A Review of Photodynamic Therapy for Inflammatory Skin Diseases

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Photodynamic therapy (PDT) is a light treatment involving application of a photosensitizing drug or prodrug, which preferentially deposits in the target cells followed by drug activation via illumination with visible light. The primary advantages of PDT over many conventional treatments include excellent cosmetic results and low invasiveness. Photodynamic therapy was initially developed as an anticancer therapy; however, the range of off-label indications has been continuously expanding. This has cultivated interest in the utilization of PDT to widen the treatment options available for inflammatory skin conditions. This article provides up-to-date information about PDT focusing on recently published studies involving the treatment of inflammatory skin conditions as well as skin infections.

Photodynamic therapy (PDT) is a modern, noninvasive treatment for skin disorders. In general, PDT involves either local or systemic administration of a photosensitizing drug followed by illumination of the involved tissue with light within the visible wavelength spectrum, usually from a laser light source. The light excites the photosensitizer resulting in formation of reactive oxygen species, primarily singlet molecular oxygen ($^1O_2$), which are responsible for a cascade of cellular and molecular events that end with immunomodulary or cytotoxic effects (Figure 1). Generally 5-aminolevulinic acid (ALA) or its methyl ester, methyl-aminolevulinate (MAL), serve as the photosensitizer. Both ALA and MAL are prodrugs which are metabolically converted into the photosensitizer protoporphyrin IX (PpIX) and potentially other intermediate photosensitizing porphyrins. Protoporphyrin IX possesses several absorption maxima in the wavelength range of visible light. In addition to the main absorption range between 400 and 450 nm, there also are absorption peaks at 505, 540, 580, and 630 nm that can be targeted by other light sources such as blue light, red light, intense pulsed light (IPL), and pulsed dye laser (PDL) to improve tissue penetration.[1] Photodynamic therapy with these agents has proven to be effective with excellent cosmetic outcomes and the ability to treat large surface areas in a noninvasive manner. The major adverse effect of PDT with ALA or MAL is a stinging pain and burning sensation during and immediately after illumination, which often limits compliance. To date, topical PDT has been approved by regulatory authorities in 18 countries worldwide for use in at least one nonmelanoma skin cancer indication.[2]

Although initially developed as an anticancer therapy, PDT also has a role in nonneoplastic pathologies. In this

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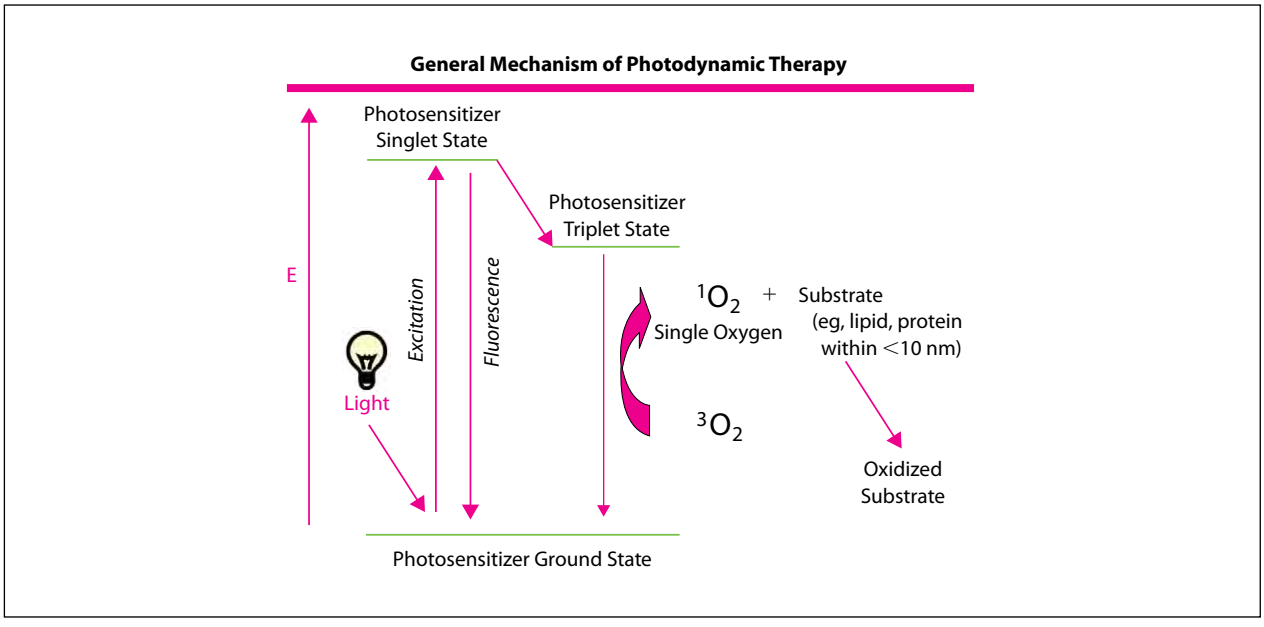

