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A Critical Reappraisal of Off-Label Use of Photodynamic Therapy for the Treatment of Non-Neoplastic Skin Conditions

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Keywords
Photodynamic therapy (PDT) · Off-label PDT · Non-neoplastic conditions

Abstract
Background: In the past 30 years, topical photodynamic therapy (PDT) has been investigated for the treatment of a broad spectrum of cosmetic, inflammatory, and infectious skin conditions with variable, and often contrasting, results. However, the non-expert clinician may be in difficulty evaluating these results because different sensitizers, concentrations, formulations, light sources, and irradiation protocols have been used. In addition, many of these studies have poor quality design being case reports and uncontrolled studies of few cases. ***Summary:*** With the aim to clarify the potential usefulness of PDT for the treatment of infectious and inflammatory skin diseases as well as selected cosmetic indications, we searched for randomized controlled clinical trials, non-randomized comparative studies, retrospective studies, and case series studies with a number of at least 10 patients, published since 1990. Later, we reappraised the results in order to give a simple critical overview. ***Key Messages:*** Evidence from the literature seems to strongly support the use of ALA- and MAL-PDT for the treatment of common skin diseases such as acne, warts, condylomata, and Leishmania skin infection and for photorejuvenation, i.e., the correction of selected cosmetic changes of aging and photoaging. For other disorders, the level of evidence and strength of recommendation are lower, and controlled randomized studies with prolonged follow-ups are necessary in order to assess the clinical usefulness and other potential advantages over current treatment options.

Introduction

Topical photodynamic therapy (PDT) is a non-invasive technique based on the sequential application of a photosensitizing drug or a precursor followed by exposure to visible light [1]. Aminolaevulinic acid (ALA) and its methyl ester (methyl-amino-levulinate [MAL]) are the most widely used drugs for PDT in dermatology [2, 3]. They are approved in European countries and USA for the treatment of actinic keratoses (AKs), in situ squamous cell carcinoma

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(or Bowen disease) and superficial basal cell carcinoma [2]. In addition, PDT has been preliminarily investigated for the treatment of a broad spectrum of cosmetic, inflammatory, and infectious skin conditions [2–5]. Unfortunately, results are not homogeneous and often contrasting, and these discrepancies are not easily understandable although they can be related, at least in part, to the different treatment protocols that have been used [6]. Additionally, the great majority of these studies had a low-quality experimental design, being case reports and uncontrolled studies including a small number of cases [6]. Finally, clinicians without an extended experience in photobiology are sometimes confused by the fact that other photosensitizers (e.g., methylene blue, toluidine blue and other phenothiazines, porphyrin derivatives, and phthalocyanines) have been studied for the same purpose. To clarify the use of PDT in the most commonly investigated non-neoplastic conditions we critically reappraised the most relevant papers of the last 30 years regarding this subject.

Methods of Literature Search

Studies published from the year 1990 regarding the PDT treatment of photoaging and infectious and inflammatory skin diseases were selected, without language restrictions, from the online databases of PubMed/MEDLINE, Web of Science, and Ovid.

The following keywords were used for the paper search: "photodynamic therapy" OR "photodynamic" OR "PDT" AND "aging" OR "photorejuvenation" OR "hidradenitis suppurativa" or "nevus sebaceous" OR "warts" OR "condyloma" OR "acne" OR "hidradenitis" OR "psoriasis" OR "lichen" OR "leishmaniasis" OR "rosacea" OR "folliculitis" OR "necrobiosis lipoidica" OR "keloids" OR "infections" OR "rosacea" OR "mycosis" OR "lupus". Additionally, two independent reviewers screened titles and abstracts to select potentially relevant articles, and then the chosen full-text papers were analyzed looking for relevant data. We selected randomized controlled clinical trials, non-randomized comparative studies, retrospective studies, and case series studies with a number of at least 10 patients. In the case of clinical indications for which studies with these designs were not available, we evaluated case reports or case series studies enrolling fewer than 10 patients.

The level of evidence and strength of recommendation of PDT were assessed for the most studied clinical indications, according to the EDF/European Centre for Guidelines Development manual [2] (Table 1).

Table 1. Strength of recommendations and quality of evidence, according to the EDF/European Centre for Guidelines Development manual [2]

Strength of recommendation	
A	There is good evidence to support the use of the procedure
B	There is fair evidence to support the use of the procedure
C	There is poor evidence to support the use of the procedure
D	There is fair evidence to support the rejection of the use of the procedure
E	There is no evidence to support the rejection of the use of the procedure
Quality of evidence	
I	Evidence obtained from at least one properly designed, randomized controlled trial
II-i	Evidence obtained from well-designed controlled trials without randomization
II-ii	Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one center or research group
II-iii	Evidence obtained from multiple time series with or without the intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
IV	Evidence inadequate owing to problems of methodology (e.g. sample size, length of comprehensiveness of follow-up, or conflicts in evidence)

Fundamentals of PDT

Photosensitizers

In Europe, four topical drug preparations are approved for PDT: Metvix® cream and Luxera® cream (Galderma, Paris, France) containing 160 mg MAL/g, Ameluz® gel (Biofrontera, Leverkusen, Germany) containing 78 mg of ALA/g in a nano-emulsion, and a 4-cm^2 patch containing 8 mg of ALA (Alacare®; Galderma). A 20% ALA solution (Levulan Kerastick, DUSA Pharmaceuticals, MA, USA) is available in the USA and Canada but not in Europe. In addition, a number of medical devices with various ALA concentrations and formulations are self-produced in clinical centers or are available on the market, although not being formally approved by the authorities.

