Review Article

Skin Appendage Disorders

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Photodynamic Therapy and Skin Appendage Disorders: A Review

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Key Words

Photodynamic therapy · Hidradenitis suppurativa · Acne · Sebaceous hyperplasia · Onychomycosis

Abstract

Photodynamic therapy (PDT) is a noninvasive treatment that utilizes light treatment along with application of a photosensitizing agent. In dermatology, PDT is commonly used and approved for the treatment of oncological conditions such as actinic keratosis, Bowen disease and superficial basal cell carcinoma. In the last 2 decades however, PDT has also been used for the treatment of several nonneoplastic dermatological diseases. The present review summarizes published data on PDT application in skin appendage disorders. Our literature review shows that: (a) PDT may be a suitable treatment for acne, folliculitis decalvans, hidradenitis suppurativa, nail diseases, and sebaceous hyperplasia; (b) there is a lack of agreement on PDT features (type, concentrations and incubation period of used substances, number and frequency of PDT sessions, optimal parameters of light sources, and patient characteristics [e.g., failure to previous treatments, disease severity, body surface area involved, etc.] which should guide PDT use in these diseases); (c) further research is needed to establish international guidelines helping dermatologists to choose PDT for the right patient at the right time.

Introduction

Photodynamic therapy (PDT) is a noninvasive treatment that utilizes light treatment along with an application of a photosensitizing agent in the presence of molecular oxygen [1–3]. The scientific basis of PDT has been recognized since 1900; Oscar Raab and Herman von Tappeiner were first to report the concept of cell death being induced by the interaction of light and chemicals [4–5]. Shortly afterwards, von Tappeiner and Jesionek [6] performed the first medical application in dermatology, using a combination of topical eosin and white light to treat skin tumors. Nevertheless, numerous studies have then concentrated on the potential role of photosensitizing agents such as porphyrins and their derivatives for detection and treatment of different tumors [7], clinical therapeutic applications of PDT in dermatology were performed only 70 years later [6, 7]. Particularly, in 1978, Dougherty [8] reported the first large series of patients with primary or secondary skin tumors successfully treated with PDT (treatment with a hematoporphyrin derivative followed by exposure to red light from a xenon arc lamp). Nowadays, PDT use in dermatology involves light sources such as laser, intense pulsed light, light-emitting diodes, blue light, red light, and many other visible lights including natural sunlight [1–3]; as regards photosensitizers, the common employed agents

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are 5-aminolevulinic acid (ALA), a naturally occurring intermediate in the heme biosynthetic pathway, and its methyl ester named methyl aminolevulinate (MAL) [1–3]. Particularly, ALA and MAL have no intrinsic photosensitizing effect; efficacy is due to their tissue metabolization, by heme pathway enzymes, to the potent photosensitizer protoporphyrin IX together with interaction with molecular oxygen and light exposure [7, 9]. These substances are applied to the skin, causing the skin to become more susceptible, or receptive, to light. Particularly, the agent is applied to the desired cutaneous area and allowed to be absorbed for a particular length of time. After the photosensitizing agent is removed, a light treatment is administered. Generally, PDT involves the light activation of a photosensitizer to create cytotoxic oxygen species and free radicals that selectively destroy rapidly proliferating cells [1–10]. Indeed, it has become an established treatment modality for oncological conditions like actinic keratosis, Bowen disease, and superficial basal cell carcinoma [11]. PDT has however also been found to be effective for the treatment of several nonneoplastic dermatological diseases like photo-aged skin, leishmaniasis, hidradenitis suppurativa (HS), sebaceous hyperplasia, acne vulgaris, etc. [1]. In addition to antitumor activities, experimental studies on PDT have demonstrated a variety of antimicrobial, anti-inflammatory and immune modulation effects as well as evidence of influence on keratinocytes, fibroblasts, mast cells, sebaceous glands, and hair follicles [12]. This review focuses on off-label use of PDT in skin appendage disorders such as acne, HS, sebaceous hyperplasia and nail diseases, analyzing the published body of evidence and studies regarding PDT in this class of diseases.