Photodynamic therapy requires 3 main components: (1) a photosensitizer, (2) a light source, and (3) molecular oxygen. The photosensitizer is administered systemically, orally, or topically. Photoirradiation with visible light of a wavelength that is absorbed by the accumulated photosensitizer will generate mainly singlet oxygen, which is highly reactive and oxidizes biomolecules nearby the photosensitizer binding sites creating an oxidative stress and cell death or lesion ablation.

review, we aim to summarize the use of PDT in inflammatory skin conditions as well as skin infections.

ACNE VULGARIS

Interest in light-based acne treatments has increased over the past several years. This increased interest has been attributed to both antibiotic resistance and the challenges of isotretinoin therapy.[3] Although the exact mechanism of action of PDT upon acne is unknown, possible mechanisms include reduction of *Propionibacterium acnes*, reduced sebum production by way of damage to sebaceous glands, anti-inflammatory activity through destruction of leukocytic infiltrates, and reduction in follicular obstruction by keratinocyte shedding.[4,5] *Propionibacterium acnes* naturally produces small amounts of porphyrins, especially coproporphyrin II, which accumulate in conjunction with topical ALA.[6]

The first clinical trial of ALA-PDT was conducted in year 2000.[4] This 22-participant, placebo-controlled study utilizing a 3-hour application time of ALA followed by broadband red light (550−700 nm) showed persistent clinical improvement of mild to moderate acne assessed using a modified inflammatory acne score on the back at 10 weeks after a single PDT treatment and clearing up to 20 weeks after multiple PDT sessions were completed.[4]

Since this initial study, several controlled studies have shown the efficacy of ALA-PDT in treating acne.[7-9] Fabbrocini et al[7] conducted a study of 10 participants with mild to moderate facial and/or chest/back acne resistant to conventional therapies. The participants received 3 sessions of ALA-PDT at 2-week intervals. Four weeks after the final PDT session, participants showed an average global reduction of 50%. Cyanoacrylate follicular biopsies demonstrated a reduction of total area, average area, and density of macrocomedones leading to the conclusion that ALA-PDT exerted an action on the comedogenic phase of acne. Similar results were observed by Sadick,[8] who conducted a randomized split-face study on 8 participants with moderate to severe acne. 5-Aminolevulinic acid was used on one side of the face and followed by exposure of the entire face with a 532-nm potassium-titanyl-phosphate (KTP) laser for a total of 3 treatments for up to 12 weeks. The use of ALA improved acne by 52% compared with 32% on the side without ALA. More recently, Wang et al[9] completed a study on 78 participants with grade 4 severe facial acne including inflammatory papules, pustules, nodules, scars and cysts, treating them with 1 to 3 courses of ALA-PDT. Seventeen of the participants (22%) showed excellent improvement (at least 90% clearance) after 1 course of treatment and 27 participants (34%) showed excellent improvement after 2 courses. The remaining 34 participants (44%) required 3 courses to further reduce the number and size of residual lesions. Adverse events were

minimal, and the signs and symptoms in recurrent cases were much more mild and showed good response to conventional topical medications.

Studies also have been conducted to determine the efficacy of ALA-PDT utilizing various wavelengths.[10-12] Results have varied regarding the use of blue light PDT in the treatment of acne. Data from the study of Goldman and Boyce[10] showed promise in a 22-participant trial using ALA and blue light in the treatment of mild to moderate inflammatory acne. Akaraphanth et al[11] later conducted a study of 20 participants with moderate to severe facial acne. The participants underwent 4 weekly treatments of ALA-PDT with 415-nm blue light on the right side of the face and blue light alone on the left side. Although the mean percent reduction in inflamed lesion counts tended to be greater in the ALA-PDT areas, there was no statistically significant ($P=.092$) difference between ALA-PDT and blue light alone. Adverse effects were pain, stinging, peeling, erythema, pruritus, oozing, and pustules. These effects were greater on the ALA-PDT–treated side. Taub[12] conducted a randomized trial with 22 participants and found ALA-PDT with activation by IPL provided greater, longer-lasting, and more consistent improvement than either radiofrequency IPL or blue-light ALA activation in the treatment of moderate to severe acne. These outcomes may suggest that the superficial penetration depth of blue light induces more melanocytic stimulation, especially in darker skin types, than yellow or red light.[13]