Unlike ALA, MAL has a methyl ester group that makes it more lipophilic, thus enhancing its penetration into cells and its tumor selectivity [1, 2, 7]. Upon cell penetration MAL is immediately demethylated to ALA, and

therefore the intracellular chemical and biochemical profile of the two compounds is the same. ALA is not photochemically reactive "per se" but it is quickly metabolized to protoporphyrin IX (PpIX) by the enzymes of the heme biosynthetic pathway, and afterwards PpIX accumulates in the cell because the next biochemical step, the iron chelation to heme, can take up to some hours [1, 2, 7].

Photoactivation of PpIX produces singlet oxygen ($^1O_2$) and other reactive oxygen species, such as superoxide anion, hydrogen peroxide, and hydroxyl radical, causing oxidative damage to nucleic acids, proteins, and lipids. According to the entity of the damage, either pro- or anti-inflammatory cellular pathways are activated, as well as either necrotic or apoptotic cascades. This sequence of events happens in all cell populations of epidermal and dermal compartments and in cells trafficking in the skin, including immuno cells, thus giving PDT an immunemodulatory effect as well [1–4, 7].

The variety of mechanisms involved in this process allows different combinations of drugs and light to act and modulate the process at different steps of the cycle, therefore obtaining a wide spectrum of possible results; this is the rationale behind the use of PDT for such a broad number of clinical indications [1].

Synthetic photosensitizers with a tetrapyrrolic chemical structure (i.e., benzoporphyrins, chlorins, and phthalocyanines, as well as phenothiazines – methylene blue and toluidine blue) are currently under laboratory and clinical investigation. After topical application, they have a poor capacity of penetration into the skin, and therefore they are of poor interest for the treatment of tumoral and inflammatory disorders. However, their use against microbial infections seems particularly promising as they can effectively sensitize microorganisms without harming skin cells [1].

Light Sources and Dosimetry

Both natural and artificial light sources can be used for PDT, provided that their emission spectrum matches, at least partially, the absorption spectrum of the photosensitizer, and the irradiance is enough to allow a reasonable duration of exposure. However, the irradiance must be lower than 100–150 mW/cm^2, in order to avoid a photothermal effect. Finally, the size and the uniformity of the irradiation field are critical issues for a successful treatment as well [1].

As the PpIX absorption spectrum covers the whole visible range, many light sources are suitable for MAL/ALA PDT. These generally emit the whole visible spectrum or selective wavebands matching only the strong absorption peak (B-band) at 406 nm, or the other four minor (20–40 lower) peaks (the Q-bands) at 506, 542, 577, and 630 nm [8]. Longer wavelengths penetrate deeper into the skin, therefore light sources with an emission peak at 630 nm are preferred to treat thicker epidermal or dermal lesions [9, 10], whereas white light and red light seem equally effective when treating superficial epidermal lesions [2].

Light sources emitting in the whole visible spectrum are natural sunlight (provided that the ultraviolet emission has been filtered with a sunscreen), fluorescent lamps, metal halide lamps, and broad-band light-emitting diodes (LEDs). Lamps emitting selected wavebands are defined as coherent (e.g., lasers, particularly the dye laser) and non-coherent (e.g., intense pulsed light [IPL], selected fluorescent lamps, filtered metal halide lamps, and narrow-band LEDs).

Careful dosimetry of light fluence is recommended, but spectroradiometers are expensive, difficult to use, and time consuming. Broad-band radiometers for visible light are more practical, but they are expensive as well and need frequent calibration. However, fortunately, in the daily clinical activity, only the first measurement is mandatory (and it is usually already done by the manufacturing company), and a frequent measurement of output is not needed because light sources emitting visible light are usually quite stable for a long time [1].

Off-Label Cosmetic Indications

A possible use of ALA/MAL PDT for aesthetic purpose is photorejuvenation, i.e., the improvement of selected clinical features of facial skin aging with aesthetic relevance [6].

Indeed, several studies with various experimental designs and different treatment protocols have shown a significant improvement of fine wrinkles, mottled hyperpigmentation, sallowness, skin texture, tactile roughness, telangiectasias, and diffuse erythema, as well as of the Glogau global score for photoaging [2–5, 7, 9–11].

Even a short-time (1–3 h) application, without occlusion, of a 20% ALA solution followed by exposure to blue light [12, 13] improved skin texture [13], global skin quality, fine wrinkling, and sallowness [12], although showing a mild [12] or poor [13] improvement in mottled hyperpigmentation and no changes in coarse wrinkles [12, 13]. A few case series studies investigated PDT with IPL devices [14–20]. In comparison to continuous red light sources, IPLs allowed significantly shorter duration of exposure and were less painful, therefore being preferred by

