GUIDELINES

European Dermatology Forum guidelines on topical photodynamic therapy 2019 Part 2: emerging indications – field cancerization, photorejuvenation and inflammatory/infective dermatoses

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Abstract

In addition to approved indications in non-melanoma skin cancer in immunocompetent patients, topical photodynamic therapy (PDT) has also been studied for its place in the treatment of, as well as its potential to prevent, superficial skin cancers in immune-suppressed patients, although sustained clearance rates are lower than for immune-competent individuals. PDT using a nanoemulsion of ALA in a daylight or conventional PDT protocol has been approved for use in field cancerization, although evidence of the potential of the treatment to prevent new SCC remained limited. High-quality evidence supports a strong recommendation for the use of topical PDT in photorejuvenation as well as for acne, refractory warts, cutaneous leishmaniasis and in onychomycosis, although these indications currently lack approvals for use and protocols remain to be optimized, with more comparative evidence with established therapies required to establish its place in practice. Adverse events across all indications for PDT can be minimized through the use of modified and low-irradiance regimens, with a low risk of contact allergy to photosensitizer prodrugs, and no other significant documented longer-term risks with no current evidence of cumulative toxicity or photocarcinogenic risk. The literature on the pharmacoeconomics for using PDT is also reviewed, although accurate comparisons are difficult to establish in different healthcare settings, comparing hospital/office-based therapies of PDT and surgery with topical ointments, requiring inclusion of number of visits, real-world efficacy as well as considering the value to be placed on cosmetic outcome and patient preference. This guideline, published over two parts, considers all current approved and emerging indications for the use of topical photodynamic therapy in Dermatology prepared by the PDT subgroup of the European Dermatology Forum guidelines committee. It presents consensual expert recommendations reflecting current published evidence.

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Conflicts of interest

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Introduction

This updated guideline seeks to promote safe and effective practice across Europe in the delivery of topical photodynamic therapy (PDT) in dermatological indications and reflects evidence derived from a systematic literature review and previous therapy guidelines and should be read in conjunction with Part I, which covers protocols, adverse effects and use of PDT in established approved indications.[1–7]

Topical PDT is approved for the treatment of certain non-melanoma skin cancers (NMSC) in the immune competent, used both as lesional and area/field therapy, and has the potential to delay/reduce the development of new AK, although direct evidence of prevention of invasive SCC remains limited. Although sustained clearance rates are lower, topical PDT has a role in the treatment as well as potential to prevent, superficial skin cancers in immune-suppressed patients. Cosmetic outcome following PDT is widely reported, and this guideline includes review of specific studies looking to use PDT for photorejuvenation. Additional potential cancer indications for topical PDT have been explored including local patch/plaque cutaneous T-cell lymphoma (CTCL). In addition, PDT can improve acne and several other inflammatory/infective dermatoses. A summary of recommendations reviewed across both sections of this guideline is listed in Table 1.

Table 1 Summary of recommendations (including indications reviewed in Part 17)

Indication	Strength of recommendation	Quality of evidence
• Actinic keratosis*	A	I
• Squamous cell carcinoma in situ*		
• Superficial Basal cell carcinoma*		
• Nodular Basal cell carcinoma*		
• Photorejuvenation		
• Treatment of NMSC in organ transplant recipients	B	I
• Prevention of NMSC in organ transplant recipients		
• Field cancerization*		
• Acne		
• Refractory warts, plane and genital warts		
• Cutaneous leishmaniasis		
• Onychomycosis		
• Superficial fungal infections	C	II-III
• Deep cutaneous mycoses		
• Hypertrophic and Keloid Scars		
• Sebaceous gland hyperplasia		
• Cutaneous T-cell lymphoma (CTCL)		
• Extramammary Paget's disease		
• Lichen sclerosus	C	III
• Granuloma annulare		
• Necrobiosis lipoidica		
• Porokeratosis		
• Psoriasis	D	I
• Invasive squamous cell carcinoma SCC	D	II-III

*PDT is approved for this indication in Europe.

Treatment of non-melanoma skin cancer in organ transplant recipients (Strength of recommendation B, Quality of Evidence I)

Photodynamic therapy, along with other non-surgical techniques, is suggested for treating AK or SCC *in situ* in OTR, with PDT permitting physician-directed treatment of multiple lesions and field therapy[8] A prospective study compared the efficacy of PDT for AK and SCC *in situ* in immunocompetent patients (IC) with OTR for one or two ALA-PDT treatments.[9] At 4 weeks, complete remission was indistinguishable in both groups (IC 94% vs. OTR 88%), but differed at 12 weeks (IC 89% vs. OTR 68%) and 48 weeks (IC 72% vs. OTR 48%). A prospective study treated 16 OTRs for AK and photodamage with 1–2 sessions of red light with clearance of 100% at 12 and 24 weeks.[10] Higher complete remission was observed when two sessions of MAL-PDT were performed: At 3 months, complete remission varied between 71% and 90%.[11] Reduced efficacy of PDT in OTR may result from the large number of intraepithelial lesions, more prominent hyperkeratosis and an altered, secondary local immune response. Location of lesions also appears important for the outcome: Response for AK to PDT on the hands ranged between 22% and 40%.[12] One study compared MAL-PDT to topical 5-fluorouracil: CR differed at 1 month with 89% for MAL-PDT and 11% for 5-fluorouracil, with more pain, but also better cosmesis following PDT.[13] An intraindividual study compared MAL-PDT to imiquimod for 572 AK in 35 OTR: PDT showed a higher CR for AK I–III with 78% compared to imiquimod with a CR in 61% at 3 months.[14]