5-Aminolevulinic acid incubation time also has been investigated. One randomized half-facial treatment study of 20 participants compared ALA-PDT with IPL using incubation times of 30 minutes to 180 minutes.[14] Although all participants showed improvement in their inflammatory acne after 3 sessions of ALA-PDT or IPL alone, the degree of improvement was greater in the long-incubation time group than the short-incubation time group or the IPL-alone group, which indicates that PDT with a long ALA incubation time may be more adequate for a pronounced outcome with inflammatory acne.[14]

Different vehicles are being explored in order to attempt to decrease the ALA concentration required and therefore reduce any associated phototoxic effects. Typically an ALA cream 20% is utilized for PDT of acne. A 32-participant study assessed the efficacy and safety of PDT for acne using ALA liposomal spray 0.5% and IPL in combination with topical peeling agents.[15] After a mean period of 7.8 months and a mean of 5.7 treatment sessions, the mean number of lesions dropped from 34.6 to 11.0 lesions with minimal side-effects. The most commonly reported adverse effects were burning or pain, which were generally well-tolerated without topical anesthetics, and posttreatment erythema.[15]

In addition to ALA, MAL also has been employed as a photosensitizer for PDT of acne with mixed results. Wiegell et al[16] conducted a randomized, controlled, investigator-blinded trial on 21 participants with at least 12 inflammatory acne lesions. The participants were treated twice with MAL-PDT over a 2-week interval. After 12 weeks, there was a 68% reduction in inflammatory skin changes in the MAL-PDT group versus 0% in the control group. Hörfelt et al[17] conducted a blind, prospective, randomized, placebo-controlled, multicenter study on 30 participants with moderate to severe acne. Each side of each participant's face was randomly assigned to treatment with MAL or placebo cream 3 hours prior to illumination with red light. There was a statistically significant ($P=.0006$) greater reduction in the total inflammatory lesion count with MAL-PDT compared with placebo PDT at 12 weeks posttreatment. However, MAL-PDT was associated with more pain than placebo. Hörfelt et al[18] later conducted a single, low-dose red light MAL-PDT study on 19 participants with moderate to severe facial acne. Using clinical photographs and skin surface biopsies, both MAL-PDT areas and areas treated with red light alone showed a significant ($P<.01$) decrease in acne score at 10 and 20 weeks posttreatment. Photodynamic therapy with MAL was associated with erythema and stinging. Fluorescence images revealed poor selectivity of MAL-induced fluorescence to acne lesions suggesting a general photo-ablating mechanism rather than selective destruction of sebaceous glands. No significant remarkable reduction in *P acnes* or sebum excretion was found. Yeung et al[19] compared MAL-PDT using IPL with IPL alone on 30 participants with Fitzpatrick skin types IV and V and moderate acne. They concluded that MAL-PDT using IPL did not lead to notable improvement of moderate inflammatory acne compared with IPL alone. Additionally, some of the participants could not tolerate the discomfort associated with the MAL-PDT.

Other compounds, such as indocyanine green (ICG), also have been investigated as an alternative to ALA and MAL. A split-face study of 16 participants examined the efficacy of PDT using topical ICG dye 0.06% with a diode laser. The right cheek of each participant was treated with topical ICG solution followed 30 minutes later with near-infrared (NIR) laser irradiation. The left cheek was irradiated with the same NIR laser dose. The participants were randomized into single- and multiple-treatment groups, which received 3 weekly treatments. The participants were followed biweekly for 2 months. Acne grading in both groups was notably improved

when compared to untreated foreheads. In addition, PDT with ICG resulted in remarkably faster improvement than NIR laser without ICG application. The most common side-effects were erythema, tingling, and crusts. Interestingly, postinflammatory hyperpigmentation was not observed. This suggests that PDT with ICG dye and diode laser may be an alternative treatment modality for acne in Asian participants at risk for postinflammatory hyperpigmentation.[20]

Adverse reactions associated with PDT in treating acne include photosensitivity, pustular eruptions, and crusting, which vary among photosensitizers and light sources.[21] In addition, postinflammatory pigmentation remains problematic and PDT protocols have yet to be optimized.[22] This is consistent with the British Association of Dermatologists' guidelines that state current evidence suggests that although topical PDT can improve inflammatory acne on the face and back, optimization of protocols to sustain response while minimizing adverse effects is awaited. The strength of this recommendation is B, signifying there is fair evidence to support the use of PDT, and quality of evidence is I, which signifies evidence from at least one properly designed randomized control trial.[2] The scale of strength being A through D: A being there is good evidence to support the use of the procedure, and D being there is good evidence to support the rejection of the use of the procedure. The quality of evidence scale being I though IV: I being evidence obtained from at least one properly designed, randomized controlled trial, and IV being evidence inadequate owing to problems of methodology.[2]

ROSACEA

Since rosacea and acne have several common features and PDT has shown encouraging results in the treatment of acne, PDT is sometimes considered as a treatment option for patients with rosacea who request an alternative to conventional therapies. Although established systemic and topical treatments are often effective, continuous medication is often required to control rosacea.