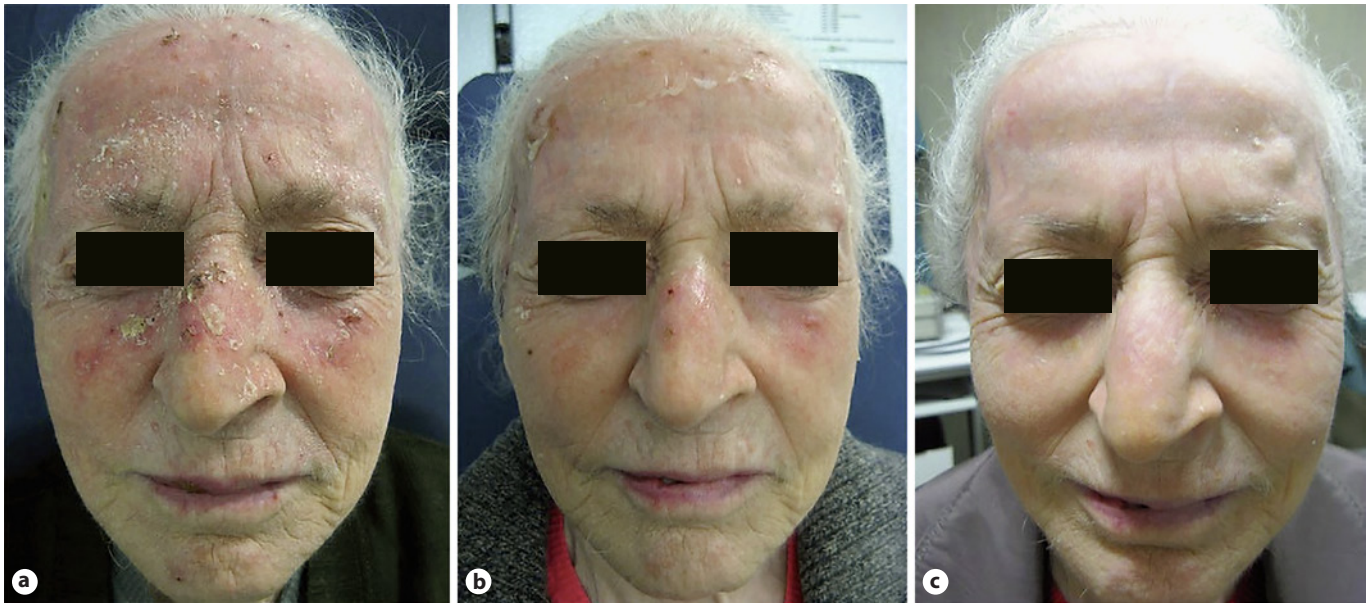

Fig. 1. Effect of PDT on multiple actinic keratoses of the face with photorejuvenation of the surrounding skin before (**a**), during (**b**), and after (**c**) treatment.

patients, particularly if broad areas (i.e., the whole face) were treated [21]. In split-face comparison studies, ALA-IPL PDT was more effective than IPL alone for the improvement of coarse wrinkles [22], fine lines [22, 23], mottled hyperpigmentation [23, 24], crow's feet [24], tactile roughness [24], and telangiectasias [24], without differing significantly in the degree of inflammation. The improvement of the overall cosmetic appearance of mild-to-moderate facial photodamage (as rated by both investigators and patients) was also achieved in 10 women treated with 3 sessions, at 30-day intervals, with hexyl ALA and IPL [25].

Although a number of studies on this matter can be found in the literature, the optimal IPL-PDT protocol is still unknown because the considered parameters (IPL wavelength, pulse duration, pulse interval, and energy density, and the ALA application time, formulation, and concentrations – from 0.5 to 20%) were often different.

Combined treatment protocols and new techniques to maximize trans-epidermal ALA penetration have been investigated in order to improve the efficacy of PDT. In a study including 21 patients, several passes with a microneedle (0.3-mm length) roller before a 1-h ALA application, combined with a double exposure to red light and IPL, gave excellent results. In a pilot split-face study, MAL-PDT combined with microneedles (1.5-mm length), it was shown that the combination had superior cosmetic results in comparison to standard MAL-PDT [26]. Although the results were good, adverse effects such as erythema, edema, crusting, and pain were significantly more frequent and intense with microneedles-PDT, and AK clearance rates were not different [26]. A split-face study of 4 patients found that fractional resurfacing followed by MAL-PDT improved fine wrinkles significantly more than MAL-PDT alone [27].

Two double-blind randomized trials investigated not only clinical but also histological changes [28, 29] of conventional MAL-PDT (MAL cream was applied under occlusion for 2–3 h before exposure to red light) versus red light alone, and the results showed that the former was significantly more effective in improving the global score of facial photodamage and all specific clinical variables, excluding telangiectasia [28]. Additionally, they showed that, at a histological level, there was an increase of functional dermal collagen and elastic fibers, coupled with a decrease of perifollicular fibrosis [29]. Subsequent studies demonstrated a reduction of epidermal thickness, dermal inflammatory and elastotic material in the dermis, and an increase of expression of procollagen type I and III [30, 31]. The positive changes of the dermal matrix were found to be more consistent after serial PDT sessions rather than after a single exposure, suggesting that repeated treatments lead to better and more stable clinical improvement [32]. High-resolution sonography was used

for non-invasive imaging of PDT effects, and it showed an increase of dermal thickness with a concurrent thinning of the subepidermal band of elastotic material [33].

Finally, aesthetic manifestations of chronic severe photodamage are often accompanied by the presence of the so-called field of cancerization, where multiple AKs are present and apparently normal keratinocytes of the surrounding skin harbor severe, UV-related, molecular DNA damages. Of great interest is the fact that PDT was effective not only against aesthetic changes of aging but also against the molecular damage present in the field of cancerization [6]. Therefore, PDT of chronically photodamaged patients with multiple AKs has at the same time a healing effect for AKs, a photorejuvenative effect with an aesthetic significance (Fig. 1) as well as a tumor-preventative potential.