Fewer studies address BCC in OTR: 21 clinically diagnosed multifocal BCCs in the face of 5 OTR were treated with ALA using thermogel with a single illumination by diode laser with 20/21 showing a CR at 12 weeks.[15] MAL-PDT was used by two studies for sBCC and nBCC with 1/18 recurring after between 12 and 23 months follow-up.[16,17]

Prevention of non-melanoma skin cancer in organ transplant recipients (Strength of recommendation B, Quality of Evidence I)

The increase in incidence of OTR to SCC has been attributed to impairment of the cutaneous immunosurveillance due to systemic immunosuppressive medication, although regularly applied photoprotection can reduce AK lesion counts, PDT is one modality that has been investigated as a preventive therapy.[18] MAL-PDT delayed the development of new lesions in an intrapatient randomized study of 27 OTR with AK (9.6 vs. 6.8 months for control site).[19] In a multicentre study of MAL-PDT compared with no treatment in 81 OTR, confirmed an

initial significant reduction in new lesions, mainly AK, but this effect was lost by 27 months, 12 months after the last of the 5 PDT treatments.[20] No significant difference in the occurrence of SCC was observed in a study of blue light ALA-PDT versus no treatment after 2 years of follow-up in 40 OTR.[21] However, another study of blue light ALA-PDT, repeated at 4- to 8-week intervals for 2 years, a reduction in SCC in 12 OTRs was observed compared with the number developing in the year prior to treatment, with a mean reduction at 12 and 24 months of 79% and 95%.[22] Another study evaluated the clearance and preventive effects of conventional PDT or daylight PDT either with or without ablative laser therapy in 16 patients. After a 3 months follow-up, lesion clearance rate was highest for ablative laser plus daylight PDT (74%, range 37–100) vs. 50% (range 25–83), 46% (range 0–75) and 5% (range 0–40) for the therapies employing daylight PDT, c-PDT or ablative laser therapy alone.[23]

A second study from the same group evaluated 35 OTR, which had their AKs treated with either 5% imiquimod cream or two cycles of conventional MAL-PDT. After 3 months of follow-up, PDT treatment was linked to a significant higher rate of CR (AK I–III median 78%; range 50–100) compared with 5% imiquimod-treated areas (median 61%, range 33–100; $P < 0.001$).[14] Thus, fewer emergent AKs were seen in PDT-treated skin vs. imiquimod-treated skin (0.7 vs. 1.5 AKs, $P = 0.04$). In this study, the lesion clearance was superior for MAL-PDT (78% vs. 61%, respectively). Intense inflammatory LSRs were significantly more common in the PDT group compared with the imiquimod group; however, they resolved faster in the PDT group (median 10 vs. 18 days, $P < 0.01$).

Field cancerization (Strength of Recommendation B, Quality of Evidence I) (Approved indication)

In the skin, the concept of field cancerization suggests that clinically normal appearing skin around AKs and SCCs has subclinical features of genetically damaged cells, which can potentially develop into a neoplastic lesion.[24] The major carcinogen for skin cancer is UV radiation, and common genetic abnormalities in NMSC are the presence of UV-induced TP53 mutations.[25] TP53-mutated clones can be found in >70% of patients over 50 years of age in sun-exposed skin.[26] Similarly, NOTCH1 mutations are present in clinically and histologically normal skin adjacent to SCC and appear to arise by contiguous growth of a clonal precursor.[27]

Field cancerization can be suspected clinically when multiple AKs are present, and is also illustrated in case of development of simultaneous multifocal SCC on the scalp. The subclinical changes can be evaluated by reflectance confocal microscopy by showing disruptive changes within individual corneocytes and parakeratosis, cellular and nuclear atypia, pleomorphism, loss of the honeycomb pattern and architectural disarray.[28] Optical coherence tomography (OCT) has also shown that 79% of apparently normal skin in field cancerization harbour dysplasia or occult carcinoma.[29]

The disappearance of TP53-mutated cells and cellular atypia in field cancerization area following PDT has been shown and emphasizes the interest of adapting the therapeutic strategy to target not only AK lesions but also the surrounding field.[30] An expert consensus has noted that PDT might prevent new AKs and the transformation of AK to invasive SCC and has proposed to evaluate the interest of repeated cyclic PDT treatment in that population.[31] The preventive potential of field PDT in OTR patients is summarized in 6.2, whilst use in immunocompetent individuals was studied in photodamaged patients with facial AK, where ALA-PDT demonstrated a significant delay over control sites of about 6 months until new AK developed.[32]

