



# Advances in Photodynamic Therapy for the Treatment of Actinic Keratosis and Nonmelanoma Skin Cancer: A Narrative Review

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## ABSTRACT

Photodynamic therapy (PDT) with photosensitization using 5-aminolevulinic acid (ALA) [including a nanoemulsion (BF-200 ALA)] is approved in the USA for the treatment of actinic keratoses (AKs); another derivative, methyl aminolevulinate, is not approved in the USA but is used in Europe. For AK treatment, the photosensitizer may be applied to individual AK lesions or, depending on treatment regimen, to broader areas of sun-damaged skin to manage field cancerization, although not all products are approved for field treatment. ALA-PDT and photosensitizers have also been used off-label for the treatment of nonmelanoma skin cancers, primarily basal cell carcinomas (BCCs) and cutaneous squamous cell carcinomas (cSCC). Advantages of PDT include potentially

improved cosmesis and patient satisfaction; disadvantages include pain and duration of treatment. Alternative illumination approaches, including intense pulsed light as well as pulsed-dye lasers, have also been used successfully. Pretreating the affected tissue or warming during incubation can help to increase photosensitizer absorption and improve therapeutic efficacy. Combinations of multiple treatments are also under exploration. Reducing incubation time between photosensitizer application and illumination may significantly reduce pain scores without affecting treatment efficacy. Substituting daylight PDT for a conventional illumination source can also reduce pain without compromising efficacy. The objective of this narrative review is to describe current and ongoing research in the use of topical photosensitizers and modified light delivery regimens to achieve improved therapeutic outcomes with less toxicity in patients with AK, cSCC, BCC, and field cancerization.

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**Keywords:** Actinic keratosis; Basal cell carcinoma; Field cancerization; Photodynamic therapy; Squamous cell carcinoma

### Key Summary Points

Photodynamic therapy using aminolevulinic acid and derivatives as a photosensitizer is approved in the USA for the treatment of actinic keratosis, but many off-label uses have been investigated.

Photodynamic therapy has been used successfully to treat field cancerization and basal cell carcinoma.

Innovations in photodynamic therapy protocols include alternative light sources, mechanical skin pretreatment or warming to increase photosensitizer absorption, and combination therapy.

Variations to improve tolerability and convenience include shortened preincubation times and daylight photodynamic therapy.

Further study is needed to explore the benefits of these innovations across larger and more diverse patient populations.

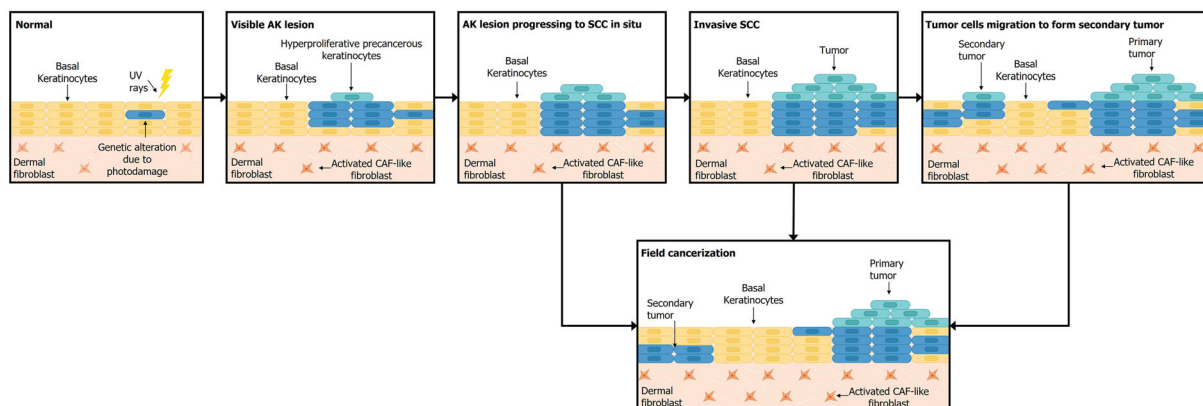
## INTRODUCTION

Nonmelanoma skin cancers (NMSCs) are a heterogeneous group of cutaneous malignancies originating from epidermal keratinocytes [1–3]. The two most common types of NMSCs, which constitute 99% of NMSC cases, are basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) [1, 3–5]. Actinic keratoses (AKs) are a precancerous form of cSCC, with a highly variable risk of malignant transformation (Fig. 1) estimated to be between 0.025% and 16% [6].

Risk factors for NMSC include but are not limited to age, skin phototype (lighter), occupational exposure, climate, and lifetime exposure to solar ultraviolet radiation [7–11]. One major modifiable risk factor for NMSC is chronic exposure to ultraviolet radiation, which may induce actinic and DNA damage to any

anatomic area with insufficient sun protection (classically, the scalp, head, neck, and dorsal extremities) [6, 12, 13]. As a result of diffuse, cumulative actinic damage, even clinically normal-appearing skin in areas adjacent to NMSC and AKs may harbor deleterious genetic alterations, termed field cancerization (Fig. 1) [14–16]. In a longitudinal cohort study conducted between 2009 and 2020 that included 220,236 patients with AK and matched healthy individuals, the mean incidence of cSCC was 1.92 per 100 person-years [95% confidence interval (CI) 1.89–1.95] in patients with AK versus 0.83 per 100 person-years in healthy individuals without AK [95% CI 0.81–0.85; subdistribution hazard ratio (95% CI) 1.90 (1.85–1.95)] [12]. Furthermore, younger patients (< 49 years of age) with AKs are seven times more likely to develop cSCC compared with the general population [12]. Hence, early detection and treatment of AKs and anatomic areas with AKs are of utmost importance for long-term NMSC management.

A nonsurgical treatment option is photodynamic therapy (PDT), which involves application of a topical photosensitizer that is then activated with visible light [2, 4]. Topical photosensitizers are precursors of protoporphyrin IX (PpIX) that, when activated, catalyze formation of reactive oxygen species (ROS) to induce apoptosis and necrosis of the atypical keratinocytes [2, 4, 17]. Three topical agents are commonly used as photosensitizers for PDT: aminolevulinic acid (ALA); an esterified formulation, methyl aminolevulinate (MAL); and a nanoemulsion-based gel formulation containing 7.8% 5-ALA (10% ALA hydrochloride) (BF-200 ALA) [2, 4, 18, 19]. In the USA, 20% 5-ALA solution with blue light illumination is indicated for the treatment of minimally to moderately thick AK of the face, scalp, or upper extremities [20], while BF-200 ALA with red light illumination is approved for both lesion-based and field-based treatment of mild-to-moderate AKs of the face and scalp [21]. In Europe, while specific approvals vary across countries, MAL and BF-200 ALA with red light are approved to treat mild-to-moderate AKs on the face and bald scalp, cSCC in situ, and superficial and nodular BCCs [19, 22]. PDT is



**Fig. 1** Chronic ultraviolet (UV) radiation damages the epidermal layer leading to atypical keratinocytes, including AK. When left untreated, the lesions can develop into SCC in situ that further progresses to invasive SCC.

not recommended for BCCs > 2 mm in thickness or for more aggressive forms such as basisquamous, morpheaform, or infiltrating subtypes [2, 23]; for lesions > 2 mm thick, debulking the lesions gently before initiating PDT is suggested [24].

PDT is relatively effective for the treatment of AK. In a meta-analysis comparing 25 European studies with ten different treatment modalities for mild-to-moderate AKs of the face and scalp including ALA applied as a gel (BF-200 ALA-PDT) or patch, MAL-PDT, imiquimod (in three different combinations of concentration and treatment duration), cryotherapy, 3% diclofenac, 0.5% 5-fluorouracil (5-FU), and ingenol mebutate, BF-200 ALA-PDT was the most effective based on total patient clearance 12 weeks after treatment (estimated odds ratio, 45.9; 95% CI 13.9–151.8) [25]. Other advantages of PDT include potentially improved cosmesis and patient satisfaction, while drawbacks include pain and duration of treatment [2, 4].

