

TOPICAL REVIEW

Topical 5-aminolaevulinic acid photodynamic therapy for the treatment of skin conditions other than non-melanoma skin cancer

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Summary

Topical 5-aminolaevulinic acid (ALA) photodynamic therapy (PDT) is used increasingly for superficial non-melanoma skin cancer (NMSC) and dysplasia. However, the relative accumulation of the photosensitizer protoporphyrin IX (PpIX) in diseased tissue is not specific for neoplastic disease, and has been shown after the application of ALA to benign proliferative skin conditions such as viral warts and psoriasis. This review appraises the quality of evidence available for the use of topical ALA–PDT in the treatment of skin conditions other than NMSC. The diseases that have been studied in most detail are recalcitrant viral warts, acne, psoriasis and cutaneous T-cell lymphoma. Publications relating to the treatment of other diseases by topical PDT are restricted to small case series or case reports. The relevant literature will be discussed and the potential for topical PDT in the treatment of several skin diseases is highlighted, although more detailed studies are required to clarify the role of PDT beyond the treatment of NMSC.

Key words: 5-aminolaevulinic acid, acne, photodynamic therapy, psoriasis, T-cell lymphoma, warts

Although the concept and use of photodynamic therapy (PDT) is not new,^{1,2} there has been a dramatic increase in the application of topical PDT since its introduction in 1990.³ The literature relating to the use of topical 5-aminolaevulinic acid (ALA)–PDT is extensive, although the majority refers to its use in the treatment of non-melanoma skin cancers (NMSC) and their precursors.^{4–7} Indeed, there is considerable evidence that topical ALA–PDT is a highly effective form of therapy for the treatment of superficial basal cell carcinomas,⁸ Bowen's disease⁹ and actinic keratosis¹⁰ and, in selected cases, may be the treatment of choice.⁹ The phenomenon of photosensitizer accumulation in diseased tissue is not specific for neoplastic or preneoplastic disease. The mechanism of specificity of ALA uptake and conversion to the active species, protoporphyrin IX (PpIX), is thought to be multifactorial, but enhanced permea-

bility of abnormal stratum corneum, relative iron deficiency and alterations in porphyrin enzyme profiles in diseased tissue may all contribute to the process of photosensitizer accumulation.¹¹ The observation of photosensitizer accumulation in benign skin diseases, such as psoriasis,¹² has led to considerable interest in the application of topical ALA–PDT to several other non-NMSC skin conditions.

The purpose of this review is to discuss the literature that is available for the study of topical ALA–PDT in the treatment of other skin conditions. This will be presented based on the rationale for the use of topical ALA–PDT and whether there is evidence for selectivity of photosensitizer accumulation and efficacy of treatment. Patient acceptability of treatment and possible clinical demand will also be considered. The literature has been appraised according to study design, size and robustness.

Topical ALA–PDT has been applied to the treatment of an extensive range of skin diseases other than non-melanoma skin cancer (Table 1). However, most

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Table 1. Non-NMSC skin diseases for which topical ALA–PDT has been applied

Most studied	Case series	Single case reports
Viral warts	Actinic cheilitis	Naevus sebaceous
Acne vulgaris	Keratoacanthoma	Epidermodysplasia verruciformis
Psoriasis	Erythroplasia of Queyrat	Lichen planus
Cutaneous T cell lymphoma	Lichen sclerosus	Malignant melanoma
	Extramammary Paget's disease	
	Condyloma acuminata	
	Scleroderma	
	Hirsutism	
	Alopecia areata	
	Vulval intraepithelial neoplasia	
	Cutaneous breast metastases	

NMSC, non-melanoma skin cancers; ALA, 5-aminolaevulinic acid; PDT, photodynamic therapy.

of the literature is based on small case series or single case reports, with few of adequate study design.

Recalcitrant viral warts

The rationale for the use of topical ALA–PDT is based on their hyperproliferative and inflammatory nature. PpIX accumulation in warts has been demonstrated after ALA application¹³ and there is a clinical demand for adjunctive therapies, as recalcitrant viral warts and verrucas can be a significant clinical problem, particularly in immunosuppressed patients.