Limited research has been conducted on the utilization of PDT for rosacea. Nybaek and Jemec[23] treated 4 participants with rosacea for 2 or 3 sessions of PDT using methyl aminolevulinate (MAL), a derivative of ALA with higher lipophilicity, activated 3 hours later with a 632-nm red diode light. Three of the 4 participants displayed skin clearing with lasting up to 9 months in 1 participant and 3 months in 2 participants.[23]

A case report of a 45-year-old woman with rosacea who underwent 6 sessions of ALA-PDT with PDL activation every 2 weeks showed improvement after the second treatment.[24] This improvement was considered excellent. Improvement continued and no flares were observed 1 month after the final treatment.[24] In addition, Bryld and Jemec[25] conducted a retrospective analysis of 17 participants who underwent 1 to 4 sessions of MAL-PDT for treatment of rosacea. Results were evaluated 1 to 2 months after PDT. Good results were reported in 10 of 17 participants and fair results in 4 of 17 participants. The majority of treated patients could stop or reduce other therapies for periods ranging from 3 months to 2 years after MAL-PDT.[25]

In contrast to these limited positive results, Togsverd-Bo et al[26] conducted a prospective case series to evaluate the effect of long-pulsed dye laser (LPDL) alone and in combination with MAL on papulopustular rosacea. Four participants were treated with MAL on 1 side of their face 3 hours prior to receiving LPDL on their entire face. None of the participants experienced a clinically relevant reduction of 50% and no differences were noted between the LPDL- and MAL-PDT–treated sides.

With only these limited studies, there is no clear evidence that PDT has a remarkable effect on rosacea. A randomized, controlled trial to investigate the effects of PDT on rosacea seems justifiable in the future.

FOLLICULITIS

Folliculitis generally is treated with antibiotic or antifungal agents. However, major limitations of these treatments include infection relapse and appearance of drug-resistance. In addition, some patients are not able to tolerate these treatments due to hepatotoxicity, gastrointestinal discomfort, and drug reactions. This has led to exploration of PDT as a treatment option for folliculitis.

Lee et al[27] treated 6 participants with recalcitrant *Malassezia* folliculitis with 3 sessions of MAL-PDT with a 3-hour incubation period followed by red-light activation at 2-week intervals. After 3 sessions, 4 participants showed obvious improvement with decreased inflammatory lesions. One participant showed a slight improvement, and the remaining participant exhibited no improvement. During the treatment course, the only adverse effect noted was temporary mild erythema and a stinging sensation which resolved within 24 hours after cessation of illumination. Horn and Wolf[28] reported a case series of 7 patients with chronic recalcitrant folliculitis treated with MAL-PDT with a 2.5-hour incubation period followed by red-light activation. Six of 7 patients exhibited remarkable clinical improvement and reduction of inflammatory follicular lesions after a single MAL-PDT session. Treatment was well tolerated by participants with the known adverse effects of immediate burning, transient erythema, and edematous follicular reactions in the PDT-treated areas.

An antimicrobial effect rather than the destruction of pilosebaceous units is thought to be responsible for the positive effect of PDT on folliculitis.[28] In addition, MAL may be the preferred photosensitizer in treating folliculitis because it has enhanced lipophilicity and therefore should be more effective than ALA for treating disorders of the pilosebaceous unit.[27] Although these results are promising, the data on PDT for the treatment of folliculitis is still limited and additional investigation is warranted.

HIDRADENITIS SUPPURATIVA

Treating hidradenitis suppurativa (HS) is challenging because common therapeutic approaches do not lead to complete remission, and relapses result after discontinuation of treatment. These challenges have lead to the exploration of PDT as a treatment option for this recalcitrant disease.

