was the most effective therapy
Chen et al. [49][a]	To investigate the efficacy and safety of topical application of ALA PDT for the treatment of condyloma accuminata	After one treatment, the complete removal rate was 95% in the ALA-PDT group and 100% in the control group. After two treatments with ALA-PDT, the complete removal rate in the treatment group was 100%. The recurrence rate in the ALA-PDT group was 6.3%, which was significantly lower than that in the control group (19.1%, P<0.05)
Wang et al. [50]	Photodynamic therapy with 20% aminolevulinic acid for the treatment of recalcitrant viral warts in an Asian population	Five patients (42%) showed complete disappearance of their warts; one patient (8%) showed partial clearance (greater than 50% decrease in the wart area), five

Table 1 (continued)

Reference	Study objective	Results
		patients (42%) had stable disease (less than a 50% decrease in the wart area), and one (8%) showed progressive disease (increase in the wart area). Adverse effects included mild to moderate and erythema, which lasted no longer than 48 h and was well tolerated by all patients
Bissonnette et al. [51]	To study the fluorescence in psoriatic plaques and peripheral blood cells by oral aminolevulinic acid	Ratios of up to 10 for protoporphyrin IX (PpIX) fluorescence between psoriatic and normal skin were obtained with a 30 mg/kg dose of ALA. Visible PpIX fluorescence was also observed in normal facial skin, and nonspecific skin photosensitivity occurred only in patients who had received 20 mg/kg or 30 mg/kg doses
Robinson et al [52]	The clinical responses of 10 patients with plaque psoriasis to multiple treatments with photodynamic therapy, using topical application of 5-aminolevulinic acid followed by exposure to broad-band visible radiation	Of a total of 10 patients 8 showed a clinical response. Of 19 treated sites, 4 cleared, 10 responded but did not clear and 5 showed no improvement
Schleyer et al. [53]	A prospective randomized, double-blind, phase I/II intrapatient comparison study conducted on 12 patients to investigate whether topical ALA PDT was an effective treatment for chronic plaque-type psoriasis	The mean percentage improvement was 37.5%, 45.6% and 51.2% in the 0.1%, 1% and 5% ALA-treated groups, respectively. Topical ALA PDT did not prove to be an appropriate treatment option for plaque-type psoriasis due to disappointing clinical efficacy and the time-consuming treatment procedure
Asilian and Davami [54]	To compare the parasitological and clinical efficacy of PDT vs topical paromomycin in patients with Old World cutaneous leishmaniasis (CL) caused by *Leishmania major* in Iran	Two months after treatment ended, 93.5% of lesions in the first group (receiving weekly PDT) had completely healed versus 41.2%in group 2 (treated twice daily with paromomycin) and 13.3% in a placebo group
Gardlo et al [55]	Comparing the efficacy of PDT with paromomycin sulfate in 10 lesions of cutaneous leishmaniasis	All 5 lesions treated by PDT and 2 of the paromomycin sulfate-treated plaques were clinically and histologically Leishmania free. Three lesions with poor response to paromomycin sulfate finally responded to subsequent PDT. Ten months after therapy there was no recurrence, and cosmetic outcome after PDT was excellent
Zane et al. [56]	To assess the efficacy of PDT with topical MAL in the treatment of unilesional MF	Of the 5 patients in the study, complete remission was observed in four and partial improvement in one. The median number of treatments was six (range 1–9). In no cases was recurrence seen at follow-up (ranging from 12 months to 34 months)
Mori et al. [57]	A report about the successful ALA PDT treatment of 3 patients with early cutaneous B-cell lymphoma	Complete remission was achieved in all the 3 patients with a maximum of 2 sessions with a 1-week interval
Lee et al. [58]	To monitor silicon phthalocyanine Pc 4 photodynamic therapy (Pc 4-PDT) in clinical trials of cutaneous T-cell lymphoma using noninvasive spectroscopy	This system integrated spectroscopy with PDT for current and anticipated clinical trials of Pc 4-PDT and emphasized the importance of optical dosimetry in the early stages of PDT clinical trials
Edström and Hedblad [59]	A long-term (6–9 years) follow-up of 10 patients with plaque-stage MF treated with PDT	Three of the 7 patients with plaque MF who showed clinical and histological clearance in the first follow-up had died before the second follow-up, as they had developed tumor-stage MF with metastasis, but not in the areas previously treated with PDT, The other 4 patients had no relapse of MF in the area treated with PDT. Three of the healed patients had received no further treatment for MF. The fourth patient had been treated with methotrexate, retinoids, interferon, Psoralea ultraviolet A. (PUVA), ultraviolet A. (UVA1) and local radiotherapy to the face, buttock, thigh and neck. The biopsies taken at the second follow-up showed loss of lymphocytic infiltrate in all 4 patients
Ruiz-Rodriguez et al. [60]	To present photodynamic therapy with topical 5-aminolevulinic acid (ALA-PDT) using IPL as a light source for treatment of AK in patients having IPL photorejuvenation	Thirty-three of 38 AKs disappeared with two ALA-PDT treatments using IPL. The follow-up period was 3 months