A report of six patients with viral warts treated with topical ALA–PDT showed lack of efficacy of treatment in five of the subjects.¹⁴ However, a single treatment (20% ALA applied for 5–6 h, slide projector irradiation for 30 min) was delivered with no repeated therapy, and the assumption from the methodology was that surface preparation of the lesions was not performed prior to treatment.¹⁴ Subsequently, four patients with recalcitrant warts successfully treated with ALA–PDT were described.¹⁵ Paring of the lesions to visible blood vessels was performed prior to application of 20% ALA cream for 12 h and irradiation with a modified slide projector at a dose of 50 J cm⁻². All patients had a complete response to therapy performed on two or three occasions without recurrence. The only adverse effects observed were of a moderate burning sensation.

The same authors retrospectively analysed the results of ALA–PDT treatment in 62 patients with recalcitrant warts.¹⁶ The regimen included paring to blood vessels, 20% ALA cream application for 4–5 h and irradiation with white light from a modified slide projector (25 mW cm⁻², 45 J cm⁻²). Treatment was repeated three times at weekly intervals and patients were encouraged to treat the warts by paring and

application of Verucid® (salicylic acid and lactic acid) once to twice a week in the follow-up period. Only 52 subjects completed treatment, with pain experienced by 50% of subjects, and 10 refused further treatment because of pain or were lost to follow-up. Of the patients who completed therapy, 58% cleared, with no recurrence in up to 17 months of follow-up. Five patients were immunocompromised and only one responded to treatment, three were treatment failures and one had to discontinue treatment because of severe pain. This retrospective study showed a lower response rate for wart clearance with ALA–PDT compared with their earlier study.¹⁵ However, the two studies were not comparative in methodologies and the previous study examined wart, rather than patient, clearance.

On the basis of these preliminary findings, the same group performed a comparative pilot study in 30 subjects with 250 recalcitrant warts.¹⁷ The average duration of warts was 3 years, and three of the subjects were immunosuppressed. After surface preparation, 20% ALA cream was applied for 5 h prior to irradiation with visible light from a modified slide projector. Randomization was performed such that comparative treatment groups were: white light (22 mW cm⁻²) three times in 10 days (W3); white light once in 10 days (W1); red light (17.4 mW cm⁻²) three times in 10 days (R3); blue light (22 mW cm⁻²) three times in 10 days (B3) or cryotherapy with a double 10-s freeze/thaw cycle, repeated up to four times in a 2-month period. The total dose of visible light in the PDT-treated groups was 40 J cm⁻². Patients were additionally encouraged to pare the warts twice per week and apply Verucid®. Assessment was open and performed 4–6 weeks after treatment. Partial responders (> 50% reduction in diameter of warts) were treated with the same treatment modality and final assessment of clearance was made within 2 months.

Non-responders and partial responders at the end of this follow-up were withdrawn, and complete responders followed up for 12 months.

Those requiring re-treatment were as follows: 78% of the W1 and W3 groups, 40% of the R3 group and 22% of the B3 group. Significantly more warts completely cleared after white light PDT (W1 and W3) than red (R3) or blue (B3) light PDT or cryotherapy, with improved results for W3. There were no significant differences between the red (R3) and blue (B3) light PDT and the cryotherapy treatment groups. Overall, 73% and 71% of the white light PDT groups (W3 and W1, respectively) cleared, compared with 42% of the red light PDT group, 28% of the blue light PDT group and 20% of the cryotherapy group. White light PDT three times in 10 days (W3) resulted in a superior response, with 25% partial responders compared with 30% treatment failure in the W1 treatment group. Treatment was complicated by mild to strong burning within a few minutes of light exposure, with some patients reporting persistent discomfort up to 48 h after treatment and three patients discontinuing treatment due to intolerable pain. One patient failed to attend after a single treatment and one patient treated with cryotherapy withdrew because of pain. Of note, two of the three immunosuppressed patients failed to respond to therapy, although the two failures were randomized to red and blue light PDT, respectively, and the responder was treated with white light PDT (W3). The low response rate to cryotherapy reflected the inclusion criteria of warts that were resistant to conventional therapies. The overall conclusions of the study were that topical white light ALA-PDT was superior in efficacy to red or blue light PDT or cryotherapy in patients with recalcitrant hand and foot warts, although pain could be a limiting factor. The increased response rate with a white light source may indicate that other photoproducts of PpIX are implicated in the photodynamic effect, explaining the superior efficacy of white light compared with either red or blue light irradiation.

