European Dermatology Forum

European Dermatology Forum Guidelines on Topical Photodynamic Therapy Updated version – 2019

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These updated guidelines consider all current and emerging indications for the use of topical photodynamic therapy (PDT) in Dermatology. In addition to undertaking an updated systematic literature review, they include evidence reviewed in previous therapy specific PDT guidelines published in 2007[1], 2013[2,3],and 2018[4] as well as disease-specific European Dermatology Forum guidelines on actinic keratosis (2011[5]) and basal cell carcinoma (2012[6]). These S2 guidelines have been prepared by the PDT subgroup of the European Dermatology Forum's guidelines committee. It presents consensual expert recommendations on the use of topical PDT in dermatological indications, reflecting current published evidence.

Abstract

Topical photodynamic therapy (PDT) is a widely approved therapy for actinic keratoses, squamous cell carcinoma *in-situ*, superficial and certain thin basal cell carcinomas. Recurrence rates when standard treatment protocols are used are typically equivalent to existing therapies, although inferior to surgery for nodular basal cell carcinoma. PDT can be used both as lesional or field therapy and has the potential to delay/reduce the development of new lesions. 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. There is an emerging literature on enhancing conventional PDT protocols or combined PDT with another treatment to increase response rates. Many additional indications have been evaluated, including photo-rejuvenation and inflammatory and infective dermatoses. This S2 guideline 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.

Keywords: 5-aminolaevulinic acid, dermatology, guidelines, methyl aminolaevulinate, non-melanoma skin cancer, topical photodynamic therapy.

1. Introduction

Photodynamic therapy (PDT) involves the activation of a photosensitizing drug by visible light to produce reactive oxygen species within target cells, resulting in their destruction with additional immune-modulatory effects observed.[7,8] In Dermatological indications, PDT is usually performed by topical application of precursors of the heme biosynthetic pathway, in particular 5-aminolaevulinic acid (5-ALA) or its ester, methyl aminolaevulinate (MAL), converted within target cells into photoactivatable porphyrins, especially protoporphyrin IX (PpIX). After an incubation period, light of an appropriate wavelength activates the photosensitizer promoting the photodynamic reaction. Before light illumination, it is possible to detect skin surface fluorescence, assisting detection and delineation of both visible and incipient lesions.

Three agents are currently licensed for use in Europe (Table 1): Methyl aminolaevulinate (160mg/g) (MAL) Metvix®/Metvixia® (Galderma, Paris, France) is used along with red light to treat non-hyperkeratotic actinic keratosis (AK), squamous cell carcinoma *in-situ* (SCC *in-situ*/Bowen's disease), superficial and nodular basal cell carcinomas (sBCC, nBCC), although approvals vary between countries. A nanoemulsion of 5-ALA (Ameluz® (Biofrontera AG, Leverkusen, Germany) is licensed for PDT in combination with red light for the treatment of mild and moderate AK, field cancerization, and superficial and low risk nodular BCC. A patch containing 5-ALA (Alacare® (Galderma-Spirig AG, Egerkingen, Switzerland) is approved for the treatment of mild AK in a single treatment session in combination with red light without pretreatment of the lesion. A 20% formulation of 5-ALA, Levulan (DUSA Pharmaceuticals, USA), is approved in N. America and certain other countries for AK, in a protocol that uses blue light. Many original studies of topical PDT used non-standardized preparations of ALA made in hospital pharmacies, so direct comparison of early studies may not be valid.

Topical PDT is approved for the treatment of certain non-melanoma skin cancers (NMSC) in the immune-competent, used both as lesional or 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. PDT has also been studied for its place in the treatment as well as potential to prevent, superficial skin cancers in immune-suppressed patients, although sustained clearance rates are lower than when used in immune-competent individuals. Additional potential cancer indications for topical PDT have been explored including local patch/plaque cutanous T-cell lymphoma (CTCL). In addition, PDT can improve acne and several other inflammatory/infective dermatoses, and improves several aspects of photoageing. Despite extensive experience beyond NMSC, there

are currently no licensed approvals for its wider use. Treatment is generally well tolerated but discomfort or pain is common during conventional PDT. Alterations in the way PDT is delivered, including the use of daylight or shorter photosensitiser application times, are associated with decreased discomfort, with licence approvals for daylight PDT for actinic keratoses using the MAL and nanoemulsion ALA.

2. Method of action

2.1 Photosensitizers

ALA is hydrophilic whilst MAL is more lipophilic, and hence MAL may penetrate more deeply into lesions although studies that have compared these agents when used to treat AK, nodular BCC or acne, failed to show a difference in response with the formulation of ALA used.[9-11] More recently, a nanoemulsion of ALA (Ameluz®), which improves ALA stability and skin penetration, has achieved significantly higher clearance of patients with AK when compared with MAL.[12] A self-adhesive 5-ALA patch (Alacare®), directly applied to AK without the need of lesion preparation, has been shown to be superior to cryotherapy for mild and moderate thickness AK, providing a clean and uniform method of photosensitizer application.[13]

Enhancing photosensitizer penetration may increase the efficacy of PDT, but currently there is no licensed approval for a protocol that uses a penetration enhancer or iontophoresis. Elevating skin temperature during ALA application may also improve efficacy as PpIX production is a temperature-dependant process.[14]

In nodular BCC of up to 2mm thickness, a 3-hour application of 160mg/g MAL showed the highest selectivity for tumour, and this procedure is licensed in the form of two treatments one week apart for BCC.[15]It is also licensed as a double treatment for SCC *in-situ*, but in AK one treatment is recommended, with non-responders receiving a second treatment at three months. Nanoemulsion ALA is also applied for 3 hours when using the conventional PDT protocol, with a repeat treatment at 1 week when treating BCC, but waiting to 3 months and assessing need for repeat therapy when treating AK.[12]

The 20% ALA formulation used with the Blu-U™ system (blue fluorescent lamps) is licensed for a drug light interval of 18-24 hours but is widely used with application times of around 1 hour for AK**.**[16]A shorter incubation time of 1 hour with MAL for AK is also an option given that in a

comparison of 1h vs. 3h, overall lesion response rates (after 1 or 2 PDT treatments) were 76% vs. 85% respectively.[17]

Additional topically applied photosensitizers including indocyanine green, indole-3-acetic acid,[18] hypericin,[19,20] silicon phthalocyanine PDT and 3,7-bis (*N*,*N*-dibutylamino) phenothiazin-5-ium bromide[22] have been assessed in specific indications but are not licensed, to date.

2.2 Light sources and dosimetry

Light sources for conventional PDT

A range of light sources can be used for topical PDT including filtered xenon arc and metal halide lamps, fluorescent lamps and light emitting diodes (LED) and even lasers although coherent light is not required. Large fields can be treated using narrowband LED devices e.g. the Aktilite 128 (Galderma, Paris, France), BF-Rhodo LED (Biofrontera, Leverkusen, Germany) and Omnilux PDT (Phototherapeutics, London, UK) each with an output that matches the 630/635 nm activation peak of PpIX whilst excluding the extraneous wavelengths present in broadband sources, permitting shorter illumination times. Filtered intense pulsed lights (IPLs) have been successfully used in PDT for AK, acne and photorejuvenation although they emit different spectra, resulting in a need to derive specific protocols to achieve identical radiant exposures.[23] Narrow spectrum light sources are associated with higher response rates, with complete patient clearance rates of 85% and 68% for nanoemulsion ALA-PDT or MAL-PDT respectively, compared with 72% and 61% when broad spectrum devices were used.[12,24]

Protoporphyrin IX has its largest absorption peak in the blue region at 410nm with smaller absorption peaks at 505, 540, 580 as well as 630nm. Most light sources for PDT use the 630nm absorption peak in the red region, in order to improve tissue penetration, although, a blue fluorescent lamp (peak emission 417nm) is recommended in Levulan-PDT. Light dose specifications are included in the product summaries of the topical photosensitizers approved for skin cancer indications, whilst dosimetry for emerging inflammatory/infective dermatoses is not yet standardized. Consideration of high and low dose regimens for PDT in acne have been reviewed although an optimal protocol has not been established.[25]

Fractionated Illumination

Discontinuous illumination (fractionation) may improve the efficacy of PDT by permitting tissue re-oxygenation during 'dark' periods. Studies support superiority of fractionation to conventional illumination in ALA-PDT for AK (94% vs. 85% at 1year) and sBCC (88% vs. 75% at 5 years), but not in SCC *in-situ* (88% vs. 80% at 1 year)**.**[26-8] Overall clearance of 95% after 2 year follow-up has been reported in a large series of 552 lesions (AK, SCC *in-situ*, sBCC, nBCC) following ALA-PDT using two light fractions of 20 and 80 J/cm² at 4 and 6 hours separated by a 2 hour dark interval.[29] An alternative ALA-PDT fractionation protocol of two doses of 75J/cm² at 4 and 5 hours was associated with an initial 94% clearance rate for nBCC, but with a cumulative failure rate of 30% by 3 years. [30] No significant difference in efficacy was observed when standard red-light MAL-PDT was compared with fractionated ALA-PDT in a study of 162 patients with superficial BCC. [31] No efficacy improvement has been reported using light fractionation in MAL-PDT, considered to be due to differences in localization between the agents.