Cutaneous T-cell Lymphoma (CTCL) (Strength of Recommendation C, Quality of Evidence II-iii)

The sensitization of skin-infiltrating malignant lymphocytes induces a selective fluorescence of skin lesions of mycosis fungoides/CTCL that is five times more intense than in normal skin.[33] Clinical evidence of PDT for CTCL is derived from case reports and series that treated lesions that were poorly or no responsive to other treatment options.[34] Early reports indicated ALA-PDT as effective and well tolerated with a clearance rate that, in a few studies, was close to 100% after 1–5 exposures without apparent differences related to the degree of infiltration of treated lesions.[35–40]

More recently, five case series and a multicentre retrospective study used MAL-PDT delivered in the same regimen as for BCC, but repeated several times, if needed.[41–45] In the first report, complete remission was observed in four of five patients with unilesional patch, plaque and nodular disease, with partial response in the remaining patient after a median of six treatments.[41] In the second report, 6 of 12 patients with plaque-type lesions had a complete clearance, five a partial response, and one no response to a mean of 5.7 MAL-PDT treatments.[42] In these two reports, no recurrences were seen after 6–24 months. Ten patients with unilesional patch- and plaque-stage CTCL were treated with 2–6 MAL-PDT treatments at 1-week intervals. Both clinical and histological clearance were seen in five patients and a partial remission in two. During follow-up (8–31 months), 6/7 patients with complete or partial remission did not show a relapse.[43] In a further study of 12 patients with pauci-lesional patch- and plaque-MF lesions, a 75% 1-month response rate (six complete responders, three partial) was observed following monthly MAL-PDT repeated for 6 months, with regression of lymphocytic infiltrate in 8/9 lesions biopsied (only one lesion biopsies/patient).[44] Response rates were similar between patches and plaques but higher in sun-protected areas. Finally, 50% complete and 50% partial clearance were seen in four patches of 4 MF patients after 4-9 PDT treatments.[45]

A retrospective observational multicentre study of 19 patients with plaque-stage unilesional MF or isolated MF lesions in body flexures has reported lower efficacy of 1–7 PDT sessions

with a complete remission only in 5 with two relapsing during follow-up.[46]

The above reports and series indicate the potential for topical PDT in localized patch/plaque CTCL, although it may be less practical and more costly than standard phototherapy for multiple lesions. Current evidence indicates that topical PDT does not have an optimized protocol and should be restricted to localized disease, with a possible indication for lesions in the body folds that cannot be exposed to phototherapy.

Acne (Strength of Recommendation B, Quality of Evidence I)

Acne can respond to PDT and has been widely investigated in a variety of protocols. The mechanism of action remains to be fully elucidated, but it is well known that PDT promotes transient antimicrobial and anti-inflammatory effects, inhibition and destruction of sebaceous glands, as well as enhanced epidermal turnover promoting reduced follicular obstruction.[47]

Topical ALA-PDT for acne was first described in 2000; in a study on 22 patients with back acne, four interventions with ALA-PDT, ALA alone, light alone and a control area were compared, using a broadband lamp (550–700 nm).[48] There was a significant reduction of inflammatory acne and decreased sebum excretion in the ALA-PDT group only, with smaller sebaceous glands at 10 weeks after one treatment. Another randomized, controlled study on 10 patients compared ALA-PDT, ALA alone, light alone and a control site using a diode laser, single treatment (635 nm, 25 mW/cm^2, 15 J/cm^2) weekly for 3 weeks. Inflammatory acne lesions were significantly reduced from ALA-PDT, but with no reduction of *P. acnes* nor sebum excretion.[49] In an open study on 13 patients with facial acne, all improved following ALA-PDT, using a halogen lamp (600–700 nm, 13 J/cm^2).[50]

MAL-PDT using red LED light (635 nm, 37 J/cm^2) for facial acne achieved a 68% reduction in inflammatory lesions versus 0% in a control group following two treatments, but with no reduction in non-inflammatory lesions.[51] In a subsequent split-face study, a single treatment of MAL-PDT was compared with ALA-PDT, using a lower fluence rate and a similar reduction in inflammatory lesions occurred for both interventions, but ALA-PDT showed more prolonged and severe side-effects.[52] Another split-face study compared MAL-PDT (two sessions) versus placebo with light only in 30 patients with facial acne, using red LED (635 nm, 37 J/cm^2, 68 mW/cm^2).[53] At 3 months, inflammatory lesions were reduced by 54% vs. 20%, along with non-significant reductions in non-inflammatory lesions of 40% and 20%.