Disorders of the Pilosebaceous Unit

Acne is a very frequent skin disease affecting approximately 85% of people aged 12–25 years [34]. Incidence decreases in adulthood, but 26% of women in their 40s still report the disease [35].

It is a disorder of the pilosebaceous unit caused by the interplay of different pathogenetic causes [36]. PDT has been demonstrated to reduce the activity of the sebaceous gland and normalize the follicular hyperkeratosis [3, 37–42]. In addition, *Propionibacterium acnes* contains the enzymatic machinery for the metabolization of ALA to endogenous fluorescent porphyrins [3, 37], and the intensity of fluorescence is related to the degree of *P. acnes* colonization [3, 38]. However, it is still debated whether clinical improvement correlates with a decrease of this colonization [38, 41].

Several studies have reported that ALA/MAL PDT is effective against acne [2, 3]. As early as 2000, Hongcharu et al. [38] treated three areas of the back of 22 acne subjects with multiple sessions of ALA plus red light, ALA alone, and red light alone, with a fourth area left untreated. They observed that clinical and histological improvement of inflammatory acne after 20 weeks was significantly better with ALA-PDT. A split-face comparative study of 20 patients showed that 4 sessions of ALA-PDT with blue light was superior to blue light alone in the reduction of both inflammatory and non-inflammatory lesions in patients with moderate-to-severe acne vulgaris, but the difference was not statistically significant [39]. A retrospective multicenter Italian observational study using MAL-PDT (average incubation of 3–4 h followed by illumination with red light at 37 J/cm^2), of 92 acne patients who received a mean number of 3.3 sessions with a mean of 19.6 days of interval between treatments, reported >75% improvement in 72.8% of patients (Fig. 2) [4]. A double-blind, randomized, vehicle-controlled multicenter trial of 153 patients with severe facial acne showed that 12 weeks after a cycle of 4 treatments (each performed 2 weeks apart from the previous one) with MAL-PDT (1.5 h of incubation followed by exposure to 37 J/cm^2 of red light) significantly reduced the inflammatory lesion count, in comparison to PDT with the vehicle alone [43]. Recently, a randomized controlled study involving 46 patients with moderately severe inflammatory acne found that 2 PDT sessions (ALA 20% cream under occlusion for 1.5 h before irradiation with 37 J/cm^2 of red light) at a 2-week interval was more effective than the combination of doxycycline and adapalene gel [44]. Several other studies (split-face comparison, prospective studies, randomized clinical trials) using 5–20% ALA and red light exposure reported clinical im-

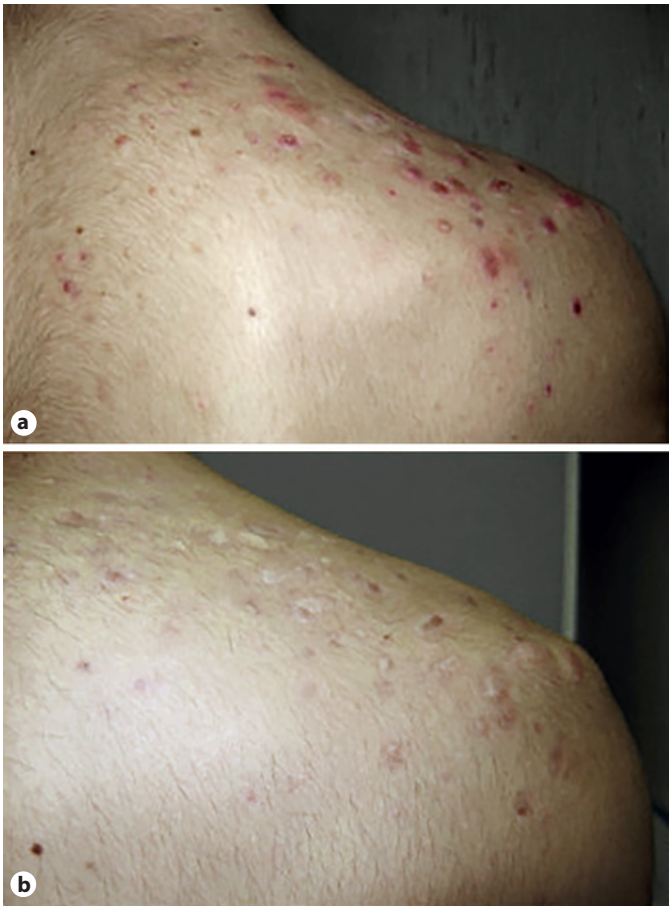

Fig. 2. Photodynamic therapy of severe papulopustular acne of the right shoulder before (**a**) and after (**b**) treatment.