Daylight, Ambulatory LED and Fabric-based laser diode illumination

Daylight is increasingly used as the light source for PDT in treating AK, with application of either nanoemulsion ALA or MAL for 0.5 hour, followed by exposure to daylight for 2 hours, with no inferiority of efficacy to red light PDT, but with the benefit of reduced pain. [32-4] As well as its potential for AK and field cancerization, daylight PDT has been assessed for treating BCC. [35]

There is also an option for patients to wear a portable LED device, permitting ambulatory PDT to reduce the need for hospital attendance, with an overall 84% lesion clearance reported for sBCC and SCC *in-situ*, 1 year following 2 treatments, one week apart, with minimal pain with another research group demonstrating 90% clearance rate at 12 months in a study of 143 sBCC. [36-7]

A novel light-emitting, fabric-based laser diode device has recently been shown to be as effective as conventional PDT in clearing AK but with minimal pain, with MAL applied under a transparent occlusive dressing for 30 minutes then fabric device is applied and switched on after 30 minutes, remaining on for 150 minutes.[38]

2.3 Lesion preparation

Protocols for topical PDT in Europe conventionally recommend some form of lesion preparation to enhance photosensitizing agent absorption and light penetration in MAL-PDT and

nano-emulsion ALA-PDT. Studies using a novel ALA plaster for mild and moderate thickness AK do not require prior preparation with results consistent with standard protocols.[13, 39] Tape-stripping, microdermabrasion or laser ablation, or gentle curettage can also be used to reduce hyperkeratosis. Some practitioners have observed reduced efficacy if lesions are not debrided prior to PDT[14,17] while others have not noted increased drug uptake following lesion preparation of SCC *in-situ* and BCC.[40] However, gentle removal of overlying crust and scale is commonly performed for moderate thickness/hyperkeratotic AK and for SCC *in-situ* and superficial BCC. Lesion preparation is probably more important when treating nodular BCC by PDT with recommended practice to gently remove overlying crust with a curette/scalpel in a manner insufficient to cause pain, and thus not requiring local anaesthesia. Some practitioners perform a more formal lesion debulking days/weeks prior to PDT, with 92% of BCC clearing following a single session of ALA-PDT in one study.[41] The effect of pre-PDT deep curettage in another study of thick (≥2 mm) BCC reduced mean tumour thickness from 2.3 mm (range 2.0–4.0) by 50%, with 3-month tumour response of 93%.[42] In a comparison study of PDT (ALA and MAL) with or without debulking immediately pre-photosensitizer application, residual nBCC was more often observed in lesions that were not debulked**.**[10] Under standardized conditions in a randomized clinical trial, PpIX accumulation was most enhanced after ablative fractional laser pretreatment, followed by microdermabrasion, microneedling, and curettage.[43]

Practitioners typically cover treatment sites with light occlusive dressings, on the presumption that full exposure to ambient light during the incubation period will lead to increased activation of PpIX superficially reducing the opportunity for deeper photosensitizer penetration before photoactivation. PDT with occlusion is routine in conventional MAL and nanoemulsion ALA PDT, but is not performed when using Levulan PDT and no occlusion is required for daylight PDT.[32-5]

3. Treatment protocols

3.1 Conventional topical PDT

Recommended protocols for ALA-PDT and MAL-PDT using currently licensed photosensitizing agents for NMSC indications are summarized in Table 1. Conventional PDT involves application of a topically applied photosensitizing agent, occluded for 3-4 hours depending

on product, then illuminated typically by a narrowband red LED light source. Protocols employed in emerging indications are discussed with each indication.

3.2 Daylight PDT (DL MAL-PDT, DL ALA-PDT)

Daylight PDT is performed with initial widespread application of an organic sunscreen followed approximately 15 minutes later by lesion preparation, then nanoemulsion ALA or MAL to treatment area, without occlusion (details Table 1).[44] Within 30 minutes of application, patients are exposed to daylight for 2.0 hours with licensed approvals for AK and field cancerization.[45] Alternative methods of delivering light equivalent to daylight, but avoiding the limitations of climate considerations, are emerging, including simple use of a greenhouse and attempting to simulate daylight indoors.[46] The potential to deliver daylight MAL-PDT at home has demonstrated high levels of patient satisfaction, effectiveness and tolerability.[47]

3.3 Ambulatory, Textile, Pulse and Temperature-modulated PDT

The protocol for **ambulatory PDT**, using an inorganic light-emitting diode device, involves lesion preparation (maximum size 1.8mm) and cream application before the light emitting 'plaster' is applied. The device automatically switches on after the incubation period, to deliver a total dose of 75J/cm at 7mW/cm, then off at end of procedure permitting treatment outwith the clinic.[36,37]

Studies are ongoing to refine '**Textile PDT'** where red 635nm light is delivered through fabric from laser diodes, to slowly expose the skin to the same light dose as for conventional PDT.[38] As light intensity is reduced and incubation short, treatment is almost pain-free. The fabric allows for uniform light distribution even on curved surfaces, with potential to treat much larger areas.

In a novel protocol '**pulse-PDT'**, MAL is applied for 30 minutes with red light illumination after 3 hours, with equivalent efficacy to conventional MAL-PDT in treating AK when compared in a randomized clinical trial.[48] Treatment induced erythema was reduced, with further reduction if a superpotent topical corticosteroid is applied just before and after PDT. Another centre has proposed '**temperature-modulated PDT'** where sustained clearance of 90% of 724 AK at 1 year was achieved by warming the skin during 1 hour Levulan ALA incubation.[49]

4. Fluorescent diagnosis

The detection of skin surface fluorescence, visible following application of ALA and MAL, can be utilized as a non-invasive method to assist in lesion definition as well as in identifying persistent/recurrent disease that may not be clinically obvious.[50] Compared with relatively subjective assessment of fluorescence using the Wood's lamp, a CCD camera system can provide semi-quantitative measurements of PpIX within dermatological lesions**.** The value of PpIX imaging to outline tumours has shown contradictory results in a review of published studies.[51] Even when utilized to reduce stages in Mohs surgery, the technique did not permit time saving overall.[52]

Measurement of fluorescence during MAL-PDT has shown extent of photobleaching, but not total initial PpIX fluorescence, as predictive of lesion clearance.[53] In another study, fluorescence diagnosis in keratinocyte intraepidermal neoplasias was unable to discriminate between lesions or proliferative activity, although hyperkeratosis was an important determinant of macroscopic fluorescence intensity.[54] Intensity of pain has been associated with fluorescence intensity and can help anticipate patients more likely to require active pain management.[55] In practice, in addition to helping predict likelihood of pain, PDT practitioners find observing strong fluorescence is helpful in supporting clinical suspicion of recurrence whilst absence can also be supportive of clinical indication of clearance of disease after treatment.