The importance of light source and photosensitizers was estimated in a critical review.[47,54] High-dose ALA- and MAL-PDT were considered to produce similar effects with incubation of 3 h or longer more likely to induce longer remission. Due to deeper penetration, red light was considered more likely to promote sebaceous gland destruction compared to blue or pulsed light sources.[47,55] A Cochrane systematic review concluded little or no difference in effectiveness between ALA-PDT (45 min incubation), activated by blue light, vs vehicle plus blue light, whilst pooled data from 3 studies showed red light MAL-PDT had a similar effect on changes in lesion counts vs. placebo cream with red light.[56]

To date, experience with DL-PDT for acne is limited. Use of an alternate day protocol along with a novel variant of a 5-ALA ester saw inflammatory and non-inflammatory lesions reduce significantly by 58% and 34%, respectively, by 12 weeks in a double-blind randomized controlled study.[57] Daylight PDT compared with laser-assisted daylight PDT also saw mean inflammatory lesion counts reduced significantly by 36% and 52%, respectively.[58]

Few studies have investigated PDT in combination with conventional acne treatments. In a randomized controlled trial involving 46 patients with facial acne, there was a small but significantly greater reduction in inflammatory lesions from two ALA-PDT treatments compared with doxycycline plus adapalene (12 weeks, 84% vs. 74% reduction).[59] In another study, minocycline plus ALA-PDT led to greater efficacy vs. minocycline alone (8 weeks, −74% vs −53%).[60]

Photodynamic therapy may emerge as an alternative to conventional systemic therapies, especially for inflammatory acne of moderate severity although it may also evolve to treat conglobate acne.[61,62] Side-effect profiles are comparable with the phototoxic reactions seen from PDT for AK and field cancerization, but can be unpredictable and severe, with pain during light exposure, followed by phototoxic skin reactions over the following days. Therapy protocols are yet to be optimized balancing efficacy, tolerability and cost-effectiveness, as multiple treatments appear necessary.

Refractory hand/foot warts, plane and genital warts (Strength of recommendation B, Quality of evidence I)

Clearance rates of recalcitrant hand and foot warts of 50–100% have been reported usually after repetitive treatments (up to 6 treatments) of PDT. A randomized study with ALA-PDT with 30 patients showed superior clearance to cryotherapy.[63] A controlled randomized trial with 232 recalcitrant warts showed, after 18 weeks, a 56% clearance rate for ALA-PDT compared to 42% for placebo-PDT.[64] Pain, during and after illumination, was the main side-effect. Several further case series including a study for recalcitrant periungual warts confirmed these results.[46,65–70]

Experience of PDT for plane warts is limited to case reports/case series.[71,72] In the series, conventional PDT with 10% ALA showed a complete response in 10 of 18 patients. Daylight PDT using methylene blue achieved a complete response in 13 of 20 patients.[73]

There are several case reports/case series of PDT for genital warts. The clearance rate for female patients varied from 66% to 100%, whereas in male patients a response rate of 73% was

reported.[74–76] A larger study with 164 patients with urethral condylomata cleared 95% after one to four ALA-PDT treatments.[77] A randomized study comparing ALA-PDT with CO_2 laser evaporation in 65 patients with condylomata acuminate showed a 95% complete removal rate for PDT and 100% for CO_2 laser, but the recurrence rate was lower for PDT (6.3 vs. 19.1%).[78] A larger study with 90 patients confirmed these excellent results including the lower recurrence rate for PDT (9% vs. 17% for laser).[79] A larger study using ALA-PDT as an adjuvant treatment to CO_2 laser evaporation, however, could not demonstrate a beneficial effect of ALA-PDT in this setting.[80] A more recent case series showed that repeat PDT treatments could eliminate subclinical genital HPV infections.[81] A series of 19 cases of anal canal condylomata with ALA-PDT showed a 100% response rate and no recurrence after 6 months.[82]

Despite these positive results, PDT is used by few practitioners routinely, probably due to the absence of optimized protocols, and pain associated with therapy.

Cutaneous leishmaniasis Strength of Recommendation B, Quality of evidence I

Photodynamic therapy has been used in cutaneous leishmaniasis caused by different types of Leishmania, especially *L. major* and *L. tropica,* with success. In a placebo-controlled, randomized clinical trial on cutaneous Leishmaniasis caused by *L. major*, weekly ALA-PDT for 1 month was more effective than 15% paromomycin–methyl benzethonium chloride ointment.[83] Two months after treatment, 94% in the PDT group were fully healed (paromomycin, 41%). All PDT patients were amastigote-free (paromomycin, 65%). Both groups experience mild and tolerable itch, burning, redness, discharge, oedema and pain as side-effects of the treatment.[84]

Additionally, there are a series of cases using different modalities of ALA- and MAL-PDT (a total of 46 lesions in 19 patients).[85–89] Red light was (570–700 nm) the most frequently used, using fluences between 75 and 100 J/cm^2 but also narrow-band Aktilite® CL128.[89,90] 96.9% to 100% of lesions treated responded. PDT was administered weekly, and 1 to 7 sessions were needed, 3 or more being more effective than 2 or less. Cosmetic results were excellent, and most lesions left only superficial scarring or slight postinflammatory hyperpigmentation.[83,89]

Red light ALA-PDT seems to be at least as effective as cryotherapy, but with better cosmetic results, healing after 6 PDT sessions or 5 applications of cryotherapy. PDT obtained better cosmetic results than cryotherapy but was perceived by the patients as more painful.[91]