Table 2. References of main studies of PDT of acne

First author (Ref.)	Study design	Enrolled patients	Photosensitizer and concentration	Incubation time	Light spectrum and dose	Treatment regimen
Hongcharu [38]	RCT	22	20% ALA	3 h	BBVL (550–700 nm) at 150 J/cm^2	4 sessions at 1-week intervals
Akaraphanth [39]	RCT	20	10% ALA	1 h	BL (415±5 nm) at 48 J/cm^2	4 sessions at 1-week intervals
Serini [40]	PT	35	5% ALA	2 h	RL (630 nm) at 25 mJ	3 sessions at 2-week intervals
Pollock [41]	RCT	10	20% ALA	3 h	RL (635 nm) at 15 J/cm^2	3 sessions at 1-week intervals
Hong [42]	RCT	8	20% ALA	4 h	RL (630±63 nm) at 18 J/cm^2	1 session
Yang [45]	RCT	75	5% ALA	3 h	RL (633±10 nm) at 50 J/cm^2	Every 10 days for 1 month
Zhang [46]	RCT	12	5% ALA	2 h	RL (633±6 nm) at 36–108 J/cm^2; IPL (590–1200 nm) at 15–17 J/cm^2	3 sessions at 2-week intervals
Rojanamatin [47]	RCT	14	20% ALA	30 min	IPL (560–590 nm) at 25–30 J/cm^2	3 sessions at 3- to 4-week intervals
Santos [48]	RCT	13	20% ALA	3 h	IPL (560 nm) at 26 J/cm^2	2 sessions at 2-week interval
Wiegell [49]	RCT	21	16% MAL	3 h	RL at 37 J/cm^2	2 sessions at 2-week interval
Kim [50]	RCT	28	16% MAL	30 min	Non-ablative fractional laser at 20 mJ/cm^2 before daylight exposure	1 session
Seo [53]	PT	47	0.1% indocyanine green	30 min	Long pulse diode laser (810–940 nm) at 18–22 J/cm^2	3 or 5 sessions at 2-week intervals
Calzavara-Pinton [4]	RS	92	16% MAL	3–4 h	RL (635±18 nm) at 37 J/cm^2	Variable (mean of 3.3 sessions at 19.6 days of interval)
Pariser [43]	RCT	100	8% MAL	1.5 h	RL (635 nm) at 37 J/cm^2	4 sessions at 2-week intervals
Nicklas [44]	RCT	23	20% ALA	1.5 h	RL with 37 J/cm^2 fluence	2 sessions at 2-week interval
Goldman [51]	PT	22	ALA	15 min	BL (417 nm) for 6 min	2 sessions at 2-week interval
Alexiades-Armenakas [52]	PT	19	ALA	45 min	Long pulsed dye laser (595 nm) at 7.0–7.5 J/cm^2	Variable

RCT, randomized clinical trial; PT, prospective trial; RS, retrospective study; BBVL broad-band visible light; RL, red light; BL, blue light; IPL, intense pulsed light.

provement of inflammatory lesions of mild-to-moderate acne vulgaris without significant adverse effects [40–42]. In an open, prospective, parallel-arm trial of 75 patients with facial conglobate acne, 3 sessions (10 days apart) of 5% ALA-PDT were found to be more effective in reducing scar formation than red light and a Chinese herbal medicine mask [45]. Taken together, these studies emphasize the therapeutic potential of PDT with exposure to continuous light sources against acne, and that adverse effects are uncommon and generally limited to transitory inflammation and pain, with rare cases of persistent dyspigmentation of the treated area [38].

A comparison split-face study between ALA-PDT with red light and ALA-PDT with IPL concluded that the former was statistically more effective, whereas the latter had less adverse reactions and better tolerability [46]. In other studies, results with ALA- or MAL-PDT with IPL were conflicting and varied from beneficial effects in inflammatory lesions in a pilot trial [47] to no apparent clinical improvement in two randomized clinical trials [48, 49]. A randomized comparative trial with MAL-PDT and fractional laser-assisted daylight irradiation showed disappointing clinical results for inflammatory acne and relevant skin toxicity with pain, discomfort, and local inflammation [50]. Perhaps through a synergy of thermal effects and photodynamic effects, multiple treatments with short-time (30–60 min) 20% ALA application followed by continuous-wave blue light or pulsed dye laser improved inflammatory acne with few short-term adverse effects and good tolerability [51, 52]. The use of indocyanine green as photosensitizer was investigated in a clinical trial [53] with partial but promising results, and further studies are desirable to explore more in depth this treatment modality. The main results of papers on PDT treatment in acne are summarized in Table 2.

Application of ALA- or MAL-PDT and different light sources to other disorders of the pilosebaceous unit has also been explored. A substantial, albeit transitory, improvement was seen in the majority of 17 rosacea patients treated with MAL-PDT [54]. PDT with intralesional ALA injections was proposed as an alternative option for localized hidradenitis suppurativa [55], and a randomized clinical trial with methylene blue activated with IPL reported successful and promising results [56]. PDT was also used to treat nevus sebaceous of the face showing mild (25%), moderate (58%), and marked (17%) improvement in all 12 patients [57]. Finally, a prospective study demonstrated the clinical improvement of folliculitis decalvans after 4 sessions of MAL-PDT in 9 out of 10 patients [58].

Inflammatory Skin Diseases

When ALA-PDT took its first steps in dermatology, psoriasis was considered one of the main potential indications because ALA accumulates to a greater extent in psoriatic plaques than in normal surrounding skin and inflammatory T lymphocytes are highly sensitive to PDT-induced apoptosis [1]. Indeed, immunohistochemical investigations of psoriatic lesions treated with PDT showed normalization of epidermal proliferation and differentiation, decreased infiltration of pathogenetically relevant T-cell subsets [59], and reduced dermal neovascularization [60]. However, clinical results have been disappointing with limited and unpredictable clinical response and significant pain, stinging, and burning during and after irradiation is frequent [60–64]. In addition, costs could most often be excessive because psoriatic lesions may cover a large part of the body surface and clearing of lesions, if any, is seen after repeated treatments.