5. Current indications

5.1 Actinic keratosis (*Strength of Recommendation A, Quality of Evidence 1*) (Approved indication)

Conventional PDT for AK*:*

Conventional PDT with 5-ALA, nanoemulsion 5-ALA and MAL have been widely studied for thin and moderate thickness non-hyperkeratotic AKs of the face and scalp with typical lesion clearance rates of 81-92% 3 months after treatment.[12,13,24,56-58] Conventional nano-emulsion ALA-PDT was superior to MAL in clearing thin and moderate thickness AK from face/scalp, with clearance of 90% vs. 83% of lesions (respective complete clearance rates of 78% vs. 64%) 12 weeks after one or two PDT treatments.[12] Similar lesion recurrence rates were observed following nanoemulsion ALA-PDT and MAL-PDT of 22% and 25% respectively at 12 months, with subset analysis showing improved response with lesions treated using the narrow wavelength LED lamps.[59]A randomized intra-individual study of 50 patients

compared nanoemulsion ALA with MAL, demonstrating similar lesion clearance rate after a single treatment (ALA: 90%, MAL: 88%) but with more intense skin reactions observed with ALA, presumed due to less selectivity, although this was associated with higher accumulation of PpIX.[60] One year lesion clearance rates of 78% and 63-79% have been reported following Levulan ALA-PDT (up to 2 treatments) and patch ALA-PDT (single treatment) respectively.[39,61] A randomized multicentre study of conventional nanoemulsion ALA-PDT achieved a patient clearance rate of 91% (vs. 22% placebo) with additional benefits to skin quality in field-directed treatment of AK.[62]

Comparison of Conventional PDT with other therapies for AK

Compared with cryotherapy, MAL-PDT achieved an initially superior cure rate than cryotherapy (87% vs. 76%), but with equivalent outcome after retreatment of non-responders (89% vs. 86%) in a randomized intra-individual study of 1501 face/scalp AK.[58] ALA-PDT using the self-adhesive patch cleared 82%-89% of mild or moderate AK in patients with 3-8 face/scalp lesions, superior to the 77% clearance rate in a comparator group receiving cryotherapy.[13] MAL-PDT is more effective than diclofenac and hyaluronic acid cream as well as to trichloroacetic acid, with non-formulary ALA-PDT more effective than CO2 laser ablation, in separate comparison studies.[63-5]

Two systematic reviews looked at the use of conventional PDT against other therapies. A Cochrane Library systematic review searched databases up to March 2011, identifying 83 RCTs covering 18 AK therapies, including PDT.[66] Whilst the primary outcome 'participant complete clearance' significantly favoured four field-directed topical treatments compared to vehicle or placebo, it favoured the treatment of individual AK lesions with PDT compared to placebo-PDT with ALA using blue light, ALA using red light, and MAL with red light. ALA-PDT was also significantly favoured compared to cryotherapy. Based on investigator and participant evaluation, imiquimod and PDT resulted in better cosmetic outcomes than cryotherapy and 5-fluorouracil. A further systematic review performed in 2013 undertook to compare the evidence of the effectiveness of PDT compared with other therapies, restricted to RCTs with at least 10 participants.[67] Thirteen studies were included in the final synthesis, of which 4 were eligible for final meta-analysis. The only comparator for which meta-analysis was performed was cryotherapy.

PDT was concluded to offer a 14% better chance of complete lesion clearance at 3 months after treatment than cryotherapy for thin AKs on the face and scalp.

Combination of conventional PDT with other therapy for AK

There is emerging use of combination therapies in AK, either combining lesional with field therapy or two field therapies. A recent meta-analysis investigated whether conventional PDT combined with other field therapies is superior to PDT alone.[68] From 1800 references, ten RCTs with a total simple of n=277 were included. Four studies explored the combination of PDT with imiquimod, 3 with 5-fluorouracil, and one each with ingenol mebutate (IM) gel, tazarotene gel, and calcipotriol ointment, respectively. Overall, patients treated with a combination showed significantly higher clearance rates compared with monotherapy. Considering the specific therapies, in a subset analysis, topical imiquimod combined with PDT, either prior to or following PDT, showed higher participant complete clearance rates than monotherapy. Pre-treatment with topical 5-fluorouracil cream, applied twice daily for 6-7 days prior to PDT (both ALA and MAL) led to a mean improvement in lesion clearance of 11-30% compared with PDT alone. Pretreatment of acral AK lesions with 0.1% tazarotene gel may also enhance the effect of PDT but this study only had 10 participants. [69] Combination ALA-PDT with ingenol did not achieve a significant differential response rate, but the response rate of 92% reduction in AK with ingenol alone is unusually high compared with routine practice.[70]

A randomized split-scalp study compared calcipotriol once day for 15 days prior to conventional MAL-PDT vs conventional PDT. Clinical and histological improvement were superior on the calcipotriol-assisted side (overall AK clearance rates were 92.1% and 82.0% respectively) with greatest improvement for grade II AKs (90% vs 63%) although pain and also local side effects were greater with the combined protocol. [71] A prospective randomized clinical trial using ablative fractional laser-assisted MAL-PDT after twice daily topical 0.005% calcipotriol pre-treatment for 2 weeks showed a higher rate of complete response of facial AK with the combined treatment (89% vs 80%) and lower recurrence rate at 12 months (5% vs 10%).[72]

A systematic review and metanalysis of laser-assisted PDT for AK identified 7 randomized controlled trials with 4 included in the analysis.[73] Laser-assisted PDT showed significantly higher clearance rates than PDT monotherapy with no difference in pain intensity between laser-assisted PDT and PDT or laser monotherapy. Such an approach potentially complicates the ease of delivery

of PDT and increases healthcare costs and may be best utilised for difficult to treat acral and/or hyperkeratotic AK and AK in the immunosuppressed.

Daylight PDT for AK:

DL MAL-PDT is as effective, but less painful, than conventional PDT with a randomized intra-individual trial of patients with multiple AK on face/scalp demonstrating a reduction, after a single treatment, of 79% on the daylight side compared with 71% when standard LED illumination was used.[74] Subsequent multicentre studies have demonstrated that daylight exposure of 1.5 hours is as effective as 2.5 hours, but that lesion response is highest for thin lesions (76%) compared with clearance rates of 61% and 49% for moderate and thick AK, respectively.[75,76] Reduced efficacy of thicker lesions was demonstrated in a trial with 3 month clearance rates for types I, II, and III AK of 76%, 61% and 49% respectively after a single treatment of DL-PDT, with considerable variation in response between centres.[77] A study assessing the impact of latitude on its delivery identified that DL MAL-PDT can be performed throughout the summer and until mid-September in Reykjavik and Oslo, late October in Copenhagen and Regensburg, mid-November in Turin, and all year in Israel.[78] During these months it should be possible to achieve active PpIX weighted daylight dose as above 8J/cm2, and a maximum daytime temperature of 10°C, to permit effective treatment.

Two pivotal intra-individual multicentre comparative studies in Australia and Europe, both observed that DL MAL-PDT was non-inferior to conventional PDT with the Australian study reporting lesion clearance rates of the mild AK treated of 89% and 93% respectively 12 weeks after one treatment session.[32, 33] The European study observed equivalent responses of 70% and 74%, both values lower as this study included patients with mild and moderate thickness lesions. Daylight PDT was virtually pain free in comparison with conventional PDT and was as effective whether performed in sun or cloudy conditions. Both high efficacy and patient satisfaction were demonstrated in a further multicentre study conducted over 6 European countries, in 325 patients receiving a single treatment of DL MAL-PDT for face and/or scalp AK, demonstrated efficacy at 3 months was at least much improved in 83.5% of patients, with 45.9% of patients requiring no retreatment.[79]