Material and Methods

We searched for English-language literature regarding PDT treatment for skin appendages disorders such as acne, HS, sebaceous hyperplasia, folliculitis decalvans (FD) and nail diseases in the following databases through September 20, 2016: PubMed, Embase, The Cochrane Library, Google Scholar, EBSCO and Scopus. The following key words were used: "photodynamic therapy," "treatment," "acne," "hidradenitis suppurativa," "nail diseases," "onychomycosis," "sebaceous hyperplasia," "folliculitis decalvans," "5-aminolevulinic acid," and "methyl aminolevulinate." Only studies including full details about used photosensitizer, incubation time, light source, and treatment session duration were analyzed in the present review.

Acne

Acne is one of the most common skin diseases, possibly affecting up to 80% of young people [13]. Acne is not only an aesthetic concern as it can leave disfiguring scars which may cause significant psychological distress [14]. It is an inflammatory disease of the pilosebaceous unit, and it is well known that follicular hyperkeratosis, *Propionibacterum acnes* colonization, and sebum secretion play a major role in acne pathogenesis [15]. PDT with ALA may be a suitable treatment for acne since ALA is metabolized to protoporphyrin IX, a photosensitizer that can also accumulate in pilosebaceous units [16–18]. Studies have shown that ALA-induced protoporphyrin IX fluorescence is greater in an acne lesion than in the surrounding skin area, being also correlated with *P. acnes* colonization of sebaceous follicles [18]. Indeed, *P. acnes* can produce porphyrins, and topical ALA can cause preferential accumulation of porphyrins in *P. acnes* [18, 19]. Therefore, topical ALA-PDT can impact acne treatment in different ways such as direct photodynamic injury of sebaceous glands with inhibition of sebum production, photodynamic killing of *P. acnes* and reduction of follicular obstruction through changing keratinocytes shedding and hyperkeratosis [18]. Therefore, ALA-PDT is able to inhibit multiple pathogenetic factors of acne [18]. It is important to note that a transient acneiform eruption, similar to the one due to systemic retinoid, may occur 3–4 days after the first ALA-PDT treatment. In addition, both ALA-PDT and MAL-PDT, which may be often painful, may also cause inflammatory side effects, and/or residual photosensitivity [18]. ALA-PDT treatment was first reported as a possible therapy for acne patients in 2000 by Hongcharu et al. [18] who showed a greater, longer and more sustained efficacy in patients receiving 4 versus 1 PDT treatment session (50 vs. 30% reduction of acne) and significant reduction of sebum output. Improvements usually started 3 weeks after PDT first session. Almost at the same time, other authors showed ALA-PDT efficacy in acne treatment, reporting also that improvements lasted for at least 6 months and that 1 PDT session may be not enough [20, 21]. Nevertheless, almost 16 years have passed since the first studies on ALA-PDT in acne therapy; there is still no consensus on how to perform PDT for acne treatment, and its use still remains an off-label option for acne patients [22]. Despite numerous studies on PDT in acne (mainly mild to severe acne on the face but also acne lesions on the back and acne conglobata) [1, 18, 20, 21, 23–42] (Table 1), they are generally difficult to compare because of the lack of controls, qualitative non-