Recently, PDT has been suggested as a new treatment option for oral lichen planus. In various randomized controlled trials [65–68], toluidine blue-mediated PDT significantly reduced inflammation and pain, but the comparison of efficacy with conventional topical corticosteroids has shown conflicting results. A randomized trial of 40 women with genital erosive lichen planus showed that efficacy and tolerability of one session of PDT with hexyl 5-aminolevulinate-hydrocloride (HAL) and daily applications of clobetasol propionate 0.05% ointment for 6 weeks were not statistically different, but authors emphasized that, unlike clobetasol, PDT does not have the hazards of long-term toxicity [69].

PDT has also been investigated in the treatment of genital lichen sclerosus, another chronic inflammatory disease with the need of safe and effective alternatives to topical corticosteroids [70–78]. In several studies of small case series, 1–4 sessions of ALA-PDT induced a complete or partial clinical remission in most patients with a symptomatic relief, and they were always well tolerated [70–75], and a randomized controlled clinical trial of 40 patients reported that 4 sessions of ALA-PDT at 2-week intervals were more effective than the daily application of clobetasol propionate ointment for 8 weeks [76]. Since therapy with red light could be connected with local pain during illumination, a case series study of 11 patients [78] evaluated the efficacy and tolerability of ALA-PDT with green light and reported a very good tolerability, an improvement of local status, and a reduction of pruritus.

The improvement of lichen sclerosus with PDT is accompanied by a reduction of expression of molecular

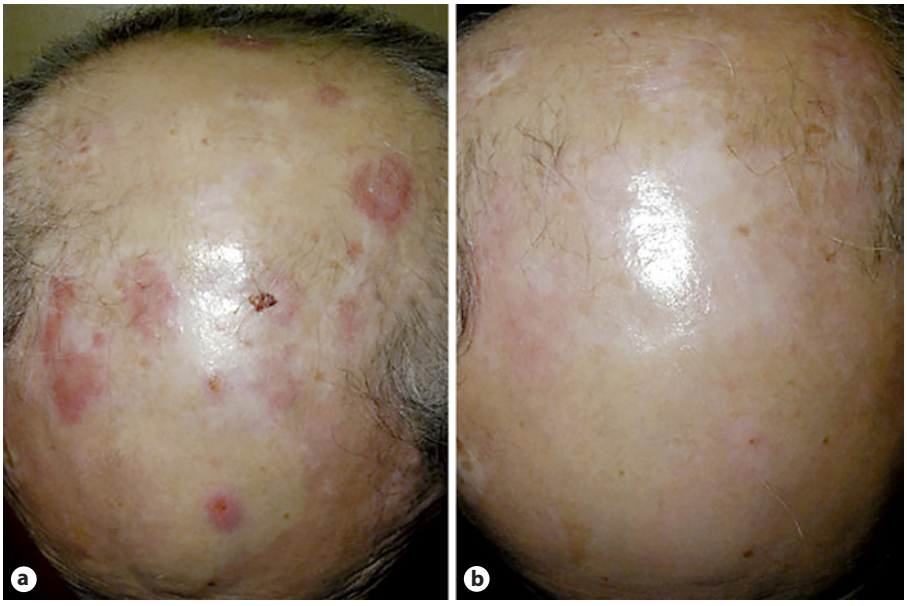

Fig. 3. Chronic cutaneous lupus erythematosus of the scalp before (**a**) and after (**b**) 10 weekly sessions of MAL-PDT.

markers of vascularization (CD34), nervous cell function (myelin basic protein), keratinocytes function (CD44), and proliferation index (Ki-67) [77].

An uncontrolled study of 5 patients with localized scleroderma showed a reduction of clinical score and an improvement of the durometer score after once- or twice-weekly sessions (for 3–6 weeks) with the application of 3% ALA gel followed by irradiation with an incoherent lamp [79]; the only adverse effect was a transient hyperpigmentation [79]. These results were challenged by another study (a single-blind, prospective, comparative trial with intraindividual controls enrolling 6 patients) that reported a poor efficacy, although it confirmed that safety and tolerability were very good [80]. A study of 20 patients without controls reported a beneficial persistent effect of 3 MAL-PDT sessions against keloids, which appeared to be due to a decrease of collagen synthesis and neovascularization [81].

To date, only few case reports have described the improvement or remission of discoid lupus erythematosus lesions of the face, neck, and scalp, following weekly sessions of MAL-PDT and 6-monthly maintenance treatments [82–84]. We also successfully treated an LED patient with 10 weekly sessions of MAL-PDT (Fig. 3). However, 2 patients with recalcitrant discoid lupus erythematosus of the face who were treated with 3 and 2 sessions of ALA-PDT, respectively, showed no clinical improvement and a bad tolerance to the therapy [85].

Another dermal disease that has attracted the attention of researchers is necrobiosis lipoidica. A retrospective study of 18 patients reported a 40% complete clearance rate with conventional MAL- or ALA-PDT [86], and another retrospective study of 65 patients reported a complete clearance in 64% (45/70 patients) with conventional MAL-PDT and 80% (8/10) with daylight PDT [87].