DL ALA-PDT using nanoemulsion ALA has is at least as effective as DL MAL-PDT in treating mild and moderate AK. In a randomized split-face trial, 13 patients with 177 grade I-III AK, DL ALA-PDT cleared 85% of AK compared with 74% treated by MAL.[80] The per patient half-

face analysis showed ALA to have a significantly higher clearance rate for grade I AKs than did MAL, but for thicker grades, clearance was equal. A recent multicentre intra-individual comparison trial has compared DL ALA-PDT with DL MAL-PDT in 52 patients with 3-9 mild to moderate thickness AK on the face/scalp.[81] Equivalent efficacy was demonstrated at 3 months, with lesion clearance rates of 79.8% with ALA and 76.5% with MAL, although recurrences at 1 year were higher with MAL (31.6% vs. 19.9%). In an non-sponsored randomized comparison trial, DL ALA-PDT was more effective than DL MAL-PDT in the per-patient half-face analysis of clearance (79.7% vs. 73.5%).[82] In an evaluation of patient self-application of DL MAL-PDT, there was high patient satisfaction and at 3 months, with 62% of treated AK were clear.[47]

Comparison of DL PDT with other therapies

There is limited direct comparison evidence of DL PDT with standard therapies. DL-PDT has been compared with ingenol mebutate in the treatment of 27 patients with 323 grade I and II AK with identical response rate.[83]

Combination therapy using DL PDT

A case series of 11 subjects with grade I-III AKs evaluated with a split-face design the effect of once-daily calcipotriol ointment for 15 days prior to DL MAL-PDT compared with PDT alone. After 3 months, the complete response rate was 85% and 70% although the combination was associated to more erythema and desquamation.[84] A randomized controlled trial compared DL MAL-PDT followed by diclofenac/hyaluronic acid gel 30 days before or after, compared with PDT alone; after 12 months no significant difference in resolution of the AK was observed (91,2% vs 90%).[85] Pre-treatment with ablative fractional laser, compared with microdermabrasion, was more effective (81% vs 60% AK clearance) in patients with extensive field cancerization using DL MAL-PDT in a recent randomized trial.[86]

PDT for Acral AK

PDT is less effective for AK on acral sites, probably in part due to a higher proportion of thicker lesions on these sites. A study comparing conventional MAL-PDT with cryotherapy for AK on the extremities demonstrated inferior efficacy with PDT, with clearance of 78% of lesions at 6 months compared with 88% for cryotherapy.[87] However, in a right/left comparison study with

imiquimod, conventional ALA-PDT cleared significantly more moderate thickness AK lesions (58% vs. 37%), and equivalent numbers of thin AK on the hands/forearms (72% lesions).[88] A further randomized placebo-controlled study of MAL-PDT using an IPL to treat AK on the dorsal hands achieved complete remission of 55% compared with 3% with light alone.[89] Similar to conventional PDT, 7 days pre-treatment with 5-fluorouracil cream has enhanced DL MAL-PDT in a study treating AK on dorsum of hands, with superior clearance rates after single PDT session of 62.7% vs. 51.8% compared with PDT alone.[90]

PDT for Actinic Cheilitis

A series of 40 patients saw complete clinical response at 3 months in 26 patients with actinic cheilitis following conventional ALA-PDT although with histological evidence of recurrence in 9 patients over 18 months of follow-up.[91] Conventional MAL-PDT clinically cleared 47% of 15 patients although histological clearance was evident in only 4.[92] In a retrospective analysis of real-life practice, PDT cleared 27 of 43 (63%) patients with complete response maintained at 4.2 +/-5.9 months.[93] A recent systematic review of PDT in actinic cheilitis reviewed 15 eligible studies with a complete response of 62% at final follow-up ranging from 3-30 months, although histological cure, where assessed, was lower, at 47% overall at final follow-up (1.5-30 months).[94]

To achieve improved response rate, cotton rolls and lip retractors can be used, as well as considering repeat treatments and/or combining with other therapies. Sequential MAL-PDT then imiquimod cream achieved clinical clearance in 80% (histological 73%) in a study of 30 patients.[95] Ablative factional laser pretreatment also has significantly improved response to use of PDT in actinic cheilitis, clearing 92% lesions at 3 months (compared with 59% by MAL-PDT alone), with an 8% recurrent rate (compared with 50% with MAL-PDT alone) at 12 months.[96]

Two recent publications detail DL MAL-PDT for actinic cheilitis which achieved sustained response in 5/10 patients over 6-12 months follow-up in a study of 2 treatments 7-14 days apart, whilst a 91% cure rate in 10/11 patients was achieved using repeated treatments – mean 2.8.[97-98]

Therapy guidelines identify PDT as effective both as a lesion and field-directed treatment and suggest PDT has a role where AK are multiple/clustered, as a suitable choice for patients wishing to manage background actinic changes, and as part of maintenance treatment for low-grade AKs in

sun damaged skin.[99,100] PDT remains a predominantly hospital-based therapy in most countries whilst many patients with AK are treated by primary care physicians. However, high quality of cosmesis consistently observed in PDT studies for NMSC indications including AK, combined with increasing emphasis on patient choice over therapy, may see increased demand for topical PDT. A recent systematic review of AK clinical guidelines to construct a treatment algorithm positioned DL-PDT a valuable option for patients with multiple AKs in small or large fields.[101]

5.2 Squamous cell carcinoma *in-situ* (Bowen's disease)/Invasive SCC

Squamous cell carcinoma in-situ(*Strength of Recommendation A,Quality of Evidence 1*) (Approved indication)Lesion clearance rates of 88-100% are reported for SCC *in-situ* 3 months after one or two cycles of conventional MAL-PDT, with 68-89% of treated lesions remaining clear over follow-up periods of 17-50 months.[102-106] Conventional MAL-PDT is approved in many countries for Bowen's disease, but no formulation of ALA-PDT is licensed.

In a Cochrane review of treatments for Bowen's disease, PDT appeared to be an effective treatment and offer the benefit of minimal scarring compared with cryotherapy or 5-fluorouracil.[107] There is limited data to demonstrate superiority of PDT to standard therapy, with conventional MAL-PDT compared with cryotherapy or topical 5-fluorouracil in a large European study with 3 month lesion response rates similar with all regimens (93% for MAL-PDT, 86% for cryotherapy, 83% for 5-fluorouracil).[102] Although PDT had a superior 1-year lesion clearance rates; all three therapies were similar after 2 years with 68% clear following PDT, 60% after cryotherapy and 59% after 5-fluorouracil.[103] A similar 3-month efficacy rate of 88% was observed in an open study of MAL-PDT for 41 SCC *in situ* with sustained clearance at 24 months of 71%.[104] Further open studies assessing durability of response to MAL-PDT observed 76% and 89% sustained clearance after follow-up periods of 17 and 50 months, respectively.[105,106] Non-formulary ALA-PDT has been compared with cryotherapy and with 5-fluorouracil in small studies where PDT proved superior in efficacy and adverse events in comparison with 5-fluorouracil, as well as being less painful compared with cryotherapy.[108,109]

Lesion size impacts on clearance rate with 82% of lesions up to 14 mm clear at 12 months reducing with increasing size to only 55% of lesions 30 mm or larger.[102] Larger plaques over 3 cm

responded to a cycle of MAL-PDT, 2 treatments 7 days apart, clearing 90% of 23 lesions and observing recurrence in only 3 up to 12 months reducing clearance to 83%, with another study of identical design initially clearing 90% of 37 lesions, noting 4 recurrences after 12 months reducing clearance rate to 78%.[110,111]

Emerging literature on combination PDT in comparison with PDT alone, observes that ablative fractional laser-assisted MAL-PDT was significantly more effective than PDT alone in 2 studies, clearing 94% of plaques compared with 73% at 1 year in one study, whilst in a 5 year follow-up study, ablative laser assisted MAL-PDT achieved sustained clearance rates of 85% vs. 45% with PDT alone.[112,113] A similar superiority of response has been observed in a small comparison trial of micro-invasive SCC where ablative fractional laser-primed MAL-PDT achieved 3 month clearance rates of 84% versus 52% with PDT alone, with reduced recurrence rates (12% compared with 64% at 2 years for PDT alone).[114] ALA-PDT combined with CO2 laser achieved clearance at 6 months of 64% of lesions compared with 18% with laser alone in a trial of 22 lesions.[115]

The therapeutic effect of PDT may be enhanced by sequential use along with topical imiquimod, although clinical experience, to date, is limited.[116, 117]