Daylight PDT is also effective and well tolerated for cutaneous leishmaniasis, with 31 patients treated weekly. Three patients with *L. tropica* failed to respond to DL-PDT, whereas all the patients with *L. major* responded. The individual lesion's cure rate was 77%, being 74% for the hospital-based treatment with a mean number of treatments of 4.6% and 82% for self-administered PDT after a mean of 7 sessions.[92] Intralesional ALA-PDT, three times at weekly intervals, has been observed to clear a patient with long-standing cutaneous leishmaniasis with 2 years of follow-up.[93]

Photodynamic therapy with porphyrin precursors does not kill the Leishmania *parasite* directly, but a systemic immune response is likely responsible for the clearance of lesions, especially as some species are deficient of some enzymes in the haem biosynthetic pathway.[94]

Photodynamic therapy is effective in treating cutaneous leishmaniasis, either in adults or children, although the evidence is greater for conventional than for DL-PDT. However, in lesions acquired more than 3 months earlier, spontaneous healing could have occurred. Leishmania species that can cause mucocutaneous (*L. braziliensis* complex) or visceral leishmaniasis (*L. donovani* complex) should not be treated with PDT.[95] Neither HIV-positive patients with cutaneous leishmaniasis nor patients with nodular lymphangitis should, as yet, be treated with PDT. Although the data remain limited, and PDT cannot be recommended in routine use, it could be very convenient for cutaneous leishmaniasis resistant to other methods of treatment and in aesthetically sensitive parts of the body.

Photorejuvenation (Strength of Recommendation A, Quality of Evidence 1)

Photodynamic therapy promotes significant improvement in fine wrinkles, mottled pigmentation, sallow complexion, skin texture, tactile roughness, telangiectasias and facial erythema, whereas coarse wrinkles and sebaceous hyperplasia are not significantly altered.[96] In the majority of studies, IPL was used, probably with a synergistic effect as IPL by itself is capable of photorejuvenating effects.[95–106] Split-face studies show the superiority of IPL-PDT as compared to sole IPL treatment.[99–101,106] Also, on the dorsal hands superiority of IPL-PDT as compared to placebo-IPL has shown improvement of overall appearance and mottled pigmentation.[107] Illumination times are shorter with IPL than red light sources, reducing pain.[108] The use of MAL-PDT with a red LED by standard protocol is feasible when AK is treated in parallel, with a significant improvement of the signs of photoaging.[109–112] Another PDT protocol licensed for AK in the USA is the combination of ALA with blue light, with a few studies confirming efficacy.[113–115] Daylight PDT might also be effective in reducing the signs of photoaging with the advantage of being nearly painless as compared to conventional PDT using red light.[116,117]

In a split-face study, conventional PDT was compared to MAL-PDT combined with microneedling with superior cosmetic results with improvement even of coarse wrinkles, although the pain was greater.[118] Shorter needle lengths (0.3 mm) provide improvement in photosensitizer penetration, whilst longer needle lengths (1.5 mm) also exhibit synergistic

effects in neocollagen formation by direct damage to the dermis.[96] MAL-PDT in combination with non-ablative fractional laser resulted in a better improvement of fine wrinkles compared to laser alone.[119] A pretreatment with an ablative fractional laser before daylight PDT was shown to be more effective as compared to a pretreatment with microdermabrasion regarding general skin cosmesis and improvement of dyspigmentation and skin texture.[120]

An increase in type I collagen and a reduction of elastotic material in the dermis reversing the signs of photoaging has been demonstrated after PDT.[30,111,121–125] PDT *in vitro* can increase production of collagen type I and also of collagen degrading matrix metalloproteinase (MMP)-3 via activation of extracellular signal-regulated kinase.[125] The authors hypothesize that an increase in MMP-3 may promote the degradation and removal of old, damaged collagen fibres, whilst the fibroblast is initiating the formation of new ones to replace them. The epithelial–mesenchymal interaction seems to play an important role in PDT-induced photorejuvenation with keratinocyte-induced cytokines stimulating collagen synthesis in fibroblasts.[126] Collagen remodelling after PDT has been also shown to be stimulated by a release of TGF-ß1 in keratinocytes.[127] Inhibition of melanogenesis through paracrine effects by keratinocytes and fibroblasts might be responsible for the improvement of mottled hyperpigmentations after PDT.[128]

Observed improvement of telangiectasias and facial erythema not only after IPL but also after LED illumination might be due to collagen deposition in the upper dermis, which compresses the telangiectatic vessels towards the deeper dermis.[30] A PDT-induced oxidative damage and apoptosis in photoaged fibroblasts *in vitro* has been proposed.[129] Immunohistochemical expression of TP-53, a marker for epidermal carcinogenesis, was reduced after PDT, indicating that PDT might reverse the carcinogenic process in photodamaged skin.[130]

There is good evidence to support the use of PDT as an effective method for skin rejuvenation, although repeated sessions are likely to be necessary to achieve a sustained effect. As AK is also often present in photodamaged skin, licensed treatment protocols should be preferred to warrant simultaneous treatment of AK.