Table 1 (continued)

Reference	Study objective	Results
Gold et al. [61]	To evaluate short-contact (30–60 min) ALA-PDT with IPL activation by comparing ALA-PDT-IPL with IPL alone	Thirteen patients completed the trial. Three months after the final treatment, improvement was greater on the ALA-PDT-IPL treated side than on the IPL-alone side for all facets of photodamage: crow's feet appearance (55 vs 29.5%), tactile skin roughness (55 vs 29.5%), mottled hyperpigmentation (60.3 vs 37.2%), and telangiectasias (84.6 vs 53.8%). The clearance rate of AK lesions was also higher (78 vs 53.6%)
Zane et al. [62]	Twenty patients with multiple (n=137) AKs and severe photodamage of the face were treated. MAL was applied under occlusion for 3 h before exposure to 37 J/cm^2 of red light. Two treatments were given at monthly intervals	The clearance rate of AKs was 88.3%, and global score which we use to rate photoaging, mottled hyperpigmentation, fine lines, roughness, and sallowness of the skin showed improvement, but deep wrinkles, telangiectasia, facial erythema, and sebaceous gland hypertrophy did not change
Serrano et al. [63]	The study included six vitiligo patients, one of them with segmental vitiligo on the chest and back. They underwent 4 PDT sessions with 2% ALA applied on the lesions at intervals of 30 days	Perifolicular pigmentation began after the first session; after the second session almost double the repigmentation was observed. At the end of the therapy, a partial repigmentation of the lesions was observed in 4 of 6 patients

[a] Studies evaluating lasers as a light source for PDT

erosion and is desirable in order to achieve clearance of lesions, which takes around 7–10 days. This phototoxic reaction may be variable in intensity and enhanced in patients who expose themselves to the sun or to powerful artificial lights during the first 2 days after topical application. Excessive phototoxic reaction— excessive burning, vesicle formation, crusting and peeling may present as a severe and undesirable end of the spectrum [55].

In a recent study comparing response rates and adverse effects after PDT using conventional 16% and 8% MAL with home-based daylight exposure for the treatment of AK, 30 patients with mostly thin-grade AK of the face or scalp were treated with 16% and 8% MAL-PDT in two symmetrical areas after application of sunscreen. Immediately after, the patients left the hospital with instructions to spend the remaining day outside at home in daylight. Patients scored pain during treatment, and light exposure was monitored with an electronic wristwatch dosimeter. After 3 months, the complete response rate was 76.9% for 16% MAL and 79.5% for 8% MAL (P=0.37). Light doses of 8–70 J/cm^2 induced similar response rates (P=0.25). Patients experienced mild to moderate pain during daylight exposure (a mean maximal pain score of 3.7). No differences in pain scores and erythema were seen between the areas treated with 16% MAL and with 8% MAL [64].