Table 1. Studies on PDT use in acne

First author [Ref.]	Patients, *n*	Photosensitizer	Incubation time	Light source	Treatment session and duration
Hongcharu [18]	22	20% ALA	3 h	Broadband light (550–700 nm) at 150 J/cm^2	4 sessions at 1-week interval
Itoh [20]	1	20% ALA	4 h	Pulsed excimer dye laser (635 nm) at 5 J/cm^2	1 session
Itoh [21]	13	20% ALA	4 h	Polychromatic visible light (600–700 nm) at 13 J/cm^2	1 session
Wiegell [23]	21	16% MAL	3 h	Red light at 37 J/cm^2	2 sessions at 2-week interval
Wiegell [24]	15	20% ALA or 16% MAL	3 h	Red light at 37 J/cm^2	1 session
Horfelt [25]	30	16% MAL	3 h	Red light (635 nm) at 37 J/cm^2	2 sessions at 2-week interval
Kimura [26]	51	ALA	4 h	Polychromatic visible light (540–800 nm) at 60–80 J/cm^2	2 sessions at 2- to 4-week interval
Gold [27]	20	20% ALA	1 h	Intense pulsed light (430–1,100 nm) at 3–9 J/cm^2	4 sessions at 2-week interval
Taub [28]	18	ALA	15–30 min	Blue light	3–6 sessions at 2-week interval
Alexiades-Armenakas [29]	19	ALA	45 min	Long pulsed dye laser (595 nm) at 7.0–7.5 J/cm^2	Variable
Santos [30]	13	20% ALA	3 h	Intense pulsed light (560 nm) at 26 J/cm^2	2 sessions at 2-week interval
Rojanamatin [31]	14	20% ALA	30 min	Intense pulsed light (560–590 nm) at 25–30 J/cm^2	3 sessions at 3- to 4-week interval
Yeung [32]	13	16% MAL	30 min	Intense pulsed light (530–750 nm) at 7–9 J/cm^2	4 sessions at 3-week interval
Pollock [34]	10	20% ALA	3 h	Red light (635 nm) at 15 J/cm^2	3 sessions at 1-week interval
Hong [35]	8	20% ALA	4 h	Red light (630 ± 63 nm) at 18 J/cm^2	1 session
Akaraphanth [36]	20	10% ALA	1 h	Blue light (415 ± 5 nm) at 48 J/cm^2	4 sessions at 1-week interval
Chen [37]	50	5% ALA	1.5 h	Infrared radiation	3 sessions at 1-week interval
Yew [38]	15	5% ALA	3 h	Red light (630 nm) 37 J/cm^2	1 session
Tao [39]	136	3.6% ALA	1.5 h	Red light (633 ± 3 nm) at 126 J/cm^2	3 sessions at 2-week interval
Asayama-Kosaka [40]	11	5% ALA	2 h	Broadband light (600–1,100 nm) at 15 J/cm^2	1 session
Yang [41]	75	5% ALA	3 h	Red light (633 ± 10 nm) at 50 J/cm^2	Every 10 days for 1 month
Fabbrocini [42]	10	10–15% ALA	1 h	Red light (550–700 nm) at 15 J/cm^2	3 sessions at 2-week interval

blinded methods, variable light dosimetry, and an extremely wide variation of the incubation time between drug application and light exposure. All these differences should not be neglected. Indeed, it is well known that many variables may enhance or interfere with PDT action such as delivery vehicle, concentration of ALA or MAL, availability of oxygen in the target tissue, metabolic capacity for heme synthesis in the target tissue, incubation time of the drug in the tissue before irradiation, wavelength of light used in treatment, light fluence, and irradiance [22, 43]. Generally, it can be speculated that low drug concentration, low light fluence, short incubation time between drug application and light exposure, and use of blue light with minimal penetration depth constitute a "low-dose" PDT treatment which can determine a temporary improvement of acne by transient antimicrobial or immunomodulatory mechanisms [22]. Conversely, "high-dose" PDT effects are presumably related to reduction/destruction of sebaceous gland function, favored by prolonged application of high ALA concentration followed by high-fluence red light [18, 22]. Moreover, even if an antibiotic effect of PDT has been described [44, 45], studies evaluating the quantity of *P. acnes* after PDT show opposite results, reporting only partial or absent bacterial reduction [46, 47]. Possible PDT mechanisms of action in acne may be numerous and complex, involving reduction of follicular obstruction and hyperkeratosis [48], a down-regulating effect on infiltrating inflammatory cells within acne lesions and reduction of the increased expression of Toll-like receptor (TLR)-2 that has been implicated in inflammatory response against the acne-related sebocytes [22]. Literature review shows that both ALA or its esters delivered topically or orally have been studied for PDT of acne [45, 49, 50]. PDT for acne has not been optimized, including topical preparation, dose-response, conditions for metabolism to porphyrins, and light exposure [49, 50]. Generally it can be stated that longer incubation times (≥3 h) are associated with long-term acne remission and that ALA-PDT and MAL-PDT have been shown to produce similar effects for acne treatment when used with high-dose conditions (long incubation time, high fluence red light exposure) [49]. Moreover, with regard to PDT activation, continuous wave, high-intensity red light sources have deeper penetration and are more likely to produce sebaceous gland destruction compared with blue light or pulsed light sources. More detailed conclusions