Cutaneous mycoses

Onychomycosis (Strength of Recommendation B Quality of evidence I)

Superficial fungal infections (Strength of Recommendation C Quality of evidence II-iii)

Deep cutaneous mycoses (Strength of Recommendation C Quality of evidence II-iii)

Photodynamic therapy has been widely studied for onychomycosis.[131,132] A single-centre open of 30 patients with onychomycosis by *T. rubrum* who had not responded to any topical antifungal; at 12 months, the clinical and microbiological cure rate after ALA-PDT was 43%, which fell to 36% at 18 months. A randomized, controlled, double-blind study compared PDT using methylene blue 2% every 2 weeks for 24 weeks versus oral fluconazole. PDT was more effective (complete response rate 90%), especially if the nail was previously abraded, than fluconazole (45%).[133] A multicentre, randomized, placebo-controlled trial in 40 patients, comparing three sessions, 1 week apart, of MAL-PDT preceded by 40% urea versus placebo-PDT and urea 40%.[134] After 36 weeks of follow-up, complete clinical and microbiological response was seen in only four patients (18%) in active PDT group although PDT resulted in better rates of clinical and microbiological cure in non-dystrophic vs. dystrophic onychomycosis patients. A trial used aluminium–phthalocyanine chloride, plus red LED light to treat onychomycosis, with prior urea, saw 60% of patients clinically clear, but only 40% after mycological examination.[135]

And open-labelled study compared ALA-PDT vs. 5% amorolfine lacquer ± fractional ablative CO_2 laser for toenail onychomycosis but did not find any benefit to the pretreatment with laser.[136] Forty patients with toenail onychomycosis were randomly assigned to methylene blue PDT or IPL in a further study; at 3 months, PDT improved the nail in 70% and IPL in 80%, but mycological study was not performed.[137]

A recent systematic review including 214 patients summarized the variety of different photosensitizers and protocols trialled to date but concluded that PDT is seen to be effective in treating onychomycosis caused by different fungal species such as *T. rubrum*, *T. mentagrophytes*, *T. interdigitale*, *Epidermophyton floccosum*, *Candida albicans*, *Acremonium spp*, *Fusarium oxisporum* and *Aspergillys terreus*.[138] The principal problem is the penetration of the photosensitizer, which could be overcome by the pretreatment with 40% urea or mechanical abrasion, better than laser.

Regarding superficial mycoses, ALA-PDT was effective in one case of pityriasis versicolor and in 4/6 patients with recalcitrant *Malassezia* folliculitis.[139,140] Regarding deep cutaneous mycoses, 10 patients with chromoblastomycosis received PDT using a 20% methylene blue cream with a reduction in volume and healing of 80–90% observed.[141] There are also two reports of refractory chromoblastomycosis successfully treated with a combination of 5-ALA-PDT plus terbinafine or itraconazole, although new lesions developed after cessation of PDT.[142,143] A complete clinical and microbiological response was reached in two patients with cutaneous sporotrichosis. In one patient, intralesional PDT was combined with low doses of itraconazole, whilst the other patient received intralesional PDT using daylight illumination.[144,145]

In summary, PDT can successfully treat onychomycosis in patients where conventional therapy failed or patient could not continue therapy due to adverse effects. Experience with superficial and deep cutaneous mycoses is more limited.

Other reported uses

Both topical ALA and MAL have been used to treat a variety of inflammatory and infective skin disorders.[2,3,146] Data are, however, often limited to case reports or short-term, non-randomized studies involving small patient numbers:

Psoriasis (Strength of Recommendation D, Quality of Evidence 1)

A prospective randomized, double-blind phase I/II intrapatient comparison study evaluated the efficacy of ALA-PDT in 12 patients with chronic plaque psoriasis. The authors reported limited mean improvement of 37.5%, 45.6% and 51.2% in the 0.1%, 1% and 5% ALA-treated groups, respectively. Treatment was, however, frequently interrupted due to severe burning and pain.[147] A retrospective study involving 17 patients reported that 6 showed short-term improvement following MAL-PDT, whilst psoriatic lesions worsened in 2 patients probably as a result of Koebner phenomenon.[146] On the basis of current evidence, PDT does not appear to be useful for psoriasis.

Sebaceous gland hyperplasia (Strength of Recommendation C, Quality of Evidence II-III)

ALA-PDT and a pulsed dye laser were used in a case series of 10 patients with sebaceous hyperplasia, with clearance after one treatment in seven patients and two treatments in 3 cases.[148] Five patients with sebaceous gland hyperplasia received standard MAL-PDT protocol with marked improvement in 2 and moderate response in 2.[146] Both MAL-PDT and short-contact ALA combined with PDT may offer benefit in sebaceous gland hyperplasia.