The purpose of this review is to synthesize and highlight recent and ongoing research on the use of PDT for the management of AK, field cancerization, and NMSC (off-label), as well as developments that may improve PDT efficacy, tolerability, and cosmesis. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. PubMed was searched from inception

Subclinical genetic alterations may progress and form field cancerization underneath normal-appearing skin [16]. *AK* actinic keratosis, *CAF* cancer-associated fibroblast, *SCC* squamous cell carcinoma, *UV* ultraviolet

to February 2022 using the search terms [(aminolevulinic acid OR aminolevulinate) AND photodynamic therapy] with (broad area OR field-directed), (squamous cell carcinoma OR basal cell carcinoma), and (efficacy OR pain OR tolerability). The most relevant findings, as well as other recent publications of interest, are summarized with respect to advances in clinical application, innovations in PDT protocols, and use in organ transplant recipients.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## ADVANCES IN CLINICAL APPLICATION

In addition to AKs, physicians have successfully explored PDT treatment for field cancerization as well as for individual superficial and nodular BCC, SCC in situ, and cSCC lesions [4, 18].

### PDT in Field Cancerization Treatment

As there is no reliable way to identify subclinical lesions or AKs with malignant potential in areas with actinic damage, it is desirable to treat the entire cancerized field in addition to individual lesions. Large body surface areas with multiple subclinical lesions are difficult to treat with

surgery, and topical therapy can be compromised by nonadherence as a result of brisk local skin reactions or prolonged treatment regimens [26]. In these cases, PDT may be useful as an alternative or adjunctive therapy to help maximize quality of life and minimize morbidity and mortality.

Clinical trials have shown ALA-PDT to be safe and highly effective in the treatment of minimally to moderately thick AKs and field cancerization (Table 1) [27, 28]. In a 52-week trial, 166 high-risk patients with facial AKs previously treated with cryotherapy and biopsy-confirmed photodamaged “clinically normal” skin were randomized to undergo two (baseline and week 4) or three (baseline, week 4, and week 24) sessions of field-directed therapy with broadly applied 20% ALA (or vehicle) to the entire face with a 1-h incubation time followed by blue light illumination [27]. At week 52, compared with the vehicle-PDT arm, patients who received three treatments with ALA-PDT had significantly fewer AKs (least squares mean, 2.1 versus 4.7;  $P = 0.0166$ ), greater probability of having no AKs (37.5% versus 18.9%,  $P = 0.0089$ ), and numerically longer duration of response [mean (95% CI), 33.3 (28.0–38.5) weeks versus 25.9 (20.2–31.6) weeks]; they also developed fewer new NMSCs (five new NMSCs in 5/56 patients versus 12 new NMSCs in 7/53 patients;  $P = 0.0014$ ) [27]. No clinically significant differences in efficacy or safety were noted between two and three ALA-PDT sessions [27]. A phase 3 multicenter, randomized, double-blind, vehicle-controlled study evaluated field-directed treatment with 10% BF-200 ALA gel and red light PDT in 87 adult patients with mild-to-moderate AKs of the face and/or scalp [28]. At the 12-week follow-up after the last PDT treatment, field-directed PDT achieved complete AK clearance in 91% of BF-200 ALA-treated patients compared with 22% of vehicle-treated patients ( $P < 0.0001$ ) [28].

### PDT for Basal Cell Carcinoma Management

PDT has shown therapeutic efficacy as an off-label treatment for BCC in clinical practice [4].

Because PDT cannot penetrate lesions beyond 2 mm deep, the use of surgical curettage to reduce tumor depth to less than 2 mm followed by subsequent PDT may be beneficial in the treatment of BCC [23, 29]. Data suggest that debulking thicker tumors prior to PDT treatment increases complete response rate after 3 years of follow-up relative to older studies where pretreatment debulking may not have been performed [29, 30].

Studies utilizing 5-ALA or MAL have demonstrated promising results for the treatment of BCC (Table 2) [29, 31–33]. In a 3-year, prospective, open-label trial of 174 adult patients with dermoscopically/histologically confirmed superficial BCC and nodular BCC, combining curettage of visible tumor (sparing dermis and adjacent normal skin) with 16% MAL cream and photoactivation with red light-emitting diode (LED) light for 23 min resulted in overall 3-year clearance rates of 96.1% after a mean of 2.6 sessions for superficial BCC and 95.2% after a mean of 2.7 sessions for nodular BCC [29]. An open-label trial assessing 12% 5-ALA-PDT gel with a 3-h incubation period and photoactivation with red light for the treatment of superficial BCCs on the head and neck, trunk, and extremities achieved a complete response rate of 95.8% at 3 months after the second treatment session and a 3-year recurrence-free survival rate of 88.3% [31]. In another interventional cohort study of histologically confirmed BCCs < 2 mm deep in adult patients, 20% 5-ALA ointment with a 4-h incubation time under occlusion and red light illumination resulted in complete response for 47/54 lesions (87%) after only one session and for an additional 5/54 lesions after two sessions [32]. In a small pilot interventional study [33], three patients with basal cell nevus syndrome (Gorlin syndrome) underwent six ALA-PDT treatments in three biweekly (day 1 and day 7) sessions spaced 2 months apart. Each tumor was treated with 20% ALA, and matching contralateral treatment zones were illuminated with red light and blue light after a 4-h incubation. Blue light treatment was noninferior to red light treatment for BCC complete response rate (98% versus 93%;  $P < 0.001$  for noninferiority with a 5% margin), and greater pain was anecdotally

**Table 1** Interventional studies of PDT for field cancerization summarized

References	Study type	Patient pop	Patient char	Lesions	Anatomical location	PDT treatment	Light source	Intervention	Results
Piacquadio et al. [27]	RCT	166 patients; 135 M, 31 F	Mean ± SD age, years: ALA 2×, 67.9 ± 9.7 ALA 3×, 66.7 ± 9.4 VEH, 65.8 ± 9.5	Multiple AK and diagnosis of NMSC on sun-exposed areas	Head and neck	20% 5-ALA for 1 h	Blue light illumination for 16 min 40 s, 2× or 3×	Broad-area PDT in patients with high risk of developing new lesions	Week 52 recurrence rates ALA 2×: 7.7% ( <i>P</i> = 0.0004) ALA 3×: 6.1% ( <i>P</i> < 0.0001); LS mean number of AKs ALA 2×: 3.0 ALA 3×: 2.1 ( <i>P</i> = 0.0166)
Reinhold et al. [28]	RCT	87 patients; 79 M, 8 F	Mean ± SD age, years: 71.6 ± 6.4	Mild-to-moderate AKs	Face and/or scalp	10% BF-200 ALA gel for 3 h ± 10 min or vehicle	BF-RhodoLED red light PDT	10% BF-200 ALA with red light PDT with vehicle	Complete AK clearance BF-200 ALA: 91% Vehicle: 22% ( <i>P</i> < 0.0001)

*AK* actinic keratosis, *ALA* aminolevulinic acid, *char* characteristics, *F* female, *LED* light-emitting diode, *LS* least squares, *M* male, *NMSC* nonmelanoma skin cancer, *PDT* photodynamic therapy, *pop* population, *RCT* randomized controlled trial, *SD* standard deviation, *VEH* vehicle