Hyperpigmentation [64] and hypopigmentation [44] have been reported as adverse affects of PDT. Also, patients developing urticaria [65] and contact dermatitis [66, 67] after treatment with MAL are known. Topical PDT treatments are intrinsically very safe. Though, theoretically, extensive topical application can lead to systemic absorption, if, somehow, all the ALA contained in a Kerastick is completely absorbed, the ALA absorbed would be 5 mg/kg for a 70 kg person. Topical application of ALA in amounts from 0.05 g /cm^2 to 0.2 g /cm^2 does not lead to measurable systemic porphyrin levels in humans [68].

Future

PDT uses a simple concept, but the multiple parameters involved in it make it complex, and more research is required to determine the exact parameters optimal for the treatment of each disease. This would include factors concerning the photosensitizing agents, such as mode of delivery and duration of application, and parameters relating to light, such as wavelength, duration and intensity.

Also, PDT is been used widely for many off-label purposes with great success. More research and data regarding the efficacy and safety of PDT in treating those diseases such as acne vulgaris, psoriasis and actinic cheilitis would help acquire their FDA approval.

The same would be true for PDT in cosmetic dermatology, where it is catching pace and needs to be explored thoroughly for extensive and safe use.

Acknowledgment The authors declare that they have no conflict of interest.