Hypertrophic/Keloid Scars (Strength of Recommendation C, Quality of Evidence II-III)

A retrospective study found a significant improvement in the appearance of hypertrophic scars after two to three PDT treatments (ALA and MAL) with similar results in a further series of eight patients with hypertrophic scars.[146,149] A marked improvement was noted in 5 without relapse during follow-up of 14.1 months. Another study showed that the positive effect of MAL-PDT in the treatment of hypertrophic scars is associated with a degradation of collagen and an increase in elastin fibres, suggesting an induction of collagen degrading enzymes.[150] Three treatments of MAL-PDT at weekly intervals were effective in reducing pruritus and pain and in improving pliability of symptomatic keloids in 20 patients.[151] In the 10 patients where PDT was applied postoperatively, there was only one recurrence.

Lichen sclerosus (Strength of Recommendation C, Quality of Evidence III)

Photodynamic therapy has been used to treat vulvar lichen sclerosus with 10/12 women showing significant improvement in pruritus that lasted from 3 to 9 months although 25% of the patients required opioid analgesia.[152] Histological evaluation was not conclusive. There have only been a few case reports that have evaluated PDT as treatment for recalcitrant vulvar lichen sclerosus. Improvement in one of two patients with severe recalcitrant lichen sclerosus after ALA-PDT with improvement in lesions and symptoms was decreased.[153] Symptomatic improvement in a further five patients treated with ALA-PDT is observed, but with minimal change in clinical appearance and no resolution on histological evaluation.[154]

Granuloma annulare (Strength of Recommendation C, Quality of Evidence III)

Two to 3 ALA-PDT sessions were performed in seven patients with granuloma annulare with a 57% response rate (complete healing in two patients, marked improvement in 2).[155] The response rate was similar (54%) in a group of 13 patients with granuloma annulare treated with MAL-PDT after a mean of 2.8 treatments.[146] PDT may be considered for patients affected by granuloma annulare resistant to conventional treatments.

Necrobiosis lipoidica (Strength of Recommendation C, Quality of Evidence III)

Photodynamic therapy achieved only a limited response in 18 patient with necrobiosis lipoidica with only 1 patient showed a complete response after nine treatment sessions, whilst 6 had a partial response after as many as 14.[156] In another retrospective study assessing eight patients, MAL-PDT achieved a 37% response rate after a mean of 10 PDT sessions.[146] A large case series on 65 patients showed that MAL-PDT performed with superficial curettage had a cure rate of 66%.[157] Overall, MAL-PDT seems to be moderately effective for some cases if performed with curettage.

Porokeratosis (Strength of Recommendation C, Quality of Evidence III)

Moderate or marked improvement in 6/16 patients (13 with disseminated porokeratosis, one with linear and two with Mibelli's type) is reported in a study of off-label use of PDT, following 2–3 MAL-PDT treatments, with three patients demonstrating excellent cosmesis and marked response.[146] However, in a case series, three patients with classical disseminated superficial actinic porokeratosis received ALA-PDT with a response noted only in the test area in one patient, and this initial response was not sustained.[158] In a case report, three MAL-PDT sessions were used to treat an extensive area of linear porokeratosis extending down one arm of a 16-year-old girl, with 1-year follow-up indicating satisfactory cosmetic and clinical response, without progression.[159] Two patients affected by porokeratosis ptychotropica showed partial response and pruritus relief after 2 and 8 sessions of MAL-PDT.[160]

Extramammary Paget's Disease (Strength of Recommendation C, Quality of Evidence II-III)

A systematic review of 21 retrospective and two prospective non-comparative studies of extramammary Paget's disease (EMPD) treated by either topical or systemic PDT reported 58% of 133 lesions clearing following PDT.[161] Two small non-randomized trials showed a reduced recurrence rate with PDT combined with surgical excision, compared with either PDT alone or surgical excision alone.[162,163] A case series of 32 patients with vulvar EMPD saw the complete resolution of symptoms, with partial resolution in 25 patients, leading the authors to conclude that 3 courses of MAL-PDT were not curative, but an option for gaining control of EMPD at this site.[164] In a multicentre analysis of real-life practice of PDT, a complete response was achieved in 3 of 8 patients with EMPD.[46]

Reactions to PDT

When asking patients, it is evident that, at least for AK, side-effects matter in choice of therapy, in particular pain and risk of ulceration from a treatment.[165] Erythema and oedema are normal phototoxic reactions after PDT, and the reaction may last 4–7 days. Pustulation is rare. Also, crusting may occur, as may hypo- and hyperpigmentation but usually disappears within months. The most dominant short time side-effect from PDT is pain.[2,3,166,167] Pain may be severe, and the mechanisms are poorly understood. Patients with large lesions and AK seem to be more affected and males have been noted to experience more pain than women, and the scalp/face may be more sensitive to pain.[168,169] Pain usually peaks within minutes after commencing PDT. It may be caused by reactive oxygen species affecting nerve endings. Factors predicting pain in PDT have been reviewed and the effect of oral analgesia, noting lesions on the trunk to be the least painful to treat and that most patients can be treated without analgesia.[170] This is supported by a national audit of PDT use predominantly to treat AK, Bowen's disease and sBCC, where overall, 10% of patients described severe pain, 18% moderate pain and 72% mild to no pain during treatment.[171] Postprocedural pain has been noted to be more severe after PDT than after surgery.[172] Pretreatment techniques, such as ablative fractional laser, may increase efficacy but can cause more intensified local reactions.[120]