An initial investigation by Gold et al[29] treated 4 participants with HS not responding to standard therapy with 3 to 4 sessions of ALA-PDT utilizing a blue light for activation. All of the patients tolerated the treatment well and clinical improvements from 75% to 100% were noted in all of the participants. In addition to these positive findings, 2 case studies have reported positive results.[30,31] One study reported a 90% to 100% decrease in the inflammation and exudate of a 41-year-old woman with a 12-year history of extensive HS in the axillary and groin regions after 2 sessions of ALA-PDT with red-light activation.[30] This effect was maintained at 4 months posttreatment. However at 12 months, there was a mild relapse in some treated areas.[30] The other reported an almost complete clinical remission of skin lesions in a 29-year-old man with an 8-year history of HS and pilonidal cysts after 9 applications of MAL-PDT activated with red light every 15 days.[31]

Negative findings were reported in 2 studies.[32,33] Strauss et al[32] enrolled 4 participants with HS to undergo a maximum of 3 weekly sessions of ALA-PDT. None of the 4 participants had a remarkable improvement in regional HS score at 8 weeks after treatment, and 2 participants showed deterioration. Another trial of 5 participants with HS who underwent 4 sessions of ALA-PDT with red-light activation at 2-week intervals reported that none of the participants exhibited a notable clinical improvement.[33] These negative findings were thought to be due to the reduced penetration of ALA caused by severe disruption of the skin architecture with permanent and deep scarring.[32,33]

Patients with HS may benefit from PDT. However, these varied and limited findings suggest that additional research is warranted to fully evaluate efficacy as well as establish optimal treatment parameters.

GRANULOMATOUS DISEASES

Interest in utilizing PDT to treat granulomatous diseases has sparked from the safety profile of PDT along with observed efficacy in other inflammatory dermatoses. However, there may be suboptimal absorption of both the PDT drug and light in lesions situated in the deeper dermis. To date, the research on using PDT to treat granulomatous diseases has primarily focused on the treatment of granuloma annulare (GA), which appears to be at least partially due to a T-cell–mediated inflammatory process. Some limited reports on the use of PDT to treat cutaneous sarcoidosis also appear in the literature.[34-38]

A case report of a 25-year-old woman with GA who underwent 4 weekly sessions of ALA-PDT with activation by 630-nm light after a 5-hour incubation period showed increased lesion regression, flattening, and decreased size with each treatment. The lesion was almost completely cleared after the fourth session and the patient remained well at 7 months after treatment.[34] Weisenseel et al[35] went on to perform 2 to 3 sessions of ALA-PDT activated by a standard red-light source on 7 participants with GA. The overall response rate was 57%. In 2 participants GA cleared completely, 2 participants showed marked improvement, and 3 participants had no observed clinical response. These promising results suggest that PDT may be a valuable treatment for GA. However, larger controlled studies are needed before a treatment recommendation can be made.

A case report of a 67-year-old woman with a 17-year history of cutaneous sarcoidosis was treated with 22 sessions of ALA-PDT over a 3-month period.[36] Roughly 4 weeks after the initiation of treatment, the plaques flattened and faded. After 3 months, the lesions resolved completely without the appearance of new lesions. Histological examination of a biopsy at 4 months after treatment showed histologically normal skin. Eighteen months after PDT the patient was still free of skin disease and visceral involvement.[36] Another report of a 42-year-old woman with cutaneous sarcoidosis who underwent 7 ALA-PDT sessions over 16 months exhibited complete clearing of her lesion clinically, but a biopsy performed 2 weeks after her final treatment showed continued presence of noncaseating granuloma.[37] Wilsmann-Theis et al[38] reported 2 cases of cutaneous sarcoidosis treated with 8 sessions of MAL-PDT every 2 to 4 weeks over the course of 16 to 32 weeks. Both showed complete clearance and were in remission up to 6 months after treatment. These case reports provide evidence that PDT may be a promising treatment for cutaneous sarcoidosis. However, like with GA, larger controlled studies are needed before a treatment recommendation can be made.

VERRUCAE

Current treatment options for viral warts include liquid nitrogen, surgical excision, dinitrochlorobenzene, podophyllin, bleomycin, topical salicylic acid, and carbon dioxide (CO_2) laser. Each of these options has associated side-effects or shortcomings making treatment of verrucae a challenge.