Severe atypia and higher age were associated with increased risk of treatment failure following PDT in a retrospective study re-examining histology and clinical features of patients treated with PDT over 5 years.[118] Failure to correctly perform PDT may also impact efficacy with a national prospective observational study of MAL-PDT in France noting incorrect delivery of treatment in 23% of patients.[119]

A comprehensive disease-specific guideline pointed to the value of PDT for all lesions in poor healing sites and for large lesions in good healing sites, supported by a recent review.[120,121] PDT is considered a fair choice for small lesions in good healing sites, multiple lesions, facial, digital, nail bed and penile lesions, in comparison with other therapeutic options. In a patient-reported outcome study, satisfaction with ALA-PDT for *SCC in situ* was high, with 90% of respondents indicating a very favourable impression of the treatment, although with burning sensation described in 21%.[122] A national audit of use of PDT in clinical practice in Scotland confirmed that 27% of all use was for patients with Bowen's, just behind use for sBCC (33%) and AK (35%).[123]

Invasive squamous cell carcinoma SCC (*Strength of Recommendation D, Quality of Evidence 11-iii*)

There remains limited data on the efficacy of topical PDT for primary cutaneous invasive SCC although MAL-PDT can achieve higher response rates in microinvasive disease - 3-month clearance rates of 80%, with 58% still clear at 24 months.[104] Although 45% of nodular invasive SCC did appear to initially clear, clearance rate dropped to 26% by 24 months. The degree of cellular atypia is a negative prognostic factor, suggesting poorly differentiated keratinocytes are less sensitive to PDT. A subsequent retrospective real-life audit of PDT identified an additional 17 invasive SCC (with initial clearance in 58.8%) with 2 recurrences reducing sustained clearance to 47%.[93] There is concern that not only does SCC not respond adequately to PDT, but that tumour could become more histologically aggressive and resistant to PDT. A study observed genomic imbalances related to CCND1, EFGR, and particularly MAP3K1 genes appear to be involved in development of resistance of SCC to PDT.[124] MAL-PDT was successfully used to treat verrucous carcinoma where surgery was contraindicated, indicating a case-specific role.[125] However, in view of its metastatic potential and reduced efficacy, PDT currently cannot be recommended for invasive SCC.

5.3 Basal cell carcinoma: Superficial Basal cell carcinoma (*Strength of Recommendation A, Quality of Evidence 1*) (Approved indication) **Nodular Basal cell carcinoma** (*Strength of Recommendation A, Quality of Evidence 1*) (Approved indication)***Efficacy of PDT for sBCC and nBCC***

Initial clearance rates after conventional MAL-PDT of 92-97% for primary sBCC are reported, with recurrence rates of 9% at 1year although 22% of initially responding lesions recurred over 5 years of follow-up.[126,127] 91% of primary nBCC were clear at 3 months following MAL-PDT, with a sustained clearance of 76% after 5 years.[15,128]

Histologically confirmed response rates were observed in a further two randomized studies of MAL-PDT for nBCC, with overall clearance in 73%, most effective for facial lesions where 89% achieved complete histological response.[129]A poorer response was reported in a large series of 194

BCC, with an 82% clearance rate for sBCC, but only 33% of nodular lesions clearing following MAL-PDT although the authors describe no debulking of the tumour prior to PDT.[130]

Ambulatory PDT has also been used to treat small sBCC with overall response rate for lesions on 84% at 1 year in one study and 90% in a more recent study.[36,37] There is limited experience of DL MAL-PDT for sBCC, which cleared 90% of 30 lesions at 3 months, although 6 recurrences occurred during 12 month follow-up.[35] Sequential topical imiquimid 5% cream followed by DL MAL-PDT versus PDT alone in sBCC achieved improved response rate if patient had 2 or more BCC, although no difference was observed for patients with single lesions.[131]

Nano-emulsion ALA-PDT was compared with MAL in the treatment of non-aggressive BCC in a randomized, phase III trial with 281 patients randomized. Of the ALA-treated patients, 93.4% were complete responders compared with 91.8% in the MAL group, establishing non-inferiority, with recurrence rate <10% by 1 year.[132]

In a randomized comparison trial of single versus fractionated ALA-PDT for sBCC, 5 years after treatment, fractionated PDT produced a superior response (88% vs. 75% respectively).[27] Fractionated ALA-PDT was equivalent to surgery in initially clearing lesions but with a 31% failure rate over a median of 5 years after PDT, compared with only 2% post-surgery when a 75J/75J protocol was used although 80% of lesions remained clear at 2 years using a 20J/80J fractionated dosing.[30, 133] Success of treatment depended on tumour thickness, with probability of recurrence-free survival over 5 years 94% if tumour $\leq$ 0.7mm, compared with 65% for thicker lesions.

A study sought to evaluate whether fractionated ALA-PDT is superior to conventional MAL-PDT for sBCC. After 12 months, 6 treatment failures followed ALA-PDT with 13 after MAL-PDT. The 12-month cumulative probability of remaining free from treatment failure was 92·3% for ALA-PDT and 83·4% for MAL-PDT, failing to reach significance.[134] In a comparison of ALA-PDT vs. simple excision surgery for sBCC and nBCC, response rates were similar at 95.83% after PDT vs. 95.65% after surgery, with similar 25 month follow-up recurrence rates of 4.16% vs. 4.34%.[135]

Comparison with other therapies

MAL-PDT was equivalent to surgery (92% vs. 99% initial clearance, 9% and 0% recurrences at 1 year) for sBCC but inferior to excision for nBCC when recurrence rates are compared (91% vs. 98% initial clearance, 14% and 4% recurrences at 5 years).[127,128] Cosmetic outcome is superior

following PDT. Clearance rates were equivalent when MAL-PDT was compared with cryotherapy for sBCC, 97% and 95% at 3 months respectively, with overall clearance after 5 years identical at 76% of lesions initially treated, but with superior cosmesis following PDT.[126] In a randomized pilot study of PDT with minimal curettage pre-ALA application versus conventional surgery, there was also no evidence of superiority of PDT to surgery.[136] A single-blind randomized non-inferiority comparison of MAL-PDT (2 treatments one week apart) with imiquimod cream or topical 5-fluorouracil for sBCC achieved tumour-free rates at 12 months of 73%, 83%, and 80% respectively, falling to 58%, 80% and 68% at 36 months, indicating that using these protocols, 5-fluorouracil was non-inferior and imiquimod superior to one cycle of MAL-PDT.[137]

Prediction of PDT response in BCC

Responsiveness of BCC is influenced by lesion thickness, with reduced efficacy with increasing tumour thickness in a study using ALA-PDT.[138] Lesions in the H-zone also have reduced sustained clearance rates.[139] A ten-year clinical and histological follow-up of 60 BCCs treated by ALA-PDT, originally less than 3.5mm thick, reported 75% of treated sites remained disease free at 120 months.[140]

There has been debate whether treatment failures of BCC could be due to PDT modifying histological subtype. However, a recent study reported aggressive treatment failure recurrences after non invasive therapy for superficial BCC occur most often within the first 3 months post-treatment, probably indicating under diagnosis of more aggressive components in the primary tumour rather than transformation.[141]

Combination therapy with PDT for BCC

Results, to date, are mixed regarding the advantage of pretreatment with laser before PDT for BCC. Combined therapy using an UltraPulse CO2 laser and MAL-PDT with repeat PDT 1 week later achieved a recurrence-free clearance rate of 97% after a mean follow-up of 32 months, in 177 BCC of different subtypes, similar to the 100% clearance rate at 18 months for 13 nodular BCC treated with this combination.[142,143] Fractional laser as pre-treatment before ALA-PDT for nBCC increased response rate from 80% to 93%.[144] In a randomized trial, facial nodular BCC received Er:YAG AFL-PDT (1 session) or conventional MAL-PDT (2 sessions), with clearance at 3

months of 76% with AFL-PDT and 43% with MAL-PDT[145] However, in a further comparison of combined laser with PDT, response rate was only slightly increased to 99% compared with 95% for MAL-PDT alone in a study of nBCC using a Er:YAG laser. [146] Long-term efficacy was similar after MAL PDT and fractional laser-mediated PDT for high risk facial BCC with clearance at 12 months of 63% compared to 56% for PDT alone. [147]