In a well-designed, controlled study by the same group,¹³ 45 patients with 232 recalcitrant hand and foot warts were randomized to receive either ALA-PDT or placebo PDT in a double-blind study. Both treatment groups used paring of the warts to blood vessels, with 20% ALA cream or placebo applied for 4 h prior to irradiation with a broadband source (590–700 nm, Waldmann 1200®). The treatment dose was 70 J cm^{-2} (50 mW cm^{-2}) and treatment was repeated weekly for 3 weeks. Patients were followed up 1 month later and

if warts persisted they were re-treated for a further three weekly treatments and then assessed at weeks 14 and 18. Patients additionally pared the warts and applied Verucid® twice a week between treatments for the whole study period. Patients with immunosuppression were excluded from the study. Complete clearance of warts by week 18 was seen in 56% of patients in the active treatment group, compared with 42% in the placebo-treated group ($P < 0.05$). There was a significant decrease in wart area in the active treatment group at weeks 14 and 18, with a median difference of 46% and 29%, respectively ($P = 0.006$, $P = 0.008$). Interestingly, a relatively high response was seen in the placebo-treated group and 60% of placebo-treated warts showed small peaks of fluorescence at 630 nm, despite the absence of ALA application. Paring, use of salicylic acid and lactic acid, and possibly a contribution of PDT with endogenous PpIX, may explain this high placebo response rate. A significantly higher proportion of the active treatment group experienced moderate to severe pain immediately and for 24 h after light exposure. This could potentially limit the use of ALA-PDT for the treatment of warts, particularly in children.

More recently, Fabbrocini *et al.* showed a superior effect of topical ALA-PDT (5 h 20% ALA, tungsten lamp 400–700 nm, 50 mW cm^{-2} , 50 J cm^{-2}) performed weekly for 3 weeks compared with vehicle and irradiation in 67 patients with 121 warts.¹⁸ Seventy-five per cent of warts resolved with ALA-PDT compared with 22.8% of the vehicle-treated group. Treatment was combined with the use of a keratolytic and gentle curettage, and only a mild burning sensation was reported.

To conclude, three studies of adequate size and design have shown superior efficacy of ALA-PDT to cryotherapy or placebo PDT in the treatment of recalcitrant warts. This remains a potentially useful therapy (Fig. 1), although no adequate study of ALA-PDT in the treatment of immunosuppressed patients with warts has been performed. Results to date suggest it may be less effective in this patient group and further work is required. Additionally, optimization of effective treatment regimens in order to minimize adverse effects, particularly pain, are required, as this currently limits its potential use in children.

Acne vulgaris

There has been considerable recent interest in the use of topical ALA-PDT in the treatment of acne, although