A large trial on 64 warts treated with ALA-PDT and 57 control warts (vehicle and illumination) showed resolution of 75% of warts treated with ALA-PDT while 22% of the control warts resolved, indicating that ALA-PDT may be a viable alternative treatment of viral warts.[39] The most common complaint was a mild burning sensation. Schroeter et al[40] conducted a trial on 31 participants with a total of 48 therapy-resistant plantar warts. Each wart was scraped to the papillary dermis prior to application of ALA with a 4- to 8-hour incubation period before activation with red light. Forty-two of 48 warts showed complete response. Similar findings were reported by Wang et al[41] in a phase II study investigating ALA-PDT for the treatment of recalcitrant viral warts. Twelve participants with viral warts were treated with ALA and irradiated 4 hours later with a red light source with a maximum of 4 sessions. Five participants exhibited complete clearance, one had partial clearing, 5 had stable disease, and one showed progressive disease concluding that ALA-PDT is a promising alternative treatment of recalcitrant viral warts.[41]

In an attempt to increase penetration through altered skin, azone (1-dodecyl-azepan-2-one) 3% was applied to plantar warts prior to application of ALA. Eighteen participants were treated with azone prior to ALA-PDT, and 18 received ALA-PDT alone.[42] The lesions pretreated with azone responded with better effectiveness with 66.7% complete response in mosaic warts and 100% in myrmecia after 2 to 3 sessions, compared with 37.5% complete response in mosaic warts and 70% of myrmecia when treated with ALA-PDT alone. This provides evidence that pretreatment with azone may enhance ALA tissue penetration and thus increase the effectiveness of PDT.[42]

Periungual and subungual warts of the hand present a unique treatment challenge as there is poor accessibility to the lesion and surgical treatment may lead to cosmetic disfigurement of the nail. Because PDT is noninvasive, it results in better healing without scarring when compared with conventional treatments. A pilot study in which 20 participants with a total of 40 periungual and subungual warts were treated with ALA-PDT for a mean of 4.5 sessions provided complete clearance of all warts in 90% (n=18) of the participants with no recurrences during the mean follow-up period of 5.9 months.[43] Pain and hyperpigmentation were the primary adverse effects of treatment.[43]

Because of the large number of treatments involved, a second pilot study looked at the potential for synergistic effects by combining ablative CO_2 fractional laser and MAL-PDT to treat recalcitrant periungual warts. Twelve participants with a total of 40 periungual warts were treated with an ablative CO_2 fractional laser. Immediately after each fractional treatment, MAL was applied and 3 hours later the lesions were illuminated with red light. After a mean of 2.2 treatments, complete clearance was achieved in 36 warts. Two warts had 50% clearance and 2 showed no response. There was no recurrence of the warts with complete clearance after 6 months.[44] A second study examined combining PDL with PDT on 86 warts undergoing treatment with ALA-PDT and PDL versus 76 warts undergoing ALA-PDT alone and 112 warts undergoing PDL alone. The combined treatment showed a 100% cure rate after an average of 1.96 sessions. Photodynamic therapy with ALA alone failed in 3 of 76 warts even after 5 sessions. Photodynamic light alone failed in 21 of 112 warts even after 5 sessions. [45] These results suggest a potential for enhanced clinical results when combining treatment techniques.

Light-emitting diodes (LED) also have been explored as a potential cost-saving alternative to laser activation of photosensitizers in the treatment of verrucae. Six participants with a total of 41 foot and hand warts were treated with ALA, which was activated 5 hours later with a red LED at a dose of 126 J/cm^2. The treatment was repeated up to 10 sessions with a maximum of 10 treatments each session every 2 to 3 weeks. Clinical improvement was achieved in 68.3% of participants suggesting that LED may offer a less expensive alternative to PDT with laser illumination in the treatment of viral warts.[46]

The British Association of Dermatologists in 2008 stated that recent studies continue to support the potential of topical PDT in viral warts. The strength of this recommendation is B, signifying there is fair evidence to support the use of PDT, and quality of evidence is I, which signifies evidence from at least one properly designed randomized control trial.[2]

CONDYLOMA ACUMINATA

Electrocoagulation and laser evaporation for condylomata acuminata have high recurrence rates and can be associated with urethral malformations making PDT an attractive treatment technique. It is hypothesized that ALA-PDT triggers both apoptosis and necrosis in keratinocytes in condylomata acuminata.[47] It has been suggested that topical application of ALA solution 5% to 10% for 3 to 5 hours is the optimal condition for PDT of condylomata acuminata allowing for selective destruction of the lesions in the epidermis without damaging the dermis

ensuring better control of recurrence and less side effects such as ulceration or scarring.[48]

A large trial utilizing ALA-PDT for the treatment of condyloma acuminata reported a complete response rate of 95% with 5% recurrence after 6 to 24 months following ALA-PDT with a 3-hour incubation period and 630-nm light activation in 164 participants with urethral condylomata. No urethral infections, ulcers, scars, or malformations were induced. Healing times were shorter and recurrence rate was lower than with conventional treatments. Participants did experience some burning and/or stinging during PDT and while urinating for several days after treatment.[47]