A pilot study of 34 patients supplemented Levulan ALA-PDT with topical imiquimod cream (twice weekly for 5 weeks after PDT) for recurrent BCC observed higher clearance rate of 75% with the combination compared with 60% by PDT alone.[148] Combining imiquimod with MAL-PDT for BCC may achieve improved response, but requires further study beyond current case series.[149,150,151]

Patients with naevoid basal cell carcinoma syndrome (NBCCS) can benefit from PDT with several series and cases reported. A large cohort of 33 patients were treated by topical or systemic PDT depending on whether lesions were less than/greater than 2mm in thickness when assessed by ultrasound, with an overall local control rate at 12 months of 56.3%.[152] A short report observed that MAL-PDT for NBCCS improves patient satisfaction and reduces the need for surgical procedures.[153]

Conventional MAL-PDT or nanoemulsion ALA-PDT should be considered in patients with non-aggressive, low-risk BCC, i.e. superficial and nodular types, not exceeding 2 mm tumour thickness, where surgery is not suitable or contraindicated due to patient-related limitations (comorbidities, medications, logistic difficulties). [6] Less common histologic variants, morphoeic, pigmented and micronodular types, as well as areas with higher risk of tumour survival and deep penetration (facial "H"-zone) should not be treated with PDT. A systematic review and metanalysis concluded that PDT is effective for low-risk BCC, with excellent cosmesis and safety. Imiquimod has higher efficacy than single-cycle PDT but more adverse effects, with surgery offering the highest efficacy.[154] This is in accordance with a further review and metanalysis of sBCC treatment options, where pooled estimates from randomized and nonrandomized studies showed similar tumour-free survival at 1 year for imiquimod and PDT, with highest success in studies with repeated treatments. [155] PDT is recommended as a good therapy for primary sBCC, fair for primary low-risk nBCC, and the treatment of choice for large low risk primary sBCC.[156]

6. Emerging indications

6.1 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, are suggested for treating AK or SCC *in-situ* in OTR, with PDT permitting physician-directed treatment of multiple lesions and field therapy[157] 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.[158] At four 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.[159] Higher complete remission was observed when two session of MAL-PDT were performed: At three months complete remission varied between 71% and 90%.[160] 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%.[161] One study compared MAL PDT to topical 5- fluorouracil: CR differed at one month with 89% for MAL-PDT and 11% for 5- fluorouracil, with more pain, but also better cosmesis following PDT.[162] 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.[163]

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.[164] MAL-PDT was used by two studies for sBCC and nBCC with 1/18 recurring after between 12-23 months follow-up.[165, 166]

6.2 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.[167] MAL-PDT delayed the development of new lesions in an intra-patient randomised study of 27 OTR with AK (9.6 vs. 6.8 months for control site)[168] 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.[169] No significant difference in the occurrence of SCC was observed in a study of blue light ALA-PDT versus no treatment after 2 years follow-up in 40 OTR.[170] However, another study of bluelight ALA-PDT, repeated at 4-8 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%.[171] 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 three 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.[172]

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 imiquimod 5%-treated areas (median 61%, range 33-100; $P < 0.001$).[173] Thus, fewer emergent AKs were seen in PDT-treated skin vs. imiquiomod-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, $P < 0·01$).

6.3 **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 have subclinical features of genetically damaged cells which can potentially develop into a neoplastic lesion.[174] The major carcinogen for skin cancer is UV radiation, and a common genetic abnormalities in NMSC is the presence of UV induced TP53 mutations.[176] TP53 mutated clones can be found in > 70% of patients over 50 years of age in sun exposed skin.[176] 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[177]

Field cancerization can be suspected clinically when multiple AK 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.[178] Optical coherence tomography (OCT) has shown also that 79% of apparent normal skin in field cancerisation harbor dysplasia or accult carcinoma[179]

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.[180] 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.[181] 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.[182]

6.4.Cutaneous T-cell Lymphoma (CTCL) (*Strength of Recommendation C, Quality of Evidence IIiii*)

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.[183] 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.[184] 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.[185-190]

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.[191-6] In the first report, complete remission was observed in four of five patients with uni-lesional patch, plaque and nodular disease, with partial response in the remaining patient after a median of 6 treatments. [191] 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.[192] 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 one-week intervals. Both clinical and histological clearance was 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.[193] In a further study of 12 patients with pauci-lesional patch- and plaque- MF lesions, a 75% one-month response rate (6 complete responders, 3 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).[194] Response rates were similar between patches and plaques but higher in sun-protected areas. Finally, 50% complete and 50% partial clearance was seen in 4 patches of 4 MF patients after 4-9 PDT treatments.[195]

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.[93]

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.

6.5 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.[196]

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 broad-band lamp (550-700 nm).[197] 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/cm2, 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.[198] In an open study on 13 patients with facial acne all improved following ALA-PDT, using a halogen lamp (600-700 nm, 13 J/cm2).[199]

MAL-PDT using red LED light (635nm, 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.[200] 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.[11] Another split-face study compared MAL-PDT (two sessions) versus placebo with light only in 30 patients with facial acne, using red LED (635nm, 37 J/cm^2, 68 mW/cm^2).[201] At 3 months, inflammatory lesions were reduced by 54% versus 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.[25, 196] High-dose ALA- and MAL-PDT were considered to produce similar effects with incubation of three hours 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.[25, 202] 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.[203]

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 randomised controlled study.[204] Daylight PDT compared with laser-assisted daylight PDT also saw mean inflammatory lesion counts reduced significantly by 36% and 52% respectively.[205]

Few studies have investigated PDT in combination with or vs 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).[206] In another study minocycline plus ALA-PDT led to greater efficacy vs. minocycline alone (8 weeks, -74% vs -53%).[207]

PDT 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.[208, 209] 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.

6.6 **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.[210] 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.[211] Pain, during and after illumination, was the main side effect. Several further case series including a study for recalcitrant periungual warts confirmed these results.[93, 212-217]

Experience of PDT for plane warts in limited to case reports/case series.[218, 219] 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 .[220]

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.[221-223] A larger study with 164 patients with urethral condylomata cleared 95% after one to four ALA-PDT treatments.[224] 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 versus 19.1%).[225] A larger study with 90 patients confirmed these excellent results including the lower recurrence rate for PDT (9% versus 17% for laser).[226] 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.[227] A more recent case series showed that repeat PDT treatments could eliminate subclinical genital HPV infections.[228] A series of 19 cases of anal canal condylomata with ALA-PDT showed a 100% response rate and no recurrence after 6 months.[229]

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

6.7 Cutaneous leishmaniasis Strength of Recommendation B, Quality of evidence I

PDT 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 one month was more effective than 15% paromomycin-methyl benzethonium chloride ointment.[230] 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.[231]

Additionally, there are a series of cases using different modalities of ALA- and MAL-PDT (a total of 46 lesions in 19 patients).[232-236] Red light was (570-700 nm) the most frequently used, using fluences between 75 and 100 J/cm^2 but also narrowband Aktilite ® CL128.[236,237] 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.[230,237]

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.[238]

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.[239] 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.[240]

PDT 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 heme biosynthetic pathway.[241]

PDT 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 occured. Leishmania species that can cause mucocutaneous (*L. braziliensis* complex) or visceral leishmaniasis (*L.donovani* complex) should not be treated with PDT.[242] Neither HIV-positive patients with cutaneous leishmaniasis nor patients with nodular lymphangitis should, as yet, be treated with PDT. Although, the data remains 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.