**Table 2** Interventional studies with PDT in BCC summarized

References	Study type	Patient pop	Patient char	BCC type	Anatomical location	PDT treatment	Light source	Intervention	Results
Gómez et al. [29]	Retrospective	174 patients; 89 M and 85 F	sBCC: 76 lesions, mean age 71.1 ± 12.9 years; nBCC: 144 lesions, mean age 73.8 ± 12.7 years	sBCC and nBCC	Face, scalp, neck, trunk, arms, and legs	16% MAL for 3 h	Red LED lamp (23 min exposure)	2–3 MAL-PDT sessions	Overall clearance rates at 3-year follow-up sBCC: 96.1% [95% (CI) 92–100%] nBCC: 95.2% [95% (CI) 92–99%]
Filonenko et al. [31]	Prospective	82 patients; 15 M, 67F	Mean age: N/A	sBCC	Face, head, neck, trunk, and extremities	12% 5-ALA gel for 3 h	630 nm laser, energy density 350 J/cm <sup>2</sup>	Two 5-ALA-PDT treatments on face, head, neck, trunk, and extremities of patients with sBCC	RFS 1 year: –92.1% 3 year: –88.3%
Wóźniak et al. [32]	RCT	50 patients; 27 M, 23 F	Mean age (M) 71.8 years and (F) 63.5 years	sBCC, nBCC, infiltrating and sclerosing	Trunk and head	20% ointment 5-ALA for 4 h	Two different wavelengths: 405 nm violet diode and 638 nm red diode	Novel laser light source in PDD and PDT in patients with BCC	CR sBCC: 97.2% nBCC: 66.7% Inflit: 50% Sct: 0%

**Table 2** continued

References	Study type	Patient pop	Patient char	BCC type	Anatomical location	PDT treatment	Light source	Intervention	Results
Maytin et al. [33]	Prospective	Three patients; 2 M, 1 F	33, 39, and 54 years of age	BCC	Scalp, face, neck, arms, legs, and back	20% solution of 5-ALA for 4 h	Half tumors illuminated with red light and half with blue light	Head-to-head comparison of blue light versus red light in Gorlin syndrome	Lesion clearance rates Blue light: 98% Red light: 93%

*5-ALA-PDT* aminolevulinic acid photodynamic therapy, *BCC* basal cell carcinoma, *char* characteristics, *CI* confidence interval, *CR* complete response, *F* female, *Iyflit* infiltrating, *LED* light-emitting diode, *M* male, *MAL* methyl aminolevulinic acid, *N/A* not applicable, *nBCC* nodular BCC, *PDD* photodynamic diagnosis, *PDT* photodynamic therapy, *pop* population, *RCT* randomized clinical trial, *RFS* relapse-free survival, *sBCC* superficial BCC, *Stl* sclerosing

reported following red versus blue light treatment (no statistical analysis) [33].

Safety and efficacy of PDT for BCC has also been reported in numerous case studies (Table 3) [34–38]. Successful treatment and/or reduced growth of treated tumors after use of 20% ALA with red light illumination or 20% 5-ALA-PDT with blue light illumination have been observed in histologically confirmed superficial BCC, nevoid BCC syndrome, and multiple pigmented BCCs [35, 36, 38].

### INNOVATIONS IN PDT

Alternative approaches have been investigated to advance efficacy (Table 4 [39–58]), tolerability (Table 5 [59–66]), and convenience of PDT.

#### Innovations to Improve Efficacy: Alternative Light Sources, Pretreatment, Thermal PDT, and Combination Therapy

Variations in ALA-PDT protocols to improve efficacy include use of alternative light sources, mechanical pretreatment or thermal conditioning during incubation to increase photosensitizer absorption, and combination therapy.

#### Alternative Light Sources

Optimal outcomes from PDT treatment depend upon the light source and absorption spectrum of photosensitizer used. In the past decade, both coherent (photons in phase with each other and focused) and noncoherent (photons not in phase with each other and usually diffuse) light sources have been used to improve tissue penetration and reduce the pain associated with PDT treatment.

Intense pulsed light (IPL) devices have been investigated as an alternative light source for PDT in the treatment of NMSC, including AK, superficial BCC, and SCC in situ [48, 49]. IPL uses high-intensity, non-laser light and produces broad-spectrum wavelength pulses on a broader skin area. The use of 20% 5-ALA or MAL in combination with IPL-based PDT activation resulted in upwards of 68–90% clearance within 3 months after 1–2 treatments [40, 48, 49].

Table 3 Case reports with PDT in BCC

References	Patient pop	BCC subtype	Anatomical location	Photosensitizer treatment	Light source	Intervention	Results
Salvio et al. [34]	Two patients; 56-year-old F, 52-year-old F	Multiple pigmented BCC	Upper limb and trunk	20% MAL for 3 h for first session and 1.5 h for second	Red LED lamp (20 min exposure)	Two sessions of MAL-PDT	No recurrence of all lesions after 24 months of follow-up
Trafalski et al. [35]	82-year-old M	Histopathologically confirmed BCC	Face	20% 5-ALA for 2 h	Red light illumination	PDT at 2-week intervals for 3 months	No recurrence after 12 months of follow-up
Chapas et al. [36]	73-year-old M	Multiple sBCC and nBCC (nevroid BCC syndrome)	Face and chest	20% 5-ALA for 1 h	Blue light source	Broad-area PDT	Reduced size and number of existing BCC
Itkin et al. [37]	Two patients; 21-year-old F, 47-year-old F	sBCC and nBCC (nevroid BCC syndrome)	21-year-old: right upper lip, left mastoid prominence, right biceps and left triceps area; 47-year-old: face, lower extremities	Delta-ALA for 1–5 h	Blue light source	Broad-area PDT, two courses 2–4 months apart	Complete clinical resolution: sBCC, face: 89% sBCC, lower extremities: 67% nBCC, face: 31%
Lane et al. [38]	56-year-old M	Unilateral localized BCC	Left scapular back and left posterior arm	5-ALA	Blue light illuminator	PDT	*Excellent therapeutic response <sup>a</sup> with no new clinically visible BCC for 18 months

*5-ALA-PDT* aminolevulinic acid photodynamic therapy, *BCC* basal cell carcinoma, *F* female, *LED* light-emitting diode, *MAL* methyl aminolevulinic acid, *nBCC* nodular BCC, *PDT* photodynamic therapy, *pop* population, *sBCC* superficial BCC



**Table 4** Summary of studies on innovations in PDT to improve effectiveness

References	Study type	Patient pop	Patient char	Lesions	Anatomical location	PDT treatment	Light exposure	Intervention	Results
Light source									
Ruiz-Rodriguez et al. [49]	Case series	17 patients; 4 M, 13 F	N/A	AKs and chronic actinic damage	Face and scalp	20% 5-ALA in oil-in-water emulsion incubated 4 h with occlusion	Epilight IPL device with 615 nm cutoff filter, total fluence 40 J/cm <sup>2</sup> , double pulse mode of 4.0 ms with a delay time of 20 ms between pulses; repeated after 1 month	IPL PDT	1 month after first treatment: Resolution of 29/38 (76.3%) AKs  1-month and 3-month follow-ups: No visible AKs in 15/17 patients; resolution of 33/38 (91%) AKs
Avram and Goldman [40]	Retrospective	17 patients; 5 M, 12 F	Mean age 52 years (range 38–78 years)	AKs and signs of photoaging	Face	20% ALA solution incubated for 1 h	Vasculite Elite IPL device with 560 nm filter, 28–32 J/cm <sup>2</sup> with a double pulse of 3.0 and 6.0 ms with a 10-ms delay	IPL PDT	68% of AKs resolved after one treatment; one nBCC did not respond after three treatments
Piccolo et al. [48]	Observational	25 patients; 15 M, 10 F	Mean age, 71.3 years; range 54–93 years	AK, sBCC, and BD	Face	MAL for 3 h	Activation with IPL device (Photosilk plus, DEKA M.E.L.A. S.r.l.) with cutoff wavelength 550 nm; fluence 18 J/cm <sup>2</sup> ; triple pulse mode 3.3, 3.9, and 4.6 ms; interpulse delay, 100 ms with epidermal cooling	MAL-treated patients with IPL in NMSC	AKs: CR: 90% PR: 10% sBCC: CR: 80% PR: 20% BD: CR: 100% PR: 0