Skin Infections

ALA has a high affinity for human papilloma virus-infected keratinocytes and, after ALA application, a higher fluorescence is detected in genital warts in comparison to the normal surrounding skin [88]. In pilot studies of small case series, the cure rates of repetitive sessions (up to 6 times) of ALA-PDT with white [89, 90] or red [91–93] light were very high, ranging from 50 to 100%, without recurrences after follow-ups of at least 4 months and a good cosmetic outcome [89–93]. Aiming to clarify the optimal light source for PDT of warts, a randomized study including 30 patients with a total of 250 recalcitrant hand and foot warts, compared ALA-PDT with white, blue, and red lights. PDT with white light was significantly more effective than PDT with red and blue lights and also more effective than cryotherapy [90]. In a randomized, double-blind clinical trial of ALA-PDT versus placebo PDT for 232 recalcitrant foot and hand warts of 45 patients, the median relative reduction in the wart area was 98% with ALA-PDT versus 52% with placebo after 14 weeks and 100% versus 71% after 18 weeks [94]. Conventional treatments of subungual and periungual warts are

often ineffective, but a pilot study of patients with a total of 40 lesions reported that ALA-PDT was effective with a 100% complete clearance in 90% of patients after a mean of 4.5 treatments [95].

The above-mentioned studies had some relevant differences in the treatment protocols, and we could not find comparative studies to establish the ideal one. However, recent findings have demonstrated that shaving or careful surgical paring of the hyperkeratosis should always precede ALA application because they can facilitate its penetration into the skin [96, 97].

Pain and transient hyperpigmentation are the only adverse effects of PDT for warts. However, pain during and after (up to 24 h) light exposure is described as severe or unbearable by about 20% of patients [94, 95, 98, 99] and, unfortunately, effective methods to decrease it have not been suggested so far.

The use of methylene blue as a photosensitizer for PDT of warts has been investigated as well. In a randomized double-blind placebo-controlled study, plane warts were successfully treated with daylight PDT with topical 10% methylene blue gel. Unlike ALA/MAL PDT the treatment was almost painless [98], and we emphasize that it is also much cheaper.

Several clinical trials have reported beneficial effects of topical PDT for the treatment of genital warts: ALA-PDT appeared to be as effective as CO_2 laser evaporation for vulvar condylomata [100] and as CO_2 laser evaporation or surgical excision for vulvar and vaginal condylomata with intraepithelial neoplasia grade III [101]. Additionally, PDT showed a shorter healing time, excellent cosmetic results, and minimal tissue destruction [100, 101]. A case series study of 12 patients demonstrated that ALA-PDT is also effective for condylomata of males, and 2 sessions of ALA-PDT 1 week apart showed an overall cure rate of 72.9% after 12 months from the end of treatment, with minimal side effects during the irradiation [102]. A following randomized study of 65 males again did not find differences of efficacy between ALA-PDT and CO_2 laser evaporation, but the recurrence rate (6.3 vs. 19.1%) and the proportion of patients with adverse effects (13.9 vs. 100%) were significantly lower with ALA-PDT [103]. Another randomized trial with 91 patients confirmed that ALA-PDT was as effective as conventional CO_2 laser evaporation but with a lower incidence of adverse effects and recurrence rate [104].

ALA-PDT was also found to be effective for the treatment of urethral condylomata acuminata of 191 patients of both sexes provided that light was delivered through an intraurethral cylindrical fiber [105]. Histological examination with light microscopy and electron microscopy of treated lesions showed both apoptosis and necrosis of HPV-infected keratinocytes [105]. Recently, the clinical effects of the combination of CO_2 laser ablation followed by 3 times ALA-PDT were investigated in a single-arm prospective study of 98 cases of both sexes. Three months after the treatment, 93.8% of patients showed complete cure of the treated area, but 18 patients showed new lesions in the surrounding skin [106]. These results were challenged by a following phase III prospective randomized double-blind study of 175 patients that reported that adjuvant ALA-PDT of condylomata acuminata after CO_2 laser ablation did not help in preventing recurrence of anogenital warts [107]. A randomized controlled trial of 141 patients was undertaken in order to assess the best method to increase the tolerability of ALA-PDT of genital warts, and a two-step irradiance schedule reduced more significantly the patients' pain degree in comparison to single-dose cold compress [108].

Another successful indication of PDT is cutaneous infection by both *Leishmania major* and *L. tropica*. In a controlled randomized trial of 60 patients suffering from cutaneous leishmaniasis caused by *L. major*, 4 weeks of therapy with a weekly treatment with 10% ALA-PDT, twice daily topical paromomycin, or twice daily placebo led to clearance of lesions in 93.5, 41, and 13% of cases, respectively, after 3 months of follow-up [109]. Furthermore, none of the patients in the PDT group showed deep and disfiguring scars, whereas scarring developed in 42% of patients treated with paromomycin and in 11% of patients treated with placebo [109]. Only slight hypopigmentation in the irradiated area was observed in a case report where the patient was successfully treated with MAL-PDT [110]. In addition to these randomized controlled trials, there are several studies of case series with similar clinical results although they used different treatment protocols (ALA applied under occlusion for 4 h or MAL for 3 h; 1–5 weekly treatment sessions). Response rates ranged from 96.9 to 100%, tolerability was always very good, cosmetic results were always excellent, and recurrences were never seen during the 1- to 6-month follow-up periods [111–114]. In comparison to cryotherapy, ALA-PDT resulted in being equally effective, but cosmetic results were better, whereas pain was more intense [115]. The place of PDT in the therapeutic armamentarium against leishmaniasis is still debated, although the technique seems particularly valuable for the treatment of lesions in aesthetically sensitive sites and for lesions resistant to other methods of treatment [2]. The mechanisms underlying the sterilizing effect of PDT on leishmaniasis

Table 3. Summary of recommendations for ALA/MAL PDT use for non-neoplastic skin conditions [2]

Strength of recommendation	Quality of Evidence	Indication
A	I	Skin aging
B	I	Acne Refractory hand/foot warts Refractory genital warts Cutaneous leishmaniasis
C	III	Keloids
C	III	Lichen sclerosus Sebaceous gland hyperplasia
D	I	Psoriasis
D	III	Rosacea Necrobiosis lipoidica

are not well understood. The yield of singlet oxygen by PpIX photoactivation was thought to have a toxic killing effect on *Leishmania* spp [113]. However, in vitro studies did not demonstrate any parasiticidal effects of PDT on amastigotes, and the clearance of cutaneous lesions after irradiation appeared to occur through a systemic immune response of the host [116]. Some species of leishmania that can cause mucocutaneous (*L. braziliensis* complex) or visceral leishmaniasis (*L. donovani* complex) have a metabolic defect in the biosynthesis of heme and therefore they should not be treated with PDT [117].