Another study compared ALA-PDT with CO_2 laser vaporization.[49] Sixty-five participants with condylomata acuminata were treated with ALA-PDT and another 21 participants were treated with CO_2 laser. After one treatment, complete removal rate was 95% in the ALA-PDT group compared with 100% in the CO_2 laser group. After 2 treatments with ALA-PDT, the complete removal rate was 100%. However the recurrence rate in the ALA-PDT group was 6.3%, which was significantly ($P<.05$) lower than the 19.1% recurrence rate found in the CO_2 laser group. The adverse effects in the participants treated with ALA-PDT were primarily mild burning and/or stinging restricted to the area of illumination.[49] Liang et al[50] also compared ALA-PDT with CO_2 laser therapy in 90 participants (67 in the ALA-PDT group and 23 in the CO_2 laser group) with condylomata acuminata. Treatments of both groups were given weekly for up to 3 weeks. One week after treatments, the complete clearance rate was 95.93% in the ALA-PDT group and 100% in the CO_2 laser group. Once again recurrence in the ALA-PDT group was significantly lower (9.38%) than in the CO_2 laser group (17.39%). These results suggest ALA-PDT is a simpler, safer, more effective therapy with a lower recurrence for treatment of condylomata acuminata compared with conventional CO_2 laser therapy.

A recent phase III, prospective, randomized, double-blind study had conflicting results.[51] One hundred seventy-five participants with condylomata acuminata received CO_2 laser vaporization followed by ALA-PDT or CO_2 laser vaporization followed by placebo-PDT. 5-Aminolevulinic acid or placebo was applied 4 to 6 hours before CO_2 laser vaporization, followed by red-light illumination. Cumulative recurrence rates at 12 weeks posttreatment were 50.0% in the ALA-PDT group versus 52.7% in the placebo-PDT group. There were no statistical differences between the group's recurrence rates up to 12 months after treatment.[51]

The British Association of Dermatologists in 2008 stated that topical PDT may be considered as a treatment option for patients with genital warts. The strength of this recommendation is B, signifying there is fair evidence to support the use of PDT, and quality of evidence is I, which signifies evidence from at least one properly designed randomized control trial.[2]

LEISHMANIASIS

Recently, PDT has been explored for the treatment of cutaneous leishmaniasis (CL), caused predominantly by *Leishmania major*. Although CL is a spontaneously resolving disease, the long duration and resulting disfigurement warrant an effective treatment. The challenge in treating this condition is to reduce the lesion size and promote healing with minimal scarring, while also eradicating the amastigotes. Currently, antimonials are the most commonly prescribed treatment. However because of resistance to drug treatment, there has not been a decrease in the number of emergent cases of CL.[52]

A comparison of MAL-PDT with red-light activation versus daily topical paromomycin sulfate on 10 lesions on the same participant revealed that after 28 PDT sessions, all 5 MAL-PDT–treated lesions and 2 of the paromomycin sulfate–treated lesions were clinically and histologically *Leishmania* free. The 3 lesions with poor response to paromomycin sulfate responded to subsequent MAL-PDT. Ten months after treatment, there was no recurrence with excellent cosmetic outcome with PDT.[53] Enk et al[54] treated 11 participants with a total of 32 CL lesions with weekly ALA-PDT sessions activated with broadband red light after a 4-hour occlusion period. Follow-up at 3 months showed 31 of 32 lesions remained amastigote negative with no relapses up to 6 months after treatment and an average reduction in lesion size of 67%. The unresponsive lesion was ulcerated and did not accumulate ALA at the necrotic center.

The first placebo-controlled, randomized study on the effectiveness of PDT on CL was published in 2006.[55] In this trial, 57 participants diagnosed with CL were randomly divided into 3 treatment groups of 20 participants each. Group 1 underwent weekly ALA-PDT with red light; groups 2 and 3 received twice-daily topical paromomycin sulfate or placebo, respectively, for 4 weeks. Eight weeks after treatment, lesion clearance was observed in 93.5% of ALA-PDT–treated participants compared with 41.2% of those treated with paromomycin sulfate and 13.3% of those who received placebo. Parasitological cure, by smear, was demonstrated in 100%, 64.7%, and 20% of the lesions, respectively.[55]

The mechanism of action of ALA-PDT on *L major* is likely the result of unspecific tissue destruction accompanied by the depopulation of macrophages rather than direct killing of the parasites.[56] Since PDT does not

influence the intact skin surrounding the CL lesions, it offers the advantage of an excellent cosmetic result.[57]