6.8 Photorejuvenation (*Strength of Recommendation A*, *Quality of Evidence1*)

PDT 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.[243] In the majority of studies IPL were used, probably with a synergistic effect as IPL by itself is capable of photorejuvenating effects.[244-253] Split-face studies show the superiority of IPL-PDT as compared to sole IPL treatment.[246-248, 253] Also on the dorsal hands superiority of IPL-PDT as compared to placebo-IPL has shown improvement of overall appearance and mottled pigmentation.[89] Illumination times are shorter with IPL than red light sources, reducing pain.[254] The use of MAL-PDT with a red LED by standard protocol is feasible when AK are treated in parallel, with a significant improvement of the signs of photoaging.[255-258] Another PDT protocol licensed for AK in the USA, is the combination of ALA with blue light, with a few studies confirming efficacy.[259-261] 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. [262,263]

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 pain was greater.[264] 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.[243] MAL-PDT in combination with non-ablative fractional laser resulted in a better improvement of fine wrinkles compared to laser alone.[265] 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. [86]

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.[180, 257 ,266-270] 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.[270] The authors hypothesize that an increase of MMP-3 may promote the degradation and removal of old, damaged collagen fibres, while the fibroblast is initiating 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.[271] Collagen remodeling after PDT has been also shown to be stimulated by a release of TGF-ß1 in keratinocytes.[272] Inhibition of melanogenesis through paracrine effects by keratinocytes and fibroblasts might be responsible for the improvement of mottled hyperpigmentations after PDT.[273]

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.[180] A PDT-induced oxidative damage and apoptosis in photoaged fibroblasts in vitro has been proposed.[274] 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.[131,211]

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.[275] As AK are often also present in photodamaged skin, licensed treatment protocols should be preferred to warrant simultaneous treatment of AK.

6.9. 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)*

PDT has been widely studied for onychomycosis.[276,277] 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 two 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%).[278] 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%.[279] 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. [280]

And open-labelled study compared ALA-PDT vs 5% amorolfine lacquer +/- fractional ablative CO2 laser for toenail onychomycosis but did not find any benefit to the pre-treatment with laser.[281]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. [282]

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*.[283] The principal problem is the penetration of the photosensitizer, which could be overcome by the pre-treatment 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.[284,285] 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.[286] 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.[287,288] 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.[289,290]

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.

6.10 Other reported uses

Both topical ALA and MAL have been used to treat a variety of inflammatory and infective skin disorders. [3,4, 291] Data is, 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 *И*I 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. [292] A retrospective study involving 17 patients reported that 6 showed short-term improvement following MAL-PDT, while psoriatic lesions worsened in 2 patients probably as a result of Koebner phenomenon. [291] 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 IIiii)

ALA-PDT and a pulsed dye laser was used in a case series of 10 patients with sebaceous hyperplasia, with clearance after one treatment in 7 patients and 2 treatments in 3 cases. [293] Five patients with sebaceous gland hyperplasia received standard MAL-PDT protocol with marked improvement in 2 and moderate response in 2.[291] 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 8 patients with hypertrophic scars. [291,294] 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. [295] Three treatments of MAL-PDT at weekly intervals was effective in reducing pruritus and pain and in improving pliability of symptomatic keloids in 20 patients. [296] In the 10 patients where PDT was applied postoperatively, there was only one recurrence.

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

PDT 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.[297] 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 were decreased.[298] Symptomatic improvement in a further 5 patients treated with ALA-PDT is observed, but with minimal change in clinical appearance and no resolution on histological evaluation.[299]

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

Two to 3 ALA-PDT sessions were performed in 7 patients with granuloma annulare with a 57% response rate (complete healing in 2 patients, marked improvement in 2).[300] 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. [291] PDT may be considered for patients affected by granuloma annulare resistant to conventional treatments.

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

PDT achieved only a limited response in 18 patient with necrobiosis lipoidica with only 1 patient showed a complete response after nine treatment sessions while 6 had a partial response after as many as 14.[301] In another retrospective study assessing 8 patients, MAL-PDT achieved a 37% response rate after a mean of 10 PDT sessions[291] A large case series on 65 patients showed that MAL-PDT performed with superficial curettage, had a cure rate of 66%.[302] 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 [291]. 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.[303] 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. [304]. Two patients affected by porokeratosis ptychotropica showed partial response and pruritus relief after 2 and 8 sessions of MAL-PDT.[305]

Extramammary Paget's Disease (Strength of Recommendation C, Quality of Evidence IIiii)

A systematic review of 21 retrospective and 2 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.[306] 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.[307,308] A case series of 32 patients with vulvar EMPD saw complete resolution of symptoms, with partial resolution in 25 patients, leading the authors to conclude that 3 courses of MAL-PDT was not curative, but an option for gaining control of EMPD at this site.[309] In a multicentre analysis of real-life practice of PDT, a complete response was achieved in 3 of 8 patients with EMPD. [93]

7. Reactions to PDT

When asking patients it is evident that, at least for AK, that side effects matter in choice of therapy, in particular pain and risk of ulceration from a treatment. [310] 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.[3, 311,312] 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.[313,314] 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.[315] 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.[123] Post procedural pain has been noted to be more severe after PDT than after surgery.[316] Pretreatment techniques, such as ablative fractional laser may increase efficacy but can cause more intensified local reactions[86]

Daylight PDT is associated with minimal pain and has permitted large facial/scalp fields to be treated in routine practice.[317] For large field conventional PDT, nerve block has proven effective to reduce pain in facial AK and field cancerization, without interfering with clinical outcome [318,319] Pain reduction for routine lesional PDT by standard protocols include use of cooling fan, water spraying water and lower light intensity or fractionated light delivery.[320] In a systematic review concerning PDT and pain, reviewing 48 studies, they report that nerve block, infiltration anesthesia, transcutaneous nerve stimulation but not topical anesthetic gels are associated with less pain during PDT.[321] 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 conclude that side effects may be minimized through the use of modified and low-irradiance regimens.[322] 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, these lesions may either represent evolution of a partially treated pre-cancer by PDT, or the coincidental development of a skin cancer in a sun-damaged field receiving PDT to treat lesions within the field.[323]

8. 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%.[324] 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. [325]

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 to IMI 5%, IMI 3.75%, IMB and diclofenac plus hyaluronate (DHA) gel for the treatment of areas <100 cm^2.[326] 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. [327] 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 US, 5-FU and MAL-PDT were the most cost-effective treatments; whereas IMB was the most expensive one.[328]

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 ($p = 0.022$). [329] 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 to surgery. [330] 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 follow-up results). [331]

9. Summary of recommendations and current approved indications*

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

****PDT is approved for this indication in Europe***

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Table 1: Treatment protocols for licensed indications