Table 4 continued

References	Study type	Patient pop	Patient char	Lesions	Anatomical location	PDT treatment	Light exposure	Intervention	Results
Kessels et al. [43]	Long-term follow-up	61 patients (M)	Mean age $\pm$ SD, 73.7 $\pm$ 7.5 years	Multiple AKs	Scalp and forehead	MAL for 3 h	PDL illumination on left side (595 nm, Vbeam, Candela Corporation®), 7 mm spot size, fluence 7 J/cm <sup>2</sup> , pulse duration 10 ms, epidermal cooling 30/10 ms, 50% overlap) and LED-PDT on right side of the face (Aklilire®, Galderma Benelux, 37 J/cm <sup>2</sup> , 635 $\pm$ 18 nm)	Compared efficacy of LED-PDT with PDL-PDT, and a long-term follow-up	Mean decrease in number of lesions from baseline to 12-month follow-up LED-PDT: -4.25 (95% CI -5.07; -3.43) PDL-PDT: -3.88 (95% CI -4.76; -2.99)
Abrouk et al. [39]	Prospective	220 patients; sex N/A	88 received treatment for AK and 126 for photodamage	AKs	Face	20% 5-ALA for 2 h	Illuminated with one of the following: (PDL, PDL + blue light, IPL, or IPL + blue light); all fluences 6–12 J/cm <sup>2</sup> , pulse width of 5–20 ms with contact cooling	IPL versus PDL with or without blue light for activation of PDT	IPL + blue light demonstrated increased efficacy when compared with IPL, PDL, or PDL + blue light
Pretreatment									
Torezan et al. [52]	Prospective split-face trial	Ten patients; 1 M, 9 F	Mean age 65.2 years	$\geq$ 3 AKs	Face	MAL cream incubated 90 min with occlusion	Red LED light, 50 mW/cm <sup>2</sup> , 37 J/cm <sup>2</sup>	Microneedle pretreatment (1.5 mm long $\times$ 0.1 mm wide, roller device) versus gentle curettage	Average AK clearance after 90 days: Microneedle-assisted PDT: 90.5% Conventional PDT: 86%

**Table 4** continued

References	Study type	Patient pop	Patient char	Lesions	Anatomical location	PDT treatment	Light exposure	Intervention	Results
Lev-Tov et al. [44]	Prospective split-face trial	48 patients completed study endpoints for pain; 40 M, 8 F	Mean age 67.7 years; range 49–86 years	AKs	Forehead	20% 5-ALA solution incubated for 20, 40, or 60 min (microneedle side) or 60 min (sham side)	Blue light exposure for 8 min, total fluence 4.8 J/cm <sup>2</sup>	Microneedle pretreatment (690 micron length) versus sham treatment	Complete AK response rate after 1 month (microneedle versus sham): 20 min: 71.4% versus 68.3% 40 min: 81.1% versus 79.9% 60 min: 72.1% versus 74.2%
Perukhova et al. [47]	Split-face RCT	32 patients; 22 M, 10 F	Mean ± SD age: 20-min arm: 62.8 ± 2.1 years 10-min arm: 65.4 ± 2.5 years	≥ 3 Grade II AKs	Face	20% 5-ALA solution incubated for 10 or 20 min	Blue light illumination for 1000 s, total fluence 10 J/cm <sup>2</sup>	Microneedle pretreatment (200 µm length, roller device) versus sham treatment	AK clearance at 1-month follow-up, microneedle versus sham: 20-min arm: 76% versus 58% ( <i>P</i> < 0.01) 10-min arm: 43% versus 38% ( <i>P</i> = 0.66)
Spencer and Freeman [51]	Prospective split-face	19 patients; sex N/A	N/A	≥ 4 nonhyperkeratotic AKs per side	Face	20% 5-ALA solution incubated for 1 h	Blue light illumination for 1000 s	Microneedle pretreatment (0.5 mm length, stamp-style device) versus no pretreatment	Mean percentage reduction in AKs after 2 and 4 months: Microneedle side: 89.3% Control side: 69.5% ( <i>P</i> < 0.05)

Table 4 continued

References	Study type	Patient pop	Patient char	Lesions	Anatomical location	PDT treatment	Light exposure	Intervention	Results
Miller et al. [45]	Proof of concept	19 patients; sex N/A	N/A	BCC, cSCC, and multiple AKs	Face, lip, scalp, forehead, temple, hand, and leg	20% 5-ALA for 1 h	Blue light exposure for 16 min and 40 s	CO <sub>2</sub> laser AFR	Pretreatment with AFR provided superior clearance of AKs and thin NMSCs at 6 months compared with 5-ALA-PDT alone
Jang et al. [57]	Prospective, single-arm	29 patients; 7 M, 22 F	Mean age 68.4 years (standard deviation, 11.1 years)	AK	Face (majority), back, leg	20% 5-ALA for 90 min (17 lesions); MAL cream for 70 min (17 lesions)	Red light at 100 J/cm <sup>2</sup> for ALA; red light at 37 J/cm <sup>2</sup> for MAL	CO <sub>2</sub> laser AFR	Complete response in 70.6% of lesions after three treatment sessions
Falkenberg et al. [56]	Prospective, single-arm	28 patients; 22 M, 6 F	Mean age 74 ± 8.9 years	AK	Scalp and/or face	5-ALA nanoemulsion for 1 h	Artificial DL-PDT for 1 h at 20 J/cm <sup>2</sup>	CO <sub>2</sub> laser AFR	91.3% reduction in lesion count after 3 months ( <i>P</i> < 0.0001)
Togsvold-Bo et al. [58]	Prospective, within-patient control	16 patients; 10 M, 6 F	Mean age 63 years (range, 54–76 years)	≥ 2 Grade II or III AK in each site	Scalp, chest, and extremities	MAL for 2.5 h (DL-PDT) or 3 h (red light PDT)	DL-PDT or red light at 37 J/cm <sup>2</sup>	2940-nm Er:YAG laser AFR	Complete response (3 months) AFR pretreatment with DL-PDT: 74% DL-PDT alone: 46% ( <i>P</i> = 0.026)
Wenande et al. [53]	RCT	18 patients; 2:1 M:F ratio	Mean age 72.5 years (range 52–85 years)	AK and photodamaged fields	Scalp, face, and chest	Fractional 2940-nm Er:YAG laser with debulking followed by 16% MAL or MD	DL-PDT for 2 h	Fractional 2940-nm Er:YAG laser versus MD	AK clearance rate AFL-DL-PDT: 81% MD-DL-PDT: 60% ( <i>P</i> < 0.001)

**Table 4** continued

References	Study type	Patient pop	Patient char	Lesions	Anatomical location	PDT treatment	Light exposure	Intervention	Results
Foged et al. [41]	RCT	12 healthy volunteers; 6 M, 6 F,	Median age of 22.5 years (range 18–25 years)	Not applicable	N/A	20% 5-ALA in cream or gel formulation for 3 h	N/A	Pretreatment with TMFI followed by 5-ALA treatment	Skin surface PpIX: TMFI ALA cream increased over ALA cream ( $P < 0.001$ ) TMFI ALA gel increased over ALA gel ( $P < 0.001$ )
Shavit et al. [50]	Proof of concept	Five healthy volunteers	35–65 years	Not applicable	Forearms	(1) 20% 5-ALA gel (2) 10% 5-ALA-microemulsion gel (3) 16.8% MAL cream (4) 20% 5-ALA solution	N/A	Compared the effect of TMFI on 5-ALA permeation into the skin	TMFI pretreatment significantly increased the percutaneous permeation of 5-ALA and MAL
Thermal PDT									
Willey et al. [55]	Single-center study	20 patients; 15 M, 5 F	Median age 70 years (range 57–90 years)	AKs	Distal extremities	20% 5-ALA with 1 h heat-assisted incubation	Blue light illumination	Heated PDT versus not heated PDT	Median percent change from baseline at 6 months Heated PDT: 88.0% ( $P < 0.0001$ )
Willey et al. [54]	Prospective pilot	Ten M patients	Median age, 68 years (range 58–82 years)	AKs	Face	20% 5-ALA with 20 min heat-assisted incubation	Blue light illumination	PpIX production with heated PDT versus not heated PDT	Increased PpIX production with heated PDT than control
Topical combination therapy									