The British Association of Dermatologists in 2008 stated that current evidence suggests that topical PDT is effective in clearing lesions of CL although further studies with culture confirmation of amastigote clearance are required. The strength of this recommendation is B, signifying there is fair evidence to support the use of PDT, and quality of evidence is I, which signifies evidence from at least one properly designed randomized control trial.[2]

PSORIASIS

Psoriasis is a disease characterized by hyperproliferation disturbed maturation, inflammation, and vascular changes in the skin. Phototherapy such as UVB (290−320 nm) and psoralen plus UVA (320−400 nm) has been shown to improve psoriasis. The responsiveness of psoriasis to phototherapy along with the early encouraging finding that ALA can penetrate the parakeratotic stratum corneum of psoriatic plaques and selectively accumulate in diseased tissue lead to further investigation into the utilization of PDT for the treatment of psoriasis.[58]

The first randomized trial utilizing PDT for the treatment of psoriasis studied 29 participants with chronic plaque-type psoriasis.[59] The participants were randomized to groups that received ALA-PDT with a light dose of 5 J/cm^2, 10 J/cm^2, or 20 J/cm^2. Participants underwent biweekly PDT sessions for 12 weeks, or until the plaques were cleared. Prior to ALA application, participants received keratolytic pretreatment with salicylic acid 10% white petrolatum ointment. Clinical response was measured using the psoriasis severity index (PSI). Keratolytic pretreatment reduced PSI by approximately 25% in each of the treatment groups. Subsequent ALA-PDT with 20 J/cm^2 resulted in a final PSI reduction of 59%, 10 J/cm^2 resulted in a 46% reduction, and 5 J/cm^2 decreased the lesion size by an average of 49%. The investigators found this clinical response to be unsatisfactory with frequent pain during and after irradiation suggesting that ALA-PDT is an inadequate treatment option for psoriasis.[59]

Additional disappointing results were found in a randomized, double blind phase I/II study conducted by Schleyer et al.[60] Twelve participants with at least 3 psoriatic plaques were randomly treated with topical ALA 0.1%, 1%, and 5%, respectively, prior to irradiation. Biweekly ALA-PDT sessions were continued for 6 weeks, or until plaque clearance was achieved. Therapeutic efficacy was assessed via PSI. The mean percentage improvement was 37.5%, 45.6%, and 51.2% in the 0.1%, 1%, and 5% ALA-treated groups, respectively. Irradiation was interrupted several times due to severe burning and pain. Again, ALA-PDT did not prove an appropriate treatment option for plaque psoriasis due to disappointing clinical efficacy, the time-consuming nature of the treatment, and associated pain and burning.

A third placebo-controlled randomized study was conducted by Smits et al.[61] Eight participants with stable plaque psoriasis were enrolled. Two symmetrical plaques on each participant were randomly allocated to 4 weekly PDT session with ALA 10% ointment or placebo. Immunohistochemical assessment was completed on biopsies taken at baseline, week 1, and week 6. Clinical assessment of the plaques was completed using the plaque severity score. Clinical improvement in ALA-PDT–treated plaques had a statistically significant (P=.009) lower sum score then the sites treated with placebo-PDT. In addition, clinical improvement during ALA-PDT for psoriasis paralleled histological improvement demonstrated by normalization of epidermal proliferation, differentiation, and infiltration of relevant T-cell subsets. However, due to the variable and mediocre efficacy compared with other established treatments, ALA-PDT of psoriasis was not recommended utilizing the current protocols. Further studies to better understand PpIX formation and its photodynamic effects in psoriasis are suggested.

There is no clear singular mechanism of action of PDT on psoriasis. Boehncke et al[62] reported that ALA-PDT exhibited a dose-dependent inhibitory effect on TNF-α, IL-1 and IL-6 secretion, a mechanism that also has been reported with psoralen plus UVA treatment. A later study suggested the PDT with systemic ALA resulted in apoptosis of CD3+ cells.[63]

The British Association of Dermatologists in 2008 stated that current evidence does not support the use of topical ALA-PDT as a practical therapy for psoriasis. The strength of this recommendation is D, signifying there is fair evidence to support the rejection of the use of PDT, and quality of evidence is I, which signifies evidence from at least one properly designed randomized control trial.[2]

SUMMARY

Photodynamic therapy is considered a valuable treatment technique in certain inflammatory skin conditions. There is currently a wide spectrum in the quality and quantity of evidence available for this therapy. Conditions such as acne, verrucae, condylomata, and leishmaniasis demonstrate good response to PDT. The status of PDT for the treatment of other inflammatory conditions needs validations in controlled clinical trials.

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