PDT showed bactericidal activity as well. Two weekly sessions of ALA-PDT were more effective than 2 sessions with red light alone in reducing the bacterial load and in promoting the healing of bilateral chronic skin ulcers infected with *Pseudomonas aeruginosa* in 26 patients [118].

Erythrasma is a superficial cutaneous infection caused by *Corynebacterium minutissimum* that has a naturally high content of endogenous porphyrins. Red light irradiation without exogenous photosensitizing molecules improved erythrasma of 13 patients [119].

Results of experimental investigations have demonstrated that dermatophytes and yeasts can be effectively sensitized in vitro by a number of photosensitizers including phenothiazine dyes, porphyrin derivatives, and phthalocyanines, as well as ALA/MAL [120]. Onychomycosis has been the most investigated clinical indication for this, mainly because of the limitations of the current topical and oral drug treatments [121–127]. Two randomized controlled trials showed that 12 sessions (a session every 15 days for 6 months) of PDT with methylene blue (2%) were significantly more effective than oral fluconazole (300 mg/week for 6 months) [121], whereas 8 sessions (a session every 15 days for 4 months) were as effective as 8 sessions of irradiation with IPL in the treatment of onychomycosis of the toenails [122]. The complete clearance rates with methylene blue PDT were 90 and 70%, respectively [121, 122]. Results of smaller uncontrolled studies with methylene blue were rather superimposable [123, 124]. PDT with a nano-emulsion of aluminium-phthalocyanine chloride effectively treated 60% of onychomycosis of 20 patients [125]. Effectiveness and safety were similar to the conventional treatments, with the advantage of the absence of collateral effects and the possibility to repeat the treatment without inducing fungal resistance [125].

In a case series study of 30 patients with toenail infection by *Trichophyton rubrum* treated with ALA-PDT (3 sessions with 2-week intervals) the cure rates were 43.3% after 12 months and 36.6% after 18 months [126]. Interestingly, a randomized controlled trial compared 3 sessions of MAL-PDT versus red light alone for onychomycosis. The comparison of overall remission rates did not show significant differences, but MAL-PDT resulted in better rates of clinical and microbiological response in non-dystrophic versus dystrophic onychomycosis patients [127]. In this and other previous studies, a pretreatment with 40% urea was used to soften the nail plate in order to increase the penetration of the photosensitizer [122, 126, 127]. Although antifungal PDT has been mainly investigated in the treatment of onychomycosis, its clinical applications for the treatment of other fungal infections were also evaluated [128–130]. Methylene blue-PDT showed promising results in patients with chromoblastomycosis [128] and sporotrichosis [131]. PDT with a porphyrin derivative was effective in the treatment of denture stomatitis [129], and PDT with ALA/MAL and various phenothiazine dyes was considered a potential approach for the treatment of antimycotic drug-refractory oral candidiasis in normal people [132] and HIV-infected patients [130].

MAL-PDT showed some efficacy against skin mycoses in immunocompetent subjects as well, but it did not seem to ensure clinical advantages over similarly effective and much cheaper topical drug treatments [133].

Conclusion

Despite a history of experimental and clinical use of more than 100 years, PDT is only now starting to be appreciated for its full potential. Particularly in the past 30 years, we have greatly improved the knowledge of PDT effects in human normal and pathological skin [3]. The broad spectrum of biochemical and pathological effects

has prompted its application for various cosmetic, inflammatory, and infectious conditions with variable success rates. Everything considered, we have enough evidence to state that MAL- and ALA-PDT may be an effective treatment option for a number of conditions, such as skin aging, acne, warts, condylomata, and Leishmania skin infection (Table 3). For other disorders, the level of evidence and strength of recommendation are lower, and large controlled studies with prolonged follow-ups are necessary in order to assess the full therapeutic potential and all its possible applications. Finally, the desirable availability of new photosensitizers, currently under preclinical and/or early clinical investigation, with better photochemical properties than PpIX, could induce a new impulse to the clinical interest for this treatment modality [2].

Key Message

We review the off-label use of photodynamic therapy for the treatment of cosmetic, infectious, and inflammatory skin conditions.

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Giuseppe Monfrecola: contributions to the design of the work, to acquisition and analysis of data for the work, and to drafting the work. Matteo Megna and Gabriella Fabbrocini: contributions to the conception or design of the work, to analysis of data for the work, and to drafting the work. Chiara Rovati and Mariateresa Rossi: contributions to acquisition of data for the work and to drafting the work. Mariachiara Arisi: contributions to analysis of data for the work and to drafting the work. Irene Calzavara-Pinton: contributions to drafting the work and to its linguistic correction. Piergiacomo Calzavara-Pinton: contributions to the conception or design of the work, to acquisition and analysis of data for the work, and to drafting the work.

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