Table 4 continued

References	Study type	Patient pop	Patient char	Lesions	Anatomical location	PDT treatment	Light exposure	Intervention	Results
Nissen et al. [46]	RCT	24 patients; 16 M, 8 F	Mean age 73.3 years (range 52–87 years)	Grade I–III AKs	Dorsal hands	BID 5-fluorouracil for 1 wk then 16% MAL for 30 min	DL-PDT for 2 h	Pretreatment with 5-FU	Mean lesion response at 3 months follow-up 5-FU: 62.7% DL-PDT: 51.8% ( $P = 0.0011$ )
Galimberti et al. [42]	RCT	11 patients; 10 M, 1 F	Mean age 55 years (range 40–70 years)	Grade I–III AKs	Face and scalp	QD calcipotriol 50 mcg/g 15 days prior to 16% MAL cream	DL-PDT for 2 h	Pretreatment with calcipotriol	Complete clinical remission Calcipotriol: 85% DL-PDT: 70%

5-ALA aminolevulinic acid, 5-FU 5-fluorouracil, AFL ablative fractional laser, AFR ablative fractional resurfacing, AK actinic keratosis, BCC basal cell carcinoma, BD Bowen's disease, BID twice daily, CI confidence interval, char characteristics, CO<sub>2</sub> carbon dioxide, CR complete response, cSCC cutaneous squamous cell carcinoma, DL-PDT daylight-photodynamic therapy, Er: YAG erbium-doped yttrium aluminum garnet laser, F female, IPL intense pulse light, LED light-emitting diode, M male, MAL methyl aminolevulinic acid, MD microdermabrasion, N/A not available, nBCC nodular BCC, NMSC nonmelanoma skin cancer, PDL pulsed-dye laser, PDT photodynamic therapy, pop population, PpIX protoporphyrin IX, PR partial response, QD once daily, RCT randomized controlled trial, sBCC superficial BCC, SD standard deviation, TMFI thermo-mechanical fractional injury

**Table 5** Summary of studies on innovations in PDT to improve tolerability

References	Study type	Patient pop	Patient char	Lesions	Anatomical location	PDT treatment	Light exposure	Intervention	Key message
Incubation									
Kaw et al. [62]	Bilaterally controlled trial	23 patients; 21 M, 2 F	Mean age M: 69.7 years (range 58–88 years) F: 50 and 75 years	AKs	Face and scalp	20% 5-ALA without incubation	Cohort 1: 30 min of blue light Cohort 2: 45 min of blue light Cohort 3: 60 min of blue light	Simultaneous versus conventional illumination in PDT	A modified PDT regimen had similar clinical response of AK lesions as ePDT (57.7%, 59.1% on face; 43.8%, 41.9% on scalp, respectively) and was essentially painless
Pariser et al. [66]	RCT	234 patients; 211 M, 23 F	Mean age 68 years (range 40–88 years)	6–20 Grade I–II AKs	Face and scalp	20% 5-ALA solution incubated for 1, 2, or 3 h	Blue light illumination for 16 min 40 s (10 J/cm <sup>2</sup> )	ALA-PDT versus vehicle-PDT with short incubation	AKCR at week 12, median ± SD, <i>P</i> versus vehicle: Broad area, 1 h incubation: 71.4 ± 34.8% ( <i>P</i> < 0.001) Broad area, 2 h incubation: 73.6 ± 31.1% ( <i>P</i> < 0.001) Broad area, 3 h incubation: 78.6 ± 30.5% ( <i>P</i> < 0.001) Spot application, 2 h incubation: 68.3 ± 39.4% ( <i>P</i> < 0.001) Vehicle: 7.1 ± 44.3%
Gandy et al. [61]	Case report	56-year-old male	Fitzpatrick skin type II	AKs	Face and scalp	5-ALA without incubation	Two cycles of blue light; 33 min 20 s each	PDT without incubation time: Two back-to-back cycles of 16 min 40 s	Treatment was noninferior to conventional protocol and nearly painless

Table 5 continued

References	Study type	Patient pop	Patient char	Lesions	Anatomical location	PDT treatment	Light exposure	Intervention	Key message
Daylight PDT									
Mei et al. [63]	Meta-analysis of six RCT	369 patients; majority male	Mean age ranged from 63 to 78 years	Multiple AKs	Predominantly face and scalp; chest and extremities in one study only	N/A	N/A	Compared efficacy and safety of DL-PDT with cPDT	DL-PDT is noninferior to cPDT with red light and MAL and highly painless
Dirschka et al. [60]	RCT	49 patients; 47 M, 2 F	Mean age 72.6 ± 7.1 years	Multiple AKs	Face and scalp	BF-200 ALA or 16% MAL cream for 30 min and during illumination	DL-illumination for 2 h	BF-200 ALA versus 16% MAL	Clearance rate BF-200 ALA: 79.8 ± 23.6% MAL: 76.5 ± 26.5% Median of differences 0.0 ( $p < 0.0001$ )
Neittraanmäki-Perttu et al. [64]	Prospective split-face trial	13 patients; 7 M, 6 F	Mean age 79.8 (66–80) years	AKs	Face	BF-200 ALA or 16% MAL cream	DL-illumination for 2 h	DL-PDT with MAL versus BF-200 ALA	Complete clearance rates BF-200 ALA: 84.5% (95% CI 75.2–90.9%) MAL: 74.2% (95% CI 64.4–82.1%)
Paasch et al. [65]	Retrospective	46 patients; 42 M, 4 F	Mean age 68.7 ± 9.4 years	> 5 AKs	Predominantly face; also included scalp, forehead, and dorsal hands	BF-200 ALA for 45–60 min	IDL for 35 min	AFL treatment with IDL DL-PDT	Complete clearance rate 71.7%



**Table 5** continued

References	Study type	Patient pop	Patient char	Lesions	Anatomical location	PDT treatment	Light exposure	Intervention	Key message
Bai-Habelski et al. [59]	Prospective	12 patients; 11 M, 1 F	Mean age 72.7 ± 10.7 years	Mild-to-moderate AK	Face and scalp	BF-200 ALA for 30 min	2 h illumination with the IndoorLux® System	IDL-PDT and BF-200 ALA	Clearance rate Individual: 83.75% (66.7–100.0%) Patients: 33.3% Lesions: 84.9%

5-ALA aminolevulinic acid, AFL ablative fractional laser, AK actinic keratosis, AKCR actinic keratosis clearance rate, char characteristics, CI confidence interval, ePDT conventional PDT, DL-PDT daylight PDT, F female, IDL indoor daylight, M male, MAL methyl aminolevulinic acid, NA not available, PDT photodynamic therapy, pop population, RCT randomized controlled trial, SD standard deviation

Pulsed-dye lasers (PDL) have also demonstrated usefulness in the management of AKs. In a split-face prospective study, patients with multiple AKs on the scalp or forehead were pretreated with curettage and MAL with a 3-h incubation and then received either PDL illumination or conventional LED light treatment on the contralateral side. At the 12-month follow-up, efficacy of PDL-PDT was similar to conventional PDT, with a mean difference in the change from baseline in number of AKs of -0.46 (95% CI -1.28 to 0.35; P = 0.258). Notably, the pain score was lower with PDL-PDT compared with LED-PDT (visual analog score mean difference, -4.55; P < 0.01) [43].

In a prospective four-arm study, 220 patients with photodamaged skin (n = 126) or multiple AKs (n = 88) received either IPL, PDL, or IPL or PDL in combination with blue LED illumination to activate 20% 5-ALA after a 2-h incubation period. Reduction of AK lesions at the 1-month follow-up was materially superior following treatment with IPL and blue LED (84.4%) relative to other light combinations (PDL, 70.5%; PDL with blue LED, 69.3%; IPL, 70.8%) [39].