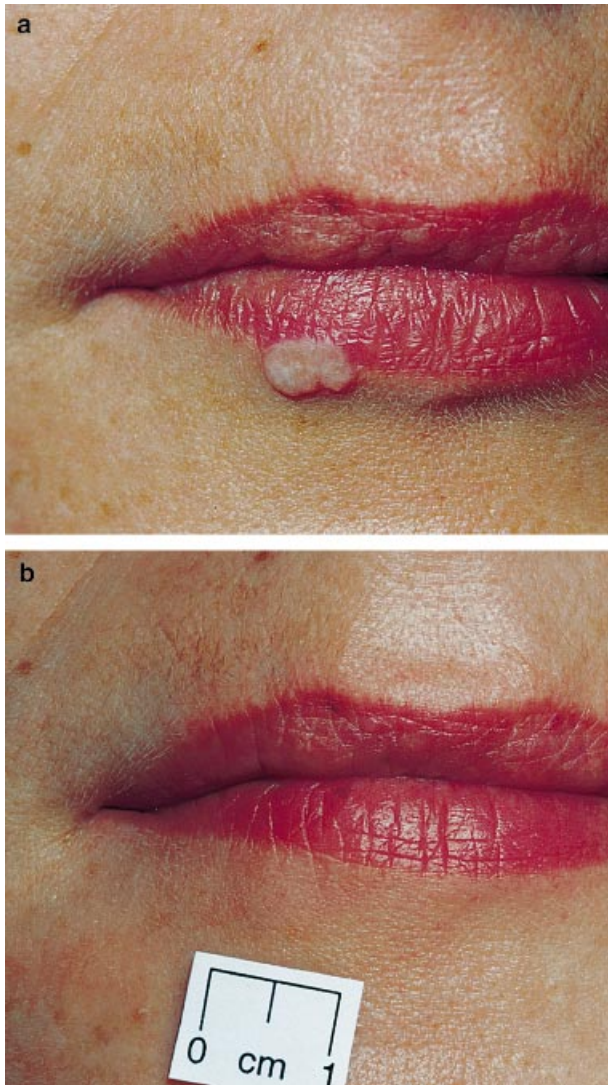


Figure 1. Recalcitrant viral wart on lower lip; (a) before treatment; (b) 3 months after two treatments with topical 5-aminolaevulinic acid photodynamic therapy.

the observation of fluorescence of *Propionibacterium acnes* is well established. The rationale for the use of PDT in the treatment of acne is based on the knowledge that *P. acnes* contain endogenous porphyrins, in particular coproporphyrin III, which are fluorescent species.¹⁹ Indeed, toxicity can be demonstrated *in vitro*.^{20,21} Additionally, selectivity of ALA-induced porphyrin fluorescence for pilosebaceous units has been shown in animals models.²² Thus, the rationale for the use of topical ALA-PDT in the treatment of acne is twofold, targeting both *P. acnes* and the pilosebaceous units. Efficacy of visible and blue light phototherapy in the treatment of acne is established.^{23–26} In a recent single-blind study, red and blue light photo-

therapy was compared with blue or white light phototherapy or benzoyl peroxide in 140 patients with mild to moderate acne. Improvement in inflammatory and comedonal acne occurred in the red and blue and blue light alone phototherapy groups and with benzoyl peroxide compared with white light. A non-significant trend to superior efficacy for the combined red and blue light treatment group was seen.²⁷ However, the mechanism of action of visible light phototherapy in the treatment of acne is likely to be multifactorial, with anti-inflammatory effects, immunomodulation and possibly endogenous PDT.

In an open randomized controlled study in 22 subjects with moderate truncal acne, ALA-PDT was performed with 20% ALA cream application for 3 h and broadband (550–700 nm) irradiation at 150 J cm^{-2} . Intra-individual comparisons were made and test areas in each subject received either one or four ALA-PDT treatments, with the appropriate control sites. With one or four topical PDT treatments, significant reduction in sebum production, *P. acnes* fluorescence and sebaceous gland size occurred, along with clinical improvement. With four treatments, improvement in these parameters was maintained for up to 20 weeks. However, there were significant adverse effects of folliculitis, discomfort and pigmentary change, suggesting that the treatment regimen could be refined.²⁸ In support of this observation of efficacy of PDT in acne vulgaris, recent work has demonstrated the efficacy of low-dose ALA-PDT in the treatment of facial acne, with improvement maintained for up to 8 months after a single treatment.^{29,30} In these latter reports 20% ALA was applied for 4 h and irradiation performed with either a pulsed excimer dye laser (635 nm, 5 J cm^{-2})²⁹ or a broadband halogen source (600–700 nm, 17 mW cm^{-2} , 13 J cm^{-2}).³⁰

Thus, the efficacy of ALA-PDT and selectivity of photosensitizer accumulation has been demonstrated in the treatment of both facial and truncal acne. Further work is required to take these findings forward, optimize the treatment regimen and compare PDT with other proven therapies. However, in a selected patient group, ALA-PDT may be an effective treatment option.

Psoriasis

There are early reports of efficacy of systemic^{31,32} and topical^{33,34} PDT in the treatment of psoriasis. Selectivity of photosensitizer accumulation in psoriatic plaques and photobleaching during PDT is established.¹² In a small study in three subjects, the same

authors showed comparable efficacy with dithranol.³⁵ In an intraindividual comparison, forearm psoriasis was treated with 10% ALA cream for 5 h prior to irradiation (600–700 nm light, Waldmann 1200 prototype at 70 mW cm⁻², 25 J cm⁻²) and compared with dithranol treatment on the contralateral forearm. Patients were treated three times weekly, although one of the subjects had guttate psoriasis and required only three treatments at weekly intervals. In the other two subjects the response to PDT paralleled that of dithranol with up to 6 months of follow-up. However, subsequent studies have revealed inconsistencies in terms of the variation in photosensitizer accumulation and PpIX fluorescence after ALA application, variation in response to treatment and in the discomfort experienced.^{36,37}