References

1. Edelson MF (1988) Light-activated drugs. Sci Am 259:68–75
2. Sternberg ED, Dolphin D, Brückner C (1998) Porphyrin-based photosensitizers for use in photodynamic therapy. Tetrahedron. 54:4151–4202
3. Bonnett R, Martinez G (2001) Photobleaching of sensitisers used in photodynamic therapy. Tetrahedron 57:9513–9547
4. Allison RR, Mota HC, Sibata CH (2004) Clinical PD/PDT in North America: an historical review. Photodiagn Photodyn Ther 1:263–277
5. Daniel MD, Hill JS (1991) A history of photodynamic therapy. Aust N Z J Surg 61:340–348
6. Fritsch C, Goerz G, Ruzicka T (1998) Photodynamic therapy in dermatology. Arch Dermatol 134:207–214
7. Peng Q, Warloe T, Berg K et al (1997) 5-Aminolevulinic acid based photodynamic therapy. Clinical research and future challenges. Cancer 79:2282–2308
8. Christiansen K, Bjerring P, Troilius A (2007) 5-ALA for photodynamic photorejuvenation–optimization of treatment regime based on normal-skin fluorescence measurements. Lasers Surg Med 39:302–310
9. Fischer AMR, Murphee AL, Gomer CJ (1995) Clinical and preclinical photodynamic therapy. Lasers Surg Med 17:2–31
10. Zeitouni NC, Shieh S, Oseroff AR (2001) Laser and photodynamic therapy in the management of cutaneous malignancies. In: Ellerin B (ed) Clinics in dermatology, Elsevier, New York, NY, pp 328–339
11. Szeimies RM, Hein R, Baumler W, Heine A, Landthaler M (1994) A possible new incoherent lamp for photodynamic treatment of superficial skin lesions. Acta Derm Venereol 74:117–119
12. Brancaleon L, Moseley H (2002) Laser and non-laser light sources for photodynamic therapy. Lasers Med Sci 17:173–186
13. Juzeniene A, Juzenas P, Man LW et al (2004) Effectiveness of different light sources for 5-aminolevulinic acid photodynamic therapy. Lasers Med Sci 19:139–149
14. Sitnik TM, Hampton JA, Henderson BW (1998) Reduction of tumour oxygenation during and after photodynamic therapy in vivo: effects of fluence rate. Br J Cancer 77:1386–1394
15. Curnow A, Haller JC, Bown SG (2000) Oxygen monitoring during 5-aminolaevulinic acid induced photodynamic therapy in normal rat colon. Comparison of continuous and fractionated light regimes. J Photochem Photobiol 58:149–155
16. Kawauchi S, Morimoto Y, Sato S et al. (2004) Differences between cytotoxicity in photodynamic therapy using a pulsed laser and a continuous wave laser: study of oxygen consumption and photobleaching. Lasers Med Sci 18:179–183
17. Miyamoto Y, Umebayashi Y, Nishisaka T (1999) Comparison of phototoxicity mechanism between pulsed and continuous wave irradiation in photodynamic therapy. J Photochem Photobiol 53:53–59
18. Alexiades-Armenakas MR, Geronemus RG (2004) Laser-mediated photodynamic therapy of actinic cheilitis. J Drugs Dermatol 3:548–551
19. Strasswimmer J, Grande DJ (2006) Do pulsed lasers produce an effective photodynamic therapy response? Lasers Surg Med 38:22–25
20. Karrer S, Bäumler W, Abels C, Hohenleutner U, Landthaler M, Szeimies RM (1999) Long-pulse dye laser for photodynamic therapy: investigations in vitro and in vivo. Lasers Surg Med 25:51–59
21. Euvrard S, Kanitakis J, Claudy A (2003) Skin cancers after organ transplantation. N Engl J Med 348:1681–1689
22. Braathen LR, Szeimies RM, Basset-Seguin N, Bissonnette R, Foley P, Pariser D, Roelandts R, Wennberg AM, Morton CA (2007) Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. J Am Acad Dermatol 56:125–143
23. Rossi R, Bruscino N, Ricceri F, Grazzini M, Dindelli M, Lotti T (2009) Photodynamic treatment for viral infections of the skin. G Ital Dermatol Venereol 144:79–83
24. Ke MS, Xue LY, Feyes DK, Azizuddin K, Baron ED, McCormick TS, Mukhtar H, Panneerselvam A, Schluchter MD, Cooper KD, Oleinick NL, Stevens SR (2008) Apoptosis mechanisms related to increased sensitivity of Jurkat T-cells *vs* A431 epidermoid cells to photodynamic therapy with the phthalocyanine Pc 4. Photochem Photobiol 84:407–414
25. Uebelhoer NS, Dover JS (2005) Photodynamic therapy for cosmetic applications. Dermatol Ther 18:242–252
26. Braathen LR, Paredes BE, Saksela O, Fritsch C, Gardlo K, Morken T, Frølich KW, Warloe T, Solér AM, Ros AM (2009) Short incubation with methyl aminolevulinate for photodynamic therapy of actinic keratoses. J Eur Acad Dermatol Venereol 23:550–555
27. Fernández-Guarino M, Harto A, Sánchez-Ronco M, Pérez-García B, Marquet A, Jaén P (2008) Retrospective, descriptive, observational study of treatment of multiple actinic keratoses with topical methyl aminolevulinate and red light: results in clinical practice and correlation with fluorescence imaging. Actas Dermosifiliogr 99:779–787
28. Tarstedt M, Rosdahl I, Berne B, Svanberg K, Wennberg AM (2005) A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp. Acta Derm Venereol 85:424–428
29. Szeimies RM, Matheson RT, Davis SA, Bhatia AC, Frambach Y, Klövekorn W, Fesq H, Berking C, Reifenberger J, Thaçi D (2009) Topical methyl aminolevulinate photodynamic therapy using red light-emitting diode light for multiple actinic keratoses: a randomized study. Dermatol Surg 35:586–592
30. Piacquadio DJ, Chen DM, Farber HF, Fowler JF Jr, Glazer SD, Goodman JJ, Hruza LL, Jeffes EW, Ling MR, Phillips TJ, Rallis TM, Scher RK, Taylor CR, Weinstein GD (2004) Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. Arch Dermatol 140:41–46
31. Tschen EH, Wong DS, Pariser DM, Dunlap FE, Houlihan A, Ferdon MB, Phase IV ALA-PDT Actinic Keratosis Study Group (2006) Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. Br J Dermatol 155:1262–1269
32. Hauschild A, Stockfleth E, Popp G, Borrosch F, Brüning H, Dominicus R, Mensing H, Reinhold U, Reich K, Moor AC, Stocker M, Ortland C, Brunnert M, Szeimies RM (2009) Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies. Br J Dermatol 160:1066–1074
33. Perrett CM, McGregor JM, Warwick J, Karran P, Leigh IM, Proby CM, Harwood CA (2007) Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. Br J Dermatol 156:320–328
34. Sami NA, Attia AT, Badawi AM (2008) Phototherapy in the treatment of acne vulgaris. J Drugs Dermatol 7:627–632
35. Taub AF (2007) A comparison of intense pulsed light, combination radiofrequency and intense pulsed light, and blue light in photodynamic therapy for acne vulgaris. J Drugs Dermatol 6:1010–1016
36. Morton CA, Scholefield RD, Whitehurst C, Birch J (2005) An open study to determine the efficacy of blue light in the treatment of mild to moderate acne. J Dermatol Treat 16:219–223