**Pretreatment**

Various approaches have been tested to prepare the skin to increase photosensitizer absorption. The most straightforward of these is microneedle-assisted incubation, in which the skin is perforated with a microneedling device before application of the photosensitizer. Several prospective trials utilizing split-face designs in which one side is pretreated with microneedling before photosensitizer application and PDT have yielded mixed results. In a pilot study (n = 10), there was no reported difference in AK clearance assessed 90 days after treatment between the sides pretreated with microneedling (90.5%) versus gentle curettage (86%) before MAL-PDT with red light illumination [52]. Similarly, there was no effect of microneedle pretreatment on AK complete response rate at the 4-week follow-up after PDT with 20% ALA solution preincubated for 20, 40, or 60 min on the microneedle-treated side versus 60 min on the sham-treated side before blue light illumination (71.4% versus 68.3%, 81.1% versus

79.9%, and 72.1% versus 74.2%, respectively, for microneedle-treated versus control sides;  $n = 15$ – $17$ ) [44]. However, in two additional studies without curettage on the control side ( $n = 16$ – $19$  per treatment arm), microneedle treatment before application of 20% ALA solution and blue light PDT resulted in significant reduction in AKs relative to the side without pretreatment (76–89.3% versus 58–69.5% after 1–4 months) [47, 51]. Given these mixed results, additional studies are needed to clarify the usefulness of microneedle pretreatment with ALA-PDT.

Ablative fractional resurfacing (AFR) using CO<sub>2</sub> and erbium-doped yttrium aluminum garnet (Er: YAG) lasers is proposed to create microscopic vertical channels that facilitate deeper penetration and uptake of photosensitizing agents such as 5-ALA [45]. These ablated vertical channels are surrounded by a coagulation zone that may serve as a reservoir to allow slow release of the photosensitizer. Several clinicians have investigated pretreatment with AFR before ALA-PDT. In a prospective single-arm study ( $n = 29$ ), pretreatment with CO<sub>2</sub> laser AFR (single pass, 50 mJ pulse with spot density of 100 spots/cm<sup>2</sup>, power of 30 W, and 120- $\mu$ m beam size) before ALA-PDT of AK with 20% 5-ALA solution or MAL cream resulted in complete response of 70.6% of lesions after three treatment sessions despite MAL incubation for only 70–90 min before illumination [57]. A similar study ( $n = 28$ ) found a 91.3% reduction in lesion count 3 months after a single treatment with CO<sub>2</sub> laser AFR (8 mJ pulse, 50 spots/cm<sup>2</sup>, power of 30 W, and 4–18 mm beam size depending on diameter) followed by ALA-PDT with ALA nanoemulsion and illumination with an artificial daylight lamp [56]. A prospective within-patient trial compared daylight (DL)-PDT with and without Er: YAG laser AFR pretreatment in organ transplant recipients (OTRs) with four comparable skin areas with field cancerization and  $\geq 2$  AKs (Grade II or III) per site [58]. Treatment areas were randomized to a single field-directed treatment with AFR-DL-PDT, DL-PDT without AFR, or conventional PDT, all with MAL cream, or AFR without ALA-PDT. The AFR was performed with a 2940-nm Er: YAG laser using two stacked pulses at 2.3 mJ

per pulse, power of 1.15 W, a 50- $\mu$ s pulse duration, and density of 2.4%. Three months after treatment, the median complete response rate was significantly higher at 74% for AFR-DL-PDT compared with 46% for DL-PDT without AFR ( $P = 0.026$ ). A side-by-side, blinded, randomized control trial ( $n = 18$ ) found the addition of AFR resulted in a significantly higher AK clearance rate at the 3-month follow-up after DL-PDT compared with microdermabrasion pretreatment and also reduced the development of new AKs [53]. A recent proof-of-concept randomized split-side study compared the efficacy and durability of response of ALA-PDT with and without CO<sub>2</sub> laser AFR pretreatment for treatment of AK and NMSC [45]. Nineteen participants with symmetrically comparable photodamage (at least one AK/cm<sup>2</sup>) to the face, scalp, and/or distal extremities and with clinically identifiable biopsy-proven NMSC (BCC or cSCC) were enrolled. Patients received topical/regional anesthesia followed by AFR treatment to one randomly selected side with the Smart-Xide DOT laser for one pass of 25 W, 1200 ms duration at 500  $\mu$ m spacing, and a 200  $\mu$ m spot size, achieving 12% surface area ablation; hyperkeratotic areas received a second pass after saline debridement. Both sides were then treated with 20% ALA solution and incubated for 1 h, followed by blue light illumination for 16 min 40 s. At the 6-month follow-up, the pretreated sides had superior AK reduction with no AK recurrences in most participants compared with 13 cases of noted AK persistence on the contralateral conventional PDT-treated side. Notably, the results were not consistent for NMSC outcomes, with persistent NMSC in both treatment arms; however, this may have been confounded by lack of cSCC at baseline on the conventional PDT-treated sides. Lesions on the scalp and face were healed an average of 7 days post-treatment, while lesions on the forearm and hand healed within 14 days and lower extremity lesions required up to 21 days for resolution of weeping/scabbing. Despite topical/regional anesthesia, mild-to-moderate pain during treatment was reported [45].

Physical pretreatment using thermo-mechanical fractional injury (TMFI) prior to photosensitizer application has also been explored

to increase uptake. TMFI creates a fractional injury using thermal energy within 5–18 ms to create micropores by vaporizing the tissue water and creates a dry zone in the dermis and epidermis, theoretically enhancing percutaneous permeation of photosensitizers [50]. Two studies conducted in healthy individuals with Fitzpatrick skin type I–III demonstrated significantly enhanced PpIX fluorescence absorption and permeation of 5-ALA treatment into TMFI pretreated tissue compared with control sites ( $P < 0.001$ ) [41, 50]. TMFI treatment was well tolerated with only mild local skin reactions and low pain intensity noted. TMFI pretreatment has not yet been studied in combination with ALA-PDT for clinical management of AKs or NMSCs [41, 50].

### **Thermal PDT**

Another potential way to increase photosensitizer absorption is to warm the skin within a physiologically tolerable range following topical drug application, particularly anatomic areas with low natural biological temperatures. In a small ( $n = 20$ ) split-sided study investigating the efficacy of blue light PDT following 1-h temperature-modulated (38.8 °C versus 29.4 °C) incubation with 20% ALA on patients with multiple AKs on the distal extremities, the median clearance was significantly higher on the heat-treated versus control sides at both the 2-month (median percentage difference from baseline, 88.0% versus 70.5%) and 6-month (88.0% versus 67.5%) follow-ups (both  $P < 0.0001$ ). However, adverse effects (erythema, stinging/burning, and oozing/crusting) were materially higher on the heated side when compared with the control side [55]. Another small ( $n = 10$ ; 363 lesions) proof-of-concept study for facial AKs using 20% 5-ALA incubated for 20 min at a mean temperature of 41 °C (range 38–42 °C) followed by blue light illumination resulted in an average lesion clearance rate of 91.5%, with 5/10 patients achieving total clearance at the 2-month follow-up [54]. Notably, although the porphyrin intensity was significantly higher after heat treatment ( $P < 0.001$ ), 8/10 patients reported no pain during incubation, two patients reported only 3/10 mild discomfort during incubation, the

mean pain score during light treatment was 5 (range 3–9), and no patients reported pain at day 1 or week 1 [54].

### **Combination Therapy**

PDT efficacy may be enhanced by combining it with topical treatments. In a randomized, controlled, split-side study in patients with multiple Grade I–III AKs on the dorsal hands, pretreatment of the skin twice daily with 5-FU for 1 week coupled with 2 h of DL-PDT resulted in significantly greater overall mean lesion response at 3 months follow-up compared with DL-PDT alone. Notably, patients did not report pain or discomfort during DL-PDT; adverse events during the 5-FU pretreatment phase consisted of erythema and were materially, but slightly, increased in the 5-FU arm 1 day post-DL-PDT [46]. Similarly, a small, split-face, randomized, controlled trial found calcipotriol pretreatment followed by application of 16% MAL cream and 2 h of DL-PDT increased complete clinical remission among patients with multiple Grade I–III AKs on the face and scalp compared with DL-PDT alone [42]. Again, erythema was subjectively noted to be more severe among patients who received calcipotriol. The authors also note patients favored conventional PDT due to increased convenience (which may have long-term implications for adherence) [42].