may be drawn. For example, Weigell and Wulf [24] conducted a randomized, split-face, blindly assessed study comparing topical 20% ALA with 16% MAL, showing no statistical difference in treatment efficacy and pain between the two drugs. PDT treatment responses are very variable, with the most significant studies (clinical trials with control groups) showing a response rate of 100% with a mean reduction in inflamed lesions of 27.6, 37.9, and 41.9% at 1, 3, and 6 months, respectively [29, 35, 41]. Generally, the effective rate was seen to rise significantly in proportion to the severity of acne [50]. With regard to the light source, continuous, high-intensity red light sources, including lasers and broad-spectrum and light-emitting diodes, have shown best results in long-term follow-up studies using either ALA or MAL for PDT of acne, but there is no consensus about optimal light dosimetry and irradiance [49]. Various skin preparations have been used in different clinical studies of PDT for acne, which creates a confounding variable when comparing the results. Generally, skin occlusion may increase drug uptake; when using ALA, degreasing skin might help drug penetration, whereas lipophilic esters might not require skin cleansing. At this point, no comparative studies have been performed [27, 29, 35, 49]. Pain, acute inflammatory skin reactions, and transient skin tanning are the most common side effects of both ALA-PDT and MAL-PDT, which are linked to accumulation of porphyrins in the epidermis. Therefore, patients should be advised to avoid bright light exposure after treatment because of persistent phototoxicity up to 48 h [49]. Permanent effects such as ulceration or scarring are rare, whereas inflammatory and pigmentary side effects may be common. Other adverse effects include erythema (common, typically reported to last 3–5 days, but occasionally up to 4 weeks), edema (common, typically 1–4 days after treatment), formation of blisters (rare), sterile pustular eruption (starting on the second or third day after treatment, lasting typically 3 days, after high-fluence red light PDT), and crusts (30% of patients, starting on the second to fourth posttreatment day), purpura, acute transient acne flare (3–4 weeks after treatment), exfoliation (4–10 days), contact hypersensitivity/irritation (rare, lasting 10 days), postinflammatory hyperpigmentation for 4 weeks to 3 months, and induction of herpes simplex eruptions in predisposed patients [18, 21, 23, 34, 36, 49]. Obviously, the intensity of side effects is related to light source and light dosimetry with high-dose red light PDT being associated with higher rates of side effects. In conclusion, PDT for acne has been extensively studied in the recent years and has been found to be effective, but its use in acne is still off-label. Both patients and dermatologists search for prolonged or permanent results with minimal side effects. This is a challenge for every treatment, especially PDT in acne, since it has not been optimized. Clinical results depend on the way PDT treatment is performed, including skin preparation, which drug is applied and for how long, whether skin occlusion is used, light source as well as light treatment parameters. Manipulating these variables, PDT can be performed in a wide variety of methods with an extremely extensive variability in efficacy, adverse events, costs, etc.

Hidradenitis Suppurativa

HS is a long-term, distressing skin condition showing multiple painful abscesses, keloids, and fistulas in several skin areas, such as the armpits, groin, and genital region.

The etiology of HS remains controversial and under investigation: probably it is caused or exacerbated by aberrant cellular immunity and dysfunction of the hair follicle in which coagulase negative staphylococcus and perhaps other bacteria appear to play a role by stimulating the immune system [51]. HS typically begins in early adulthood, showing a large impact on quality of life because of pain, scarring, and low self-esteem. [51]. HS treatment choices should be influenced by disease severity and the impact of the disease on patient's quality of life. Several authors have suggested new staging techniques, as well as therapeutic management proposals. According to recent guidelines, among topical therapies, clindamycin is the only antibiotic that has been studied as a topical agent for HS [52–54]. Systemic therapies are significantly more used. The combination of clindamycin (300 mg bid) and rifampicin (600 mg daily given either as 1 or 2 doses) for 10 weeks has been proved beneficial in more widely spread Hurley stage I or mild stage II disease [55–57]. Significantly lower results are reported with acitretin, cyclosporin A, oral dapsone, oral isotretinoin [58–60]. Moreover, the European Medicine Agency has recently accepted HS as an indication of a monoclonal anti-TNF-α antibody such as adalimumab [61–63]. These interventions are able to achieve acceptable outcomes even if they are not able to prevent disease recurrence, being often disfiguring and not always curative [64]. Other treatments which have also been proposed for HS include PDT (Table 2). It is well known that PDT shows antibacterial effects [44, 45] and that the role of a bacterial component could be considered in HS pathogenesis. PDT likely benefits HS because it disrupts