37. Ryou JH, Lee SJ, Park YM, Kim HO, Kim HS (2009) Acne-photodynamic therapy with intra-lesional injection of 5-aminolevulinic acid. Photodermatol Photoimmunol Photomed 25:57–58
38. Haedersdal M, Togsverd-Bo K, Wiegell SR, Wulf HC (2008) Long-pulsed dye laser versus long-pulsed dye laser-assisted photodynamic therapy for acne vulgaris: a randomized controlled trial. J Am Acad Dermatol 58:387–394
39. Wiegell SR, Wulf HC (2006) Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. J Am Acad Dermatol. 54:647–651
40. Rhodes LE, de Rie MA, Leifsdottir R, Yu RC, Bachmann I, Goulden V, Wong GA, Richard MA, Anstey A, Wolf P (2007) Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch Dermatol 143:1131–1136
41. Szeimies RM, Ibbotson S, Murrell DF, Rubel D, Frambach Y, de Berker D, Dummer R, Kerrouche N, Villemagne H, Excilight Study Group (2008) A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8–20 mm), with a 12-month follow-up. J Eur Acad Dermatol Venereol. 22:1302–1311
42. Basset-Seguin N, Ibbotson SH, Emtestam L, Tarstedt M, Morton C, Maroti M, Calzavara-Pinton P, Varma S, Roelandts R, Wolf P (2008) Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. Eur J Dermatol 18:547–553
43. de Haas ER, Kruijt B, Sterenborg HJ, Martino Neumann HA, Robinson DJ (2006) Fractionated illumination significantly improves the response of superficial basal cell carcinoma to aminolevulinic acid photodynamic therapy. J Invest Dermatol 126:2679–2686
44. Whitaker IS, Shokrollahi K, James W, Mishra A, Lohana P, Murison MC (2007) Combined CO2 laser with photodynamic therapy for the treatment of nodular basal cell carcinomas. Ann Plast Surg 59:484–488
45. Morton C, Horn M, Leman J, Tack B, Bedane C, Tjioe M, Ibbotson S, Khemis A, Wolf P (2006) Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: results of a multicenter randomized trial. Arch Dermatol 142:729–735
46. Varma S, Wilson H, Kurwa HA, Gambles B, Charman C, Pearse AD, Taylor D, Anstey AV (2001) Bowen's disease, solar keratoses and superficial basal cell carcinomas treated by photodynamic therapy using a large-field incoherent light source. Br J Dermatol 144:567–574
47. Berking C, Herzinger T, Flaig MJ, Brenner M, Borelli C, Degitz K (2007) The efficacy of photodynamic therapy in actinic cheilitis of the lower lip: a prospective study of 15 patients. Dermatol Surg 33:825–830
48. Smucler R, Jatsová E (2005) Comparative study of aminolevulic acid photodynamic therapy plus pulsed dye laser versus pulsed dye laser alone in treatment of viral warts. Photomed Laser Surg 23:202–205
49. Chen K, Chang BZ, Ju M, Zhang XH, Gu H (2007) Comparative study of photodynamic therapy vs CO2 laser vaporization in treatment of condylomata acuminata: a randomized clinical trial. Br J Dermatol 156:516–520
50. Wang YS, Tay YK, Kwok C, Tan E (2007) Photodynamic therapy with 20% aminolevulinic acid for the treatment of recalcitrant viral warts in an Asian population. Int J Dermatol 46:1180–1184
51. Bissonnette R, Zeng H, McLean DI, Korbelik M, Lui H (2001) Oral aminolevulinic acid induces protoporphyrin IX fluorescence in psoriatic plaques and peripheral blood cells. Photochem Photobiol 74:339–345