### **Innovations to Improve Tolerability and Convenience: Incubation Time, Interventions, and Daylight PDT**

Improving tolerability and post-procedural downtime due to local skin reactions are desirable both to improve the patients' experience and also to increase likelihood of adherence to repeated future treatments. Pain reduction can be achieved through invasive and noninvasive interventions including nerve blocks, intravenous analgesia, cold air analgesia, or inhalational analgesia, as reviewed in Ang et al. [67]. Topical analgesia for pain reduction (e.g., morphine gel, tetracaine gel, or lidocaine and prilocaine eutectic mixtures) has also been studied, but no significant pain reduction was

observed [68–70]. Several studies have investigated the efficacy of nerve blocks to reduce pain from PDT, including a study by Klein et al. comparing nerve blocks to intravenous analgesia plus cold air analgesia, and cold air analgesia alone during scalp PDT [67, 71]. Klein et al. found that pain intervention via nerve block had the lowest pain rating score on the visual analog scale, followed by intravenous analgesia and cold air analgesia [71]. Inhalation analgesia using a 1:1 mixture of nitrous oxide and oxygen was reported to significantly decrease pain compared with controls [72]. However, since there is no standard protocol for PDT, the varying designs of these studies contributed to the observed heterogeneity of the results, and further study for different pain management practices is warranted [67]. Given that interventions for analgesia may be considered insufficient or unacceptably invasive, clinicians have also explored variations in ALA-PDT protocols, including shorter incubation time and DL-PDT, to improve tolerability.

### **Incubation Time**

While ALA-PDT-associated pain correlates with the length of incubation time on the skin, it is unclear what length of incubation optimizes photosensitizer penetration [62]. An observational kinetics study of relative changes in PpIX accumulation following application of 20% 5-ALA on multiple AKs and adjacent tissue of the face and scalp demonstrated that PpIX accumulated linearly and was statistically higher over background levels in half of lesions after 20 min and in all lesions by 2 h after application [73].

However, over the last two decades, physicians have gradually reduced the 5-ALA incubation time in clinical practice with minimal effect on therapeutic efficacy [66, 74, 75]. A randomized, vehicle-controlled study investigated broad-area application of 20% 5-ALA with various incubation times (1, 2, and 3 h) followed by blue light PDT for AKs of the face or scalp on 234 patients. Treatment with 1 h or 3 h of incubation resulted in comparable 100% lesion clearance rates (week 12, 29.8% versus 27.7%; week 24, 23.4% versus 25.5%), and both were significantly more efficacious relative to

vehicle-PDT; however, patients who underwent 1-h incubation reported materially lower rates of moderate–severe stinging/burning immediately post-PDT and at the 2-week follow-up (post-PDT, 63.8% versus 78.7%; week 2, 21.3% versus 57.4%) and erythema (post-PDT, 38.3% versus 61.7%; week 2, 2.1% versus 6.4%) compared with 3-h incubation patients [66]. In a split-face trial comparing the efficacy of blue light illumination either immediately after 20% 5-ALA application or following a 1-h incubation in patients with multiple AKs on the face and scalp, clinical efficacy at the 3-month follow-up was nearly identical between the two treated sides; however, pain was markedly reduced on the side with immediate illumination [62]. Similar results were reported in a case study in which a patient was treated with 5-ALA immediately followed by blue light PDT. The treatment was painless, and the patient's face and scalp showed near clearance of AKs at the 4-month follow-up [61]. While the mechanism behind the preservation of efficacy and mitigation of pain is unclear, it may be a result of continuous photon-driven degradation of intralosomal PpIX, which prevents excessive accumulation and diffusion of PpIX into neighboring nerves [62, 76]. Notably, a randomized, vehicle-controlled trial of broad-area PDT with 20% 5-ALA with blue light illumination for the management of field cancerization in high-risk patients also demonstrated success with a short incubation time (1 h) [27].

### **DL-PDT**

Another approach to reduce pain associated with PDT is illumination using naturally occurring ultraviolet (UV) radiation in sunlight. In a meta-analysis of six randomized, controlled trials comparing MAL with either DL-PDT (2–2.5-h sunlight exposure) or conventional red light PDT for the treatment of AKs, the pooled results showed no statistically significant difference in treatment response rates for lower-grade AKs (i.e., Grade I–II) [risk ratio (RR), 0.97; 95% CI 0.91–1.04;  $P = 0.41$ ;  $I^2 = 78\%$ ]; notably, when including studies with higher-grade (i.e., Grade III) AKs, DL-PDT had significantly less efficacy compared with conventional red light PDT (RR, 0.87; 95% CI 0.81–0.94;  $P < 0.001$ ,

$I^2 = 0$ ). These findings were not affected by the duration of the follow-up period. Patient-reported maximal pain scores were significantly lower for DL-PDT (mean difference,  $-4.51$ ;  $P < 0.001$ ) compared with conventional PDT [63]. Adverse events associated with DL-PDT include mild local skin reactions such as erythema, blistering, itching, and crusting, with scarring being a rare occurrence [77]; these are common local skin reactions experienced by  $> 90\%$  of patients treated with ALA-PDT [78]. These findings suggest DL-PDT may serve as a less painful alternative for lower-grade AK treatment.

Head-to-head, randomized split-side studies have found DL-PDT may also be efficacious in conjunction with multiple photosensitizers. In a randomized, split-side, noninferiority study comparing DL-PDT with either BF-200 ALA or MAL for the treatment of Grade I–II AKs, clearance rates after 12 weeks were comparable following one treatment session ( $79.8 \pm 23.6\%$  and  $76.5 \pm 26.5\%$ , respectively;  $P < 0.0001$  for noninferiority) [60]. The sides treated with BF-200 ALA gel also had lower 1-year recurrence rates (19.9%) compared with sides treated with MAL cream (31.6%,  $P = 0.01$ ) [60]. Another randomized split-face trial of 13 patients with a total of 177 Grade I–III AKs compared treatments using either BF-200 ALA or 16% MAL cream followed by DL-PDT and found both regimens effectively cleared AKs (by 85% with BF-200 ALA and 74% with MAL;  $P = 0.099$ ), suggesting that DL-PDT activation is not limited to only one group of photosensitizers [64].

A potential limitation of DL-PDT is its reliance on natural sunlight, which is affected by seasonal variations, ambient temperature fluctuations, and UVB emission. A small, retrospective, proof-of-concept pilot study overcame this limitation by using 35-min exposure to an indoor DL-PDT multilight lamp device emitting 415 nm (blue), 585 nm (yellow), and 635 nm (red) wavelengths sequentially to mimic the solar radiation spectrum after CO<sub>2</sub> AFR pretreatment and a 45–60-min incubation with BF-200 ALA [65]. An average of 3.5 months after one session, 72% of patients with field cancerization of the scalp, face, neck, and/or dorsal hand (defined as  $> 5$  AKs) were noted to be in

complete remission, but the maximal pain intensity reported was severe (mean  $\pm$  SD,  $9.0 \pm 2.0$  out of 10.0). Because less pain was reported in other studies using either BF-200 ALA [28, 60] or ablative fractional laser (AFL) [53] in conjunction with ALA, the authors attributed this finding to potential free radical byproducts from AFL-irradiated PpIX [65]. Interestingly, treatment of patients with mild-to-moderate AK on the face and scalp with BF-200 ALA photosensitizer and indoor simulated daylight resulted in an individual AK clearance rate of 67–100% and an overall lesion clearance rate of 85%, with half of participants reporting no pain at all in a small ( $n = 12$ ) prospective open-label trial [59].