Table 2. Studies on PDT use in HS

First author [Ref.]	Patients, *n*	Photosensitizer	Incubation time	Light source	Treatment session and duration
Fadel [67]	11	Niosomal methylene blue gel	30 min	Intense pulsed light with a 630-nm filter at 25 J/cm^2	12 sessions at 2-week interval
Andino Navarrete [70]	5	20% ALA	1.5 h	Red light (635 nm) at 37 J/cm^2	4 sessions at 1- to 2-week interval
Schweiger [71]	12	20% ALA	2 h	Two blue light sources and intense pulsed light	4 sessions at 1-week interval
Fabbrocini [73]	15	10% ALA	2 h	Red light (630 nm) at 15 J/cm^2	6 sessions at 1-week interval
Rodríguez-Prieto [74]	3	1% ALA	3 h	A diode laser beam of 630 nm applied with a fiberoptic probe at a strength of 1 W to each 1-cm^3 area for 3 min	1 session
Valladares-Narganes [75]	30	16% MAL	3 h	Red light (635 nm) at 37 J/cm^2	2 sessions at 2-week interval
Agut-Busqet [76]	7	Intralesional methylene blue	15 min	Red light (635 nm) at 37 J/cm^2	2 sessions at 2-week interval

the biofilm that is commonly created by *Staphylococcus epidermidis* and *Staphylococcus aureus* in HS lesions [65]. The effect of *S. epidermidis* on the human skin is controversial. According to some authors, it seems to be part of the normal skin flora, and therefore it would be responsible for infectious and inflammatory processes in very few cases [65]. Conversely, other authors have dealt with PDT for the treatment of *S. epidermidis* as an infection rather than as a mere colonizer [65]. Many studies showed the efficacy of PDT against this bacterial component, with different types of methods and photosensitizers. The substance that is activated by PDT is usually ALA or MAL, which is applied topically as a photosensitizer before activation with visible light. Most clinicians recommend that MAL should be used under occlusion for 3 h before red light therapy. The advantages of topical PDT include the ability to treat multiple lesions simultaneously, its low invasiveness, good tolerance, and positive cosmetic results. The clinical heterogeneity of HS suggests that its response to treatment will be heterogeneous. Among others photosensitizers, excellent results were obtained with methylene blue [66, 67], toluidine blue [68], neutral red [69], rose bengal [70], and tetrasubstituted N-methyl-pyridylporphine [71]. Several authors reported studies on patients with HS treated with the protocol based on ALA-PDT and MAL-PDT as photosensitizers and light sources at 635 nm [70–73]. Treatment effectiveness was evaluated using the Sartorius severity score and the Dermatology Life Quality Index. Significant improvements were registered, and the effects remained visible at 8 weeks. Schweiger et al. [71] reported 12 subjects treated with ALA PDT once weekly for 4 weeks. In these cases, treatments were more tolerable for subjects treated with blue light than with intense pulsed light. Uncertain results have been obtained with intralesional PDT [74–75]. Agut-Busquet et al. [76] recently reported a retrospective experience in the treatment of HS with PDT using intralesional methylene blue and a 635-nm light-emitting diode lamp in 7 patients. At 1 month follow-up, good response was achieved in 6 patients. After 6 months, 5 patients (71%) maintained remission of the disease in the treated area. The type of photosensitizer to be preferred and how to apply these agents are widely-debated issues. There are a number of drug delivery systems available to increase drug delivery to the target organ. Niosomes are nonionic surfactant-based liposomes and, as a novel drug delivery system, can play an important role in improving the topical delivery of photosensitizers. Fadel and Tawfik [67] enrolled 11 patients with HS in their study, which was a randomized split-body study: one side of an anatomical site was randomized to receive niosomal methylene blue (NMB) gel PDT or free methylene blue (FMB) gel PDT once every 2 weeks for up to 6 months. Drug release from the FMB gel was significantly higher ($p > 0.05$) than from the NMB gel. Lesions showed a 77.3 and 44.1% reduction on the NMB and FMB sides, respectively. A significant reduction in the Hidradenitis Suppurativa Lesion, Area and Severity Index (HS-LASI) after treatment was elicited in both groups, with no pain, erythema, or hyperpigmentation. The most recent and up-to-date review on PDT treatment for HS, analyzing studies and case series on 64 patients, suggest that MAL-PDT or intralesional ALA-PDT may be the best PDT modalities to treat HS, acting as an adjuvant to therapies such as clindamycin and rifampicin [74].