52. Robinson DJ, Collins P, Stringer MR, Vernon DI, Stables GI, Brown SB, Sheehan-Dare RA (1999) Improved response of plaque psoriasis after multiple treatments with topical 5-aminolaevulinic acid photodynamic therapy. Acta Derm Venereol 79:451–455
53. Schleyer V, Radakovic-Fijan S, Karrer S, Zwingers T, Tanew A, Landthaler M, Szeimies RM (2006) Disappointing results and low tolerability of photodynamic therapy with topical 5-aminolaevulinic acid in psoriasis. A randomized, double-blind phase I/II study. J Eur Acad Dermatol Venereol 20:823–828
54. Asilian A, Davami M (2006) Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: a placebo-controlled, randomized clinical trial. Clin Exp Dermatol. 31:634–637
55. Gardlo K, Horska Z, Enk CD, Rauch L, Megahed M, Ruzicka T, Fritsch C (2003) Treatment of cutaneous leishmaniasis by photodynamic therapy. J Am Acad Dermatol 48:893–896
56. Zane C, Venturini M, Sala R, Calzavara-Pinton P (2006) Photodynamic therapy with methylaminolevulinate as a valuable treatment option for unilesional cutaneous T-cell lymphoma. Photodermatol Photoimmunol Photomed 22:254–258
57. Mori M, Campolmi P, Mavilia L, Rossi R, Cappugi P, Pimpinelli N (2006) Topical photodynamic therapy for primary cutaneous B-cell lymphoma: a pilot study. J Am Acad Dermatol 54:524–526
58. Lee TK, Baron ED, Foster TH (2008) Monitoring Pc 4 photodynamic therapy in clinical trials of cutaneous T-cell lymphoma using noninvasive spectroscopy. J Biomed Opt 13:030507
59. Edström DW, Hedblad MA (2008) Long-term follow-up of photodynamic therapy for mycosis fungoides. Acta Derm Venereol 88:288–290
60. Ruiz-Rodriguez R, Sanz-Sánchez T, Córdoba S (2002) Photodynamic photorejuvenation. Dermatol Surg 28:742–744, discussion 744
61. Gold MH, Bradshaw VL, Boring MM, Bridges TM, Biron JA (2006) Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. Dermatol Surg 32:795–801, discussion 801–803
62. Zane C, Capezzera R, Sala R, Venturini M, Calzavara-Pinton P (2007) Clinical and echographic analysis of photodynamic therapy using methylaminolevulinate as sensitizer in the treatment of photodamaged facial skin. Lasers Surg Med 39:203–209
63. Serrano G, Lorente M, Reyes M et al (2009) Photodynamic therapy with low-strength ALA, repeated applications and short contact periods (40-60 minutes) in acne, photoaging and vitiligo. J Drugs Dermatol 8:562–568
64. Wiegell SR, Hædersdal M, Eriksen P, Wulf HC (2009) Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial. Br J Dermatol 160:1308–1314
65. Monfrecola G, Procaccini EM, D'Onofrio D, Roberti G, Liuzzi R, Staibano S, Manco A, De Rosa G, Santoianni P (2002) Hyperpigmentation induced by topical 5-aminolaevulinic acid plus visible light. J Photochem Photobiol B 68:147–155
66. Kaae J, Philipsen PA, Haedersdal M, Wulf HC (2008) Immediate whealing urticaria in red light exposed areas during photodynamic therapy. Acta Derm Venereol 88:480–483
67. Harries MJ, Street G, Gilmour E, Rhodes LE, Beck MH (2007) Allergic contact dermatitis to methyl aminolevulinate (Metvix) cream used in photodynamic therapy. Photodermatol Photoimmunol Photomed 23:35–36
68. Fritsch C, Stege H, Saalmann G, Goerz G, Ruzicka T, Krutmann J (1997) Green light is effective and less painful than red light in photodynamic therapy of facial solar keratoses. Photodermatol Photoimmunol Photomed 13:181–185