	Indication	Preparation/drug application	Illumination recommendations	Protocol	Reference
16.0% MAL (Metvix(R) Lausanne, CH)	Conventional PDT: Thin, non-hyper keratotic AK (face/scalp), SCC *in-situ*, sBCC,nBCC	Remove scales/crusts, roughen surface (remove intact epidermis over nBCC) Apply a layer of cream approx 1mm thick via spatula to lesion and surrounding 5-10mm of skin. Cover with occlusive dressing for 3 hours, then wipe clean with saline	After 3 hours, remove dressing, wipe clean with saline, then illuminate using red light of spectrum 570-670nm, total dose 75 J/cm2 (red light with narrower spectrum, giving the same activation, can be used: ~630nm, tlight dose of 37 J/cm²)	AK – one treatment, assess 3 months, SCC *in-situ* and BCC – two sessions 7 days apart, reassess after 3 months. Remaining lesions may be retreated	Full details @ https://www.medicines.org.uk/emc/product/6777/smpc (accessed 5/2/19)
16.0% MAL (Metvix(R) Lausanne, CH)	Daylight PDT: mild to moderate AK	Apply sunscreen, once dried, scales and crusts should be removed and the skin surface roughened before applying a thin layer of Metvix to treatment areas. No occlusion.	Patient to go outside within 30 minutes, dry day with temperature >10oC, for 2 hours	Single treatment, evaluate at 3 months, repeat if required	Full details @ https://www.medicines.org.uk/emc/product/6777/smpc (accessed 5/2/19)
8 mg 5-ALA (2 mg/cm²) medicated plaster (Alacare(R), Medac, Wedel, Germany)	Mild AK (≤ 1.8 cm in diameter) face/bald scalp	Apply medicinal plaster up to a maximum of 6 patches on 6 different lesions. Incubate for 4 hours.	After 4 hours, remove and expose to red light (spectrum of 630 ± 3 mm, total light dose of 37 J/cm2).	Single use treatment, reassess after 3 months, retreat remaining lesions with alternative therapies.	Full details @ https://www.medicines.org.uk/emc/product/8958/smpc (accessed 5/2/19)
78 mg/g 5-ALA gel (Ameluz(R), Biofrontera, Leverkusen, DE)	Conventional PDT: Mild to moderate AK face/scalp, field cancerization, superficial and/or nodular BCC	Remove scales/crusts, gently roughen surface, degrease skin. Apply a layer of cream approx 1mm thick and surrounding 5mm of skin or entire cancerized fields of about 20 cm^2. Cover with occlusive dressing for 3 hours.	After 3 hours, remove dressing, wipe clean, then illuminate using red light either with a narrow spectrum (~630 nm, light dose 37 J/ cm²) or a broad spectrum (570-670 nm, 75- 200 J/cm2).	One treatment, reassess after 3 mths, remaining lesions may be retreated	Full details @ https://www.medicines.org.uk/emc/product/3158/smpc (accessed 5/4/19)
78 mg/g 5-ALA gel (Ameluz(R), Biofrontera, Leverkusen, DE)	Daylight PDT: Mild to moderate AK face/scalp, field cancerization,	Apply sunscreen, once dried, wipe with an ethanol or isopropanol-soaked cotton pad then remove scales and crusts, roughen skin surface before applying a thin layer of Ameluz to treatment areas. No occlusion.	Patient to go outside within 30 minutes, dry day with temperature >10oC, for 2 hours	One treatment, reassess after 3 mths, remaining lesions may be retreated	Full details @ https://www.medicines.org.uk/emc/product/3158/smpc (accessed 5/2/19)
20% ALA solution (Levulan KerastickTM) (DUSA Wilmington, MA)	Minimal/ moderate AK, face/scalp	Lesions should be clean and dry. Following solution admixture, apply directly to lesions by dabbing gently with the wet applicator tip, and reapply once dry. Treatment site not occluded, but protect from sun/bright light	After 14-18hrs, 10 J/cm2 light dose BLU-U (1,000sec), positioning lamp as per manufacturer's instructions (shorter application times are often used in practise)	One application and one dose of illumination per treatment site per 8-week treatment session	Full details @ http://www.dusapharma.com/kerastick.html (accessed 5/2/19)

Conflicts of interest

		Morton	Szeimies	Besset-Seguin	Calzavara-Pinton
1	Grant	No	European Commission, photonamic	No	No
2	Consulting fee or honorarium	Galderma International, Biofrontera	Galderma International, Biofrontera, Leo Pharma, Almirall	Galderma	Galderma
3	Support for travel to meetings for the study or other purposes	No	none	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	none	No	No
5	Payment for writing or reviewing the manuscript	No	none	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	none	No	No
7	Other	No	none	No	no

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work

1	Board membership	Board member, Euro-PDT	Vice-President EURO-PDT	no	President Italian Society of Dermatology and STDs (SIDEMAST) and board member European Society of PhotoDermatology (ESPD)
2	Consultancy	No	No	Galderma Leo, Roche, Sun Pharma, Pierre Fabre	Leo, Almirall, Abbvie, Lilly, Sanofi, Pierre Fabre, Roche, Mylan Cantabria, Celgene, Novartis
3	Employment	No	No	No	no
4	Expert testimony	No	No	No	no
5	Grants/grants pending	No	Dr. Wolff-Group, Eli Lilly, Galapagos, Janssen, Novartis	No	no
6	Payment for lecture including service on speakers bureaus	No	ALK-Scherax, Janssen, P&M Cosmetics	No	Galderma, Cantabria
7	Payment manuscript preparation	No	none	No	Galderma,Leo, Mylan
8	Patents (planned, pending, issued)	No	none	No	no
9	Royalties	No	none	No	no

10	Payment for development of educational presentations	No	none	No	Cantabria, Pierre Fabre
11	Stock/stock options	No	none	No	no
12	Travel/accommodation/meeting expenses unrelated to activities listed**	No	no	No	no
13	Other	No	no	no	no

* This means money that your institution received for your efforts. **For example, if you report a consultancy above there is no need to report travel related to that consultancy on

Other relationships

1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	Member of Guideline Committee for BCC (European) and PDT (UK)	Member of Guideline Committee for BCC (European) and AK&SCC (German)	no	no

Conflicts of interest

		Gilaberte	**Haedersdal**	**Hofbauer**	**Hunger**
1	Grant	No	No	No	No
2	Consulting fee or honorarium	Isdin, Leo, Sun Pharma, Almirall, Galderma,	No	Louis Widmer, Galderma	Galderma

		Abbvie			
3	Support for travel to meetings for the study or other purposes	No	No	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	Galderma	No	No	No
5	Payment for writing or reviewing the manuscript	Isdin, Galderma	No	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
7	Other	No	No	No	No

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work

1	Board membership	No	No	No	No
2	Consultancy	No	No	No	No
3	Employment	No	No	No	No
4	Expert testimony	No	No	No	No
5	Grants/grants pending	No	Leo, Lutronic, Novoxel, Procter & Gamble, Sebacia	No	Galderma
6	Payment for lecture including service on speakers bureaus	No	No	No	No

7	Payment manuscript preparation	No	No	No	No
8	Patents (planned, pending, issued)	No	No	No	No
9	Royalties	No	No	No	No
10	Payment for development of educational presentations	Isdin, Leo, Novartis, Almirall, Galderma, Mylan, Biofrontera	No	No	No
11	Stock/stock options	No	No	No	No
12	Travel/accommodation/meeting expenses unrelated to activities listed**	No	No	No	Galderma
13	Other	No	No	No	No

Other relationships

1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	No	no	No

Conflicts of interest

		Karrer	**Piaserico**	**Ulrich**	**Wennberg**
1	Grant	No	No	None	None
2	Consulting fee or honorarium	No	No	Galderma	None
3	Support for travel to meetings for the study or other purposes	No	No	Galderma	None

4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	Galderma Biofrontera	None
5	Payment for writing or reviewing the manuscript	No	No	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
7	Other	No	No	None	None

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work

1	Board membership	No	ABBVIE, ALMIRAL, CELGENE, GALDERMA, JANSSEN, LILLY NOVARTIS, PFIZER	None	None
2	Consultancy	No	No	None	None
3	Employment	No	No	No	No
4	Expert testimony	No	No	No	No
5	Grants/grants pending	No	No	No	No
6	Payment for lecture including service on speakers bureaus	No	ABBVIE, ALMIRAL, CELGENE, GALDERMA, JANSSEN, LILLY NOVARTIS, PFIZER	No	No
7	Payment manuscript preparation	No	Janssen	No	No
8	Patents (planned, pending, issued)	No	No	no	no

9	Royalties	No	No	No	No
10	Payment for development of educational presentations	No	No	No	No
11	Stock/stock options	No	No	No	No
12	Travel/accommodation/meeting expenses unrelated to activities listed**	Galderma	No	No	No
13	Other	no	No	No	No

* This means money that your institution received for your efforts. **For example, if you report a consultancy above there is no need to report travel related to that consultancy on

Other relationships

1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	no	No	No

Conflicts of interest

		Braathen
1	Grant	No
2	Consulting fee or honorarium	No
3	Support for travel to meetings for the study or other purposes	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No
5	Payment for writing or reviewing the manuscript	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No

7	Other	No

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work

1	Board membership	President, Euro-PDT
2	Consultancy	No
3	Employment	No
4	Expert testimony	No
5	Grants/grants pending	No
6	Payment for lecture including service on speakers bureaus	No
7	Payment manuscript preparation	No
8	Patents (planned, pending, issued)	No
9	Royalties	No
10	Payment for development of educational presentations	No
11	Stock/stock options	No
12	Travel/accommodation/meeting expenses unrelated to activities listed**	No
13	Other	No

* This means money that your institution received for your efforts. **For example, if you report a consultancy above there is no need to report travel related to that

Other relationships

1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No