## ORGAN TRANSPLANT RECIPIENTS

Patients who have received organ transplants are usually on immunosuppressive drugs and are at increased risk of developing NMSC, especially cSCC [58, 79, 80]. In OTR, cSCCs tend to be more aggressive and more highly metastatic than in the general population, highlighting the need for prevention in these patients [58].

Data suggest the efficacy of conventional PDT is lower in OTR patients, with complete response rate at 48 weeks after 20% 5-ALA solution for 5 h followed by visible light illumination of 0.55 (95% CI 0.38–0.71) versus 0.72 (95% CI 0.54–0.86) in immunocompetent controls [81]. While there is limited evidence for the treatment of NMSCs in OTR candidates [82], systematic reviews of randomized clinical trials have found that complete clearance rates are superior following MAL-PDT (40–76.4%) versus imiquimod (27.5–62.1%), diclofenac (41%), and 5-FU (11%) [82], and support use of PDT for preventing additional AKs/SCCs at least 3 months after treatment as well as achieving complete clearance of AK/SCC [80].

Advantages of PDT compared with surgery in OTRs include potential for treating larger affected areas and no documented reports of infection after PDT treatment. In recipients with lower pain thresholds, alternative modalities such as DL-PDT or AFL-assisted PDT can be employed to minimize treatment-associated

pain [58]. Similar to other patients with AKs, transplant recipients with cancerized fields may benefit from AFL pretreatment followed by MAL–DL–PDT [58]. In a study comparing several modalities in 16 OTR patients with multiple AKs (10 males, mean age 63 years), the median complete response after 3 months of follow-up was 74% for AFL-assisted MAL–DL–PDT, significantly higher compared with MAL–DL–PDT without AFL (46%;  $P = 0.026$ ), MAL-conventional PDT with red light LED (50%;  $P = 0.042$ ), or AFL alone (5%;  $P = 0.004$ ) [58].

Perhaps more so than in immunocompetent patients, early intervention to treat photodamaged skin might be considered prudent in OTR patients due to their increased risk for (aggressive) NMSC. A retrospective survey of patient-reported data from 2013 to 2018 revealed that field treatment initiation is most likely to be provided to transplant recipients with more advanced stages of cSCC (> 10 AKs or > 6 cSCCs) compared with those with AKs or early-stage cSCCs [79]. In the 57-point questionnaire collected from 295 patients (193 males, mean age 56 years), only 31 (11%) patients reported receiving field therapy, of which the majority were high-risk patients (defined as > 10 AKs and  $\geq 6$  cSCCs). The authors noted that this may be a missed opportunity for early intervention in a high-risk population, as early intervention with field therapy could decrease future skin cancer development [79].

## DISCUSSION AND FUTURE DIRECTIONS

Additional treatment strategies are needed to address the growing incidence of NMSC. The studies described here will provide direction for future large-scale clinical trials to define the role of PDT in field cancerization, BCC, and cSCC and to further improve ALA-PDT protocols. Although PDT has been effectively used as a nonsurgical modality in patients with NMSC for decades, 10% 5-ALA gel with red light illumination is the only treatment approved in the USA for field-directed treatment of AKs, while treatment for NMSC remains off-label. Multiple interventional studies and case reports have

found mounting evidence for the effectiveness of PDT to mitigate field cancerization and treat patients with superficial or nodular BCC and cSCC. Although no studies on SCC are currently recruiting, there are several ongoing clinical trials evaluating efficacy and efficiency of ALA-PDT in patients with BCC (Table 6).

There is also a great deal of interest to develop methods to minimize PDT-associated pain and discomfort both by using alternative light sources (such as daylight, PDL, or IPL) instead of conventional light as well as by modifying how photosensitizers are administered. Field cancerization treatments, including PDT, require frequent administration, and patients with decades of ultraviolet damage need repeated treatments to obtain complete clearance. Therefore, aspects of treatment that maximize future adherence—such as minimizing pain and other adverse events, covering larger surfaces in a single treatment, decreasing incubation times, and decreasing the frequency at which treatment is needed—may be as important as the efficacy of a single treatment. Occlusion of the treatment area during incubation might allow further reduction of incubation time, but the effects of such occlusion on both efficacy and PDT-associated pain should be explored. Research is also active in novel ways to improve photosensitizer penetration, including pretreating the lesions with AFR or TMFI, with the clinical efficacy and safety of the latter remaining to be explored. Finally, combination of PDT with other topical and physical modalities used for the treatment of AK and NMSC seems to hold potential and is an area for future research.

Although PDT is a commonly used modality, there is a striking paucity of clinical and real-world studies in the published literature. Additional research is needed to evaluate combination therapies using different light sources, photosensitizing agents, pretreatments, and different incubation times, as well as how PDT may complement prescription topical and potentially systemic regimens. Furthermore, clinical studies should include a greater diversity of patients with respect to Fitzpatrick skin types, age groups, and anatomic locations to appropriately evaluate PDT efficacy across

**Table 6** Ongoing clinical trials

Trial number	Intervention	Patient population	Primary outcome measure
NCT04936932 <sup>a</sup>	To examine nonablative laser treatment in sBCC	20 adult participants (Phase N/A)	Complete clearance of BCC
NCT05020912 <sup>a</sup>	To understand the immune response to BCC treated with PDT to develop new methods of treating BCC	28 patients with biopsy-proven BCC (Phase 2)	(1) Time to maximum expression of immune checkpoint molecules (2) Altered expression of immune checkpoint molecules (3) Altered recruitment of different immune cell subtypes in BCC tumor specimens
NCT03573401 <sup>a</sup>	To compare the safety and efficacy of BF-200 ALA and PDT-lamp BF-RhodoLED® to placebo in sBCC	186 adult patients with sBCC (Phase 3)	Composite clinical and histological response main target lesion at 12 weeks from baseline <sup>c</sup>
NCT04552990 <sup>a</sup>	Safety assessment of injecting 5-ALA into the skin with a jet-injection device and activating the drug with light	17 adult patients with mixed sBCC and nBCC or only nBCCs (Phase 2)	Clinical evaluation of local skin responses up to 3 months
NCT02367547 <sup>b</sup>	To compare three photosensitizers: HAL, BF-200 ALA, and MAL	117 adult patients with sBCC (Phase 1 and 2)	Histological lesion clearance up to 5 years
NCT03110159 <sup>a</sup>	Comparative study to evaluate the safety and efficacy of the cyclic PDT for the prevention of AK and NMSC in solid OTRs	20 patients (OTR) (Phase 1 and 2)	Prevention of AKs and NMSC in recently transplanted OTR; time to occurrence of AKs and NMSC in OTR

*AK* actinic keratosis, *ALA* aminolevulinic acid, *BCC* basal cell carcinoma, *HAL* hexyl aminolevulinate, *MAL* methyl aminolevulinic acid, *N/A* not available, *nBCC* nodular BCC, *NMSC* nonmelanoma skin cancer, *OTR* organ transplant recipient, *PDT* photodynamic therapy, *sBCC* superficial BCC

<sup>a</sup>Recruiting

<sup>b</sup>Active not recruiting

<sup>c</sup>Baseline defined as the start of the last PDT cycle that included treatment of the main target lesion

populations. Finally, advances in our understanding of tumor biology may assist in the identification of early-stage BCC, cSCC, and even cancerized fields that may respond more robustly to PDT.

## CONCLUSION

Various forms of PDT are being used successfully for treatment of BCC, cSCC, and field

cancerization, as well as individual AKs. Clearance rates higher than 90% have been reported in patients with multiple mild-to-moderate AKs and BCC. Improvements in terms of illumination technologies and photosensitizer application and delivery have been investigated and demonstrated to have potential for success. Further studies are warranted to determine how protocols may be optimized to improve efficacy and duration of lesion clearance, as well as patient experience, thereby potentially

improving long-term adherence for a chronic condition, especially among high-risk individuals.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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