Daylight PDT is associated with minimal pain and has permitted large facial/scalp fields to be treated in routine practice.[173] For large-field conventional PDT, nerve block has proven effective to reduce pain in facial AK and field cancerization, without interfering with clinical outcome.[174,175] Pain reduction for routine lesional PDT by standard protocols includes use of cooling fan, water spraying water and lower light intensity or fractionated light delivery.[176] In a systematic review concerning PDT and pain, reviewing 48 studies, they report that nerve block, infiltration anaesthesia, transcutaneous nerve stimulation but not topical anaesthetic gels are associated with less pain during PDT.[177] ALA may be associated with more pain than MAL, and daylight PDT gives less pain than conventional PDT as well as use of lower irradiance levels.

A recent comprehensive review article on adverse events concludes that side-effects may be minimized through the use of modified and low-irradiance regimens.[178] Other adverse effects include the risk of contact allergy to photosensitizer prodrugs, with no other significant documented longer-term risks and, to date, no evidence of cumulative toxicity or photocarcinogenic risk. Squamous cell skin cancer has been reported at sites of previous PDT but seems to be extremely rare, and these lesions may either represent evolution of a partially treated precancer by PDT, or the coincidental development of a skin cancer in a sun-damaged field receiving PDT to treat lesions within the field.[179]

Pharmacoeconomics

In a study from the UK, conventional MAL-PDT has been found less cost-effective [measured as incremental cost-effectiveness ratio (ICER) and quality-adjusted life year (QALY) gained] than imiquimod (IMI) 5%.[180] Conventional cost-effectiveness thresholds were used in the model with simulated patients with limited disease (specifically 4–9 AKs). In a study from Finland, conventional MAL-PDT was found to be less cost-effective (ICER and QALY gained) than ingenol mebutate (IMB) and IMI 5%, specifically assessing the cost utility of treated areas <25 cm^2.[181]

However, the results of these studies exclusively apply to experimental models in which only a single box of drug is given to complete the treatment cycle. In real life, according to the European Medical Agency approval status the direct cost of a treatment should be calculated by multiplying the cost of a box by the number of boxes needed to treat the whole cancerization field and to complete a treatment cycle. Furthermore, costs (per cleared patient or per cleared lesion)/effectiveness ratio should be calculated on the basis of the real-life direct cost. With this assumption, conventional MAL-PDT remained the most costly topical option in comparison with IMI 5%, IMI 3.75%, IMB and diclofenac plus hyaluronate (DHA) gel for the treatment of areas <100 cm^2.[182] However, for areas larger than 100 cm^2, conventional MAL-PDT was the least expensive option and is the treatment of shortest duration, as it requires a single day of treatment for an area of up to 200 cm^2, thus lowering the individual loss of productivity due to the treatment.

In another study, the average treatment costs (studying a cohort of 100 patients with multiple AKs) with conventional PDT, DL-PDT, DHA, IMB and IMI were € 364.2, € 255.5, € 848.7, € 1039.1 and € 628.3, respectively. Taking into account the number of lesions cleared per patient (according to published meta-analyses), the size of the cancerization area and the number of visits required with each treatment, the total costs per lesion treated per patient were estimated as € 37.9, € 29, € 264.7, € 103.5 and € 115.4, respectively.[183] The calculation was done according to ex-factory prices of drugs in Italy, but results remained consistent when they were replicated in other countries. Also, in a

systematic review of pharmacoeconomic studies done in the USA, 5-FU and MAL-PDT were the most cost-effective treatments, whereas IMB was the most expensive one.[184]

Focusing on patients' clearance rates with daylight and conventional MAL-PDT, the total costs per patient in Finland were significantly lower for daylight PDT (€132) compared with conventional PDT (€170), giving a cost-saving of €38 (P = 0.022).[185] The estimated probabilities for patients' complete response were 0.429 for daylight PDT and 0.686 for conventional PDT. ICER showed a monetary gain of €147 per unit of effectiveness lost. So, in conclusion, daylight PDT is less costly but less effective than conventional PDT; therefore, in terms of a cost-effectiveness, daylight PDT provides lower value for money compared with conventional PDT.

Unlike AK, the cost of treatment of BCC is calculated according to the size of the lesion and not the size of the cancerization field, and surgery is added as a comparator. In a Spanish study, the mean saving per lesion of the lower limbs (at least after 2 years of follow-up) was 307 € with IMI 5%, and 322 € with MAL-PDT in comparison with surgery.[186] Finally, in the UK healthcare perspective, IMI-5% and 5-FU were more cost-effective than MAL-PDT for the treatment of sBCC (based on the 12 months of follow-up results).[187]

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