Greater absorption of ALA together with higher production of protoporphyrin IX in hair follicles compared to other tissues has been suggested as the mechanism of action of PDT for HS [70]. The enigmatic nature of HS continues to challenge clinicians. PDT shows mixed results for the treatment of HS, together with the lack of standardized PDT treatment modalities (type of light source, photosensitizer agent, number of treatments, etc.). Its efficacy is based on the ability of PDT to both break up biofilms and kill bacteria [74].

Nail Diseases

Nail diseases are very numerous. They stand out due to their etiology and pathogenesis, as well as clinical manifestations, often linked by difficult therapeutic management. Here, onychomycosis and nail psoriasis deserve special interest. Onychomycosis is a common fungal infection of the nails that is increasing in prevalence in the old, diabetics, and immunocompromised subjects. Onychomycosis presents a therapeutic challenge that can lead to significant reductions in quality of life leading to both physical and psychological consequences. Current treatment modalities are difficult to implement due to the poor penetration of topical treatments to the nail bed, the slow growing nature of nails and the need for prolonged use of topical and/or oral medications [77]. Nail psoriasis is estimated to affect 80% of psoriatic patients at some time during their lives [78]. The main clinical features are pitting and ridging as expression of nail matrix involvement, and onycholysis, "oil drop" change, subungual hyperkeratosis, and splinter hemorrhages as involvement of the nail bed and hyponychium. The majority of patients (93.3%) consider their nail changes cosmetically disturbing, and most of them (58%) suffer from pain [79–81]. Treatment of nail psoriasis is disappointing, with only 19.3% of patients showing marked improvement during any topical treatment. In addition, 77% would like to receive a more effective therapy for their nails [80, 82]. Traditional topical and systemic treatments are sometimes ineffective for these two conditions. For onychomycosis, oral antifungals in combination with topical treatments have to be extended by a year or more. Typical medications include polyenes (amphotericin B and nystatin), azoles (itraconazole and miconazole), and allylamine and thiocarbamates (terbinafine and tolnaftate) [81]. Conversely, treatment for nail psoriasis includes topical therapies, such as corticosteroids, tazarotene, calcipotriol, cyclosporin, anthralin, and 5-fluorouracil. Other treatment choices include injected corticosteroids, and local or systemic psoralen plus ultraviolet A [82]. Watanabe et al. [83] looked at 2 patients with onychomycosis, whose nails were incubated with ALA for 5 h before using a 630-nm light to activate it. Patients were treated once weekly until there was clinical improvement of the onychomycosis. Complete clinical and mycological cure was observed at 3 months in one patient and 6 months in the other. Piraccini et al. [84] used ALA-PDT in a 78-year-old patient with onychomycosis. An incubation time of 3 h was performed. A diode laser emitting broad band red light at 630 nm was used delivering 37 J/cm^2 over 7 min. No pain or local affects were seen, and complete clinical and mycological cure was seen at 2 years of follow-up. Sotiriou et al. [85] looked at 20 men and 10 women who had *Trichophyton rubrum*-confirmed onychomycosis who also had contraindications to receiving oral antifungals. The patients were followed for 18 months after 3 treatments with 2-weekly intervals; 13 patients were cured according to clinical and mycological evaluation at 1 year, but only 11 maintained clearance of the infections at 18 months. Based on the literature, Robres et al. [86] proposed a protocol of 3 PDT sessions, separated by an interval of 1 or 2 weeks, using MAL 16% as a photosensitizing agent and red light (630 nm, 37 J/cm^2). Each session was preceded by the topical application of urea 40% over several days. The photosensitizing agent most used in the literature for onychomycosis treatment was 20% ALA or its derivative 16% MAL. 2% methylene blue and a hematoporphyrin derivative are other 2 effective photosensitizers (Table 3). Most authors reported a clinical and microbiological cure rate of 90–100% following treatments. PDT efficacy depends however on the pretreatment of the nail with urea and/or mechanical abrasion to increase its permeability to the photosensitizing agent and active removal of hyperkeratosis [85, 87].

Among nail psoriasis, Fernández-Guarino et al. [80] compared the efficacy of PDT and pulsed-dye laser (PDL) in the treatment of nail psoriasis (Table 3). They studied 61 nails treated with PDT, and 60 nails with PDL among 14 patients. MAL was used as a photosensitizer for 3 h using a bioadhesive patch. The nails treated were evaluated at baseline, and after 3 and 6 months. A decrease in the Nail Psoriasis Severity Index (NAPSI) score was observed. No statistical differences were found between PDT and PDL ($p = 0.632$, $p = 0.084$, $p = 0.535$, at baseline, and 3 and 6 months, respectively), and between nail matrix and nail bed NAPSI scores ($p = 0.423$ and $p = 0.853$, respectively). Additional PDT with methylaminolevulinic acid or tazarotene did not significantly change the NAPSI results;

Table 3. Studies on PDT use in nail diseases

First author [Ref.]	Patients, *n*	Photosensitizer	Incubation time	Light source	Treatment session and duration
Fernández-Guarino [79]	14 (NP)	16% MAL	3 h	Pulse dye laser	6 sessions at 4-week interval
Aspiroz [80]	1 (O)	16% MAL	3 h	Red light (635 nm) at 37 J/cm^2	3 sessions at 2-week interval
Watanabe [83]	2 (O)	20% ALA	5 h	Pulsed laser light (630 nm) at 100 J/cm^2	6–7 sessions at 1-week interval
Piraccini [84]	1 (O)	16% MAL	3 h	Red light (630 nm) at 37 J/cm^2	3 sessions at 2-week interval
Sotiriou [85]	30 (O)	20% ALA	3 h	Red light (570–670 nm) at 40 J/cm^2	3 sessions at 2-week interval
Robres [86]	Literature review (O)	16% MAL	3 h	Red light (630 nm) at 37 J/cm^2	3 sessions at 1- to 2-week interval
Souza [87]	22 (O)	2% methylene blue	None	Red light (630 nm) at 36 J/cm^2	12 sessions at 2-week interval

O, onychomycosis; NP, nail psoriasis.

however, a significantly higher percentage of patients had improvement after 6 months of treatment with topical tazarotene plus PDL than after tazarotene treatment alone [88, 89].

The optimal treatment for a patient depends on many individual factors, such as the impact on quality of life, disease severity, nail bed or nail matrix disease, number of involved nails, compliance and other comorbidities. Within the small possibility of therapeutic options, PDT can be considered an alternative therapy for described nail diseases, despite variable results found in the literature.

Sebaceous Hyperplasia

Sebaceous gland hyperplasia (SGH) is a benign cutaneous condition often presenting as a sign of photoaging. These lesions are a common cosmetic concern and have proven to be difficult to treat. Due to the well-known possible accumulation of porphyrins in sebaceous glands, PDT may be an effective treatment option. Gold et al. [90] reported that ALA-PDT with either blue light or intense pulsed light photoactivation may provide therapeutic benefit without significant adverse effects in patients with SGH. Particularly, they showed more than a 50% reduction in the number of SGH lesions after 4 months of therapy (1 session per month) after a total of 12 weeks of follow-up. A very recent review reported that PDT, lasers, and combinations of the two treatments were found to offer alternatives to the more conventional techniques with better outcomes for SGH. In particular, the combination PDT with ALA and pretreatment with carbon dioxide laser ablation or pulsed-dye laser was shown to offer higher cure rates over stand-alone laser or PDT treatments in a shorter number of sessions with similar transient side effects [91]. The ALA-PDT and carbon dioxide laser association was also demonstrated by another study where CO_2 laser ablation was performed before ALA application to reduce lesion size and facilitate access of ALA and light, showing a higher marked improvement rate compared to PDT alone [92].

PDT combination treatments were also evaluated by Alster and Tanzi [93] who demonstrated that a combination of topical ALA-PDT and 595-nm PDL treatment (topical 20% ALA followed 1 h later by 595-nm PDL irradiation) effected better clinical results than PDL treatment alone. Side effects were mild and limited to transient erythema, edema, and focal crusting, offering a safe and effective therapy for sebaceous hyperplasia. In addition, Richey [94] recently performed a thorough review of the literature on the role of PDT in SGH patients, concluding that ALA PDT represents a safe and effective modality for the treatment of SH lesions of all sizes (Table 4). The author showed that 1-h ALA incubation time is sufficient to achieve clearance, and that ALA-induced protoporphyrin IX may be activated with a 585-nm PDL device, blue light source, or an intense pulsed light device. Complete clearance may be achieved with 1–6 treatments, but long-term recurrence rates are not established yet. The author, however also concluded that such studies on SGH are limited by the small sample size and short follow-up times after treatment (average 5.33 months). Therefore, future larger-powered studies are required to determine the most optimal treatment modality, which resolves the lesions long term in a shorter number of treatment sessions with the smallest side effect profile.

Table 4. Studies on PDT use in sebaceous hyperplasia

First author [Ref.]	Patients, *n*	Photosensitizer	Incubation time	Light source	Treatment session and duration
Gold [90]	12	20% ALA	30–60 min	Blue light (405–420 nm) or intense pulsed light (500–1,200 nm)	4 sessions at 4-week interval
Kim [92]	8	20% ALA	4 h	Red light (630 nm) at 50–120 J/cm^2	1–5 sessions at 4-week interval
Alster [93]	10	20% ALA	1 h	Pulsed dye laser (595 nm)	1–2 sessions at 6-week interval

Table 5. Studies on PDT use in FD

First author [Ref.]	Patients, *n*	Photosensitizer	Incubation time	Light source	Treatment session and duration
Castaño-Suárez [97]	1	16% MAL	3 h	Red light (630 nm) at 37 J/cm^2	2 sessions at 2-week interval (cycle repeated 2 times at 8-week interval)
Miguel-Gomez [98]	10	16% MAL	3 h	Red light (630 nm) at 37 J/cm^2	4 sessions at 4-week interval
Burillo-Martinez [99]	3	16% MAL	3 h	Red light (630 nm) at 37 J/cm^2	Mean of 11 PDT sessions during a mean of 9 months

Folliculitis Decalvans

FD is a chronic neutrophilic inflammation of the scalp characterized by painful, recurrent purulent follicular exudation resulting in primary cicatricial alopecia [95]. Surviving hairs may group so that multiple hairs are seen emerging from a single follicular orifice (tufted folliculitis). Treatment is extremely difficult with a resulting poor prognosis and with disease activity frequently expanding over many years. FD etiology is still not clear, but it may represent an interaction between bacteria (mainly *S. aureus*) and the host with immune system involvement. PDT, especially MAL-PDT, has also been proposed for FD since it presents immunomodulatory, anti-inflammatory, and bactericidal activity due to its phototoxic effects, preventing the proliferation of *S. aureus* apart from the well-known possible accumulation of porphyrins in the pilosebaceous unit [96]. However, studies on this topic are not so numerous [97–99] (Table 5). The most interesting data came from Miguel-Gomez et al. [98], who performed a protocol of 4 sessions of MAL-PDT at 4-week intervals in 10 FD patients with clinical improvement in 90% of cases. Four months following the first treatment, the clinical response persisted in 60% of cases even if half of these patients required another therapy to maintain the response. The literature, however, has also shown an experience with 3 patients who were unsuccessfully treated with MAL-PDT (2 patients showed mild improvement immediately after PDT sessions but early relapse occurred before the next cycles) [99]. Limited data are available regarding PDT in the treatment of FD. Further randomized control studies are required to determine the eventual long-term effectiveness and the factors that would predict the therapeutic response to PDT in patients with FD.

Conclusion

PDT has been studied and found to be an effective treatment modality for different skin appendage diseases such as acne, FD, HS, nail diseases, and sebaceous hyperplasia; however, more research is needed to establish standard guidelines regarding the type, concentrations, and incubation period of photosensitizers, and optimal parameters of light sources. Further studies are also needed to better identify what patient features (e.g., failure to previous treatments, disease severity, body surface area involved, etc.) should guide PDT use in these diseases, helping the dermatologist to choose PDT for the right patient at the right time.

Disclosure Statement

The authors have no conflicts of interest to declare.

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