In one study in 22 subjects, 10 of 36 sites (2 cm²) treated within psoriasis plaques cleared, but all relapsed within 2 weeks.³⁷ The regimen that had been applied involved a 4-h 20% ALA application and irradiation with a modified slide projector (400–650 nm, 25 mW cm⁻², up to 16 J cm⁻²). Peak plaque fluorescence was demonstrated 6 h after ALA application,³⁸ and in a preliminary dose-ranging study using ALA and ultraviolet (UV) A, reciprocity between ALA concentration and UVA dose was demonstrated.³⁹

More recently, a study in 10 subjects with plaque psoriasis showed that multiple treatments (4-h ALA (20%) application and irradiation using a slide projector at 15 mW cm⁻²) up to three times a week, with a maximum of 12 treatments and an irradiation dose of 8 J cm⁻² at each treatment, improved clinical response.⁴⁰ Eight of the 10 subjects responded, but of 19 treated sites, only four cleared and only one showed complete response. The intensity of PpIX fluorescence before treatment varied between sites on the same patient as well as between patients, and although fluorescence reduced after each application as the study progressed, there was variation in these responses. Fluorescence microscopy of skin biopsies confirmed the variation in localization of fluorescence, which was mainly in the epidermis and stratum corneum. Interestingly, fluorescence was observed at sites of plaque psoriasis distant to those that had been treated with ALA cream, although no evidence was found of systemic absorption, and this phenomenon remains unexplained.^{36,40} A significant degree of discomfort was experienced with treatment and therefore, although the clinical response was improved by multiple treatments, pain and unpredictable response to therapy are major causes for concern in the use of this

treatment modality for psoriasis. In future, the development of a systemic photosensitizer without associated prolonged photosensitivity would potentially facilitate the use of PDT as an alternative therapy to PUVA, and preliminary results are encouraging.⁴¹ The role of topical ALA–PDT in the treatment of psoriasis remains to be clarified and optimization of the treatment regimen is required in order to reduce the unpredictable nature of response and patient discomfort.

Cutaneous T-cell lymphoma

Cutaneous T-cell lymphoma (CTCL) can present a difficult management problem and, for patients with localized plaque or patch stage disease, the addition of an alternative therapy to existing treatment options may be helpful in selected cases. There is considerable literature to support the rationale for use of PDT in the treatment of CTCL and selective photosensitizer accumulation in lymphocyte cell lines has been shown.^{42–44} In particular, PpIX accumulation has been demonstrated in lymphocytes *in vitro* with both B- and T-cell toxicity with PDT.^{43,45} In addition, PDT has been shown to induce lymphoblast mutations and thus to have potential for induction of toxicity in T-cell lines.^{46,47}

Clinical studies of the use of topical ALA–PDT in the treatment of CTCL are limited. In a study in two subjects with plaque-stage mycosis fungoides, clinical and histological response was obtained after ALA–PDT was performed on up to five occasions. 20% ALA cream was applied to affected sites for 4–6 h and typical PpIX fluorescence was observed prior to irradiation with a modified slide projector at 40 J cm⁻² (44 mW cm⁻²). Treatment was well tolerated and follow-up showed recurrence at 8 months in one patient and maintained remission at 14 months in the other.⁴⁸ A report of the treatment of patch mycosis fungoides in one subject with a single PDT session showed clinical but not histological clearance.⁴⁹ Indeed, this observation of clinical clearance without histological resolution of disease activity emphasizes the need for histological examination during the follow-up period.⁵⁰

In a further study of four lesions of CTCL in two patients, a 50% response rate occurred with a single treatment of PDT (4–6 h 20% ALA and irradiation with a pulsed frequency doubled Nd:YAG dye laser at 630 nm, < 110 mW cm⁻², 60 J cm⁻²), although a 5 : 1 ratio of fluorescence was observed between tumour and adjacent normal tissue.⁵ Methodology has not been standardized, and ALA applications of up

to 16 h with irradiations at 170–380 J cm⁻² (580–720 nm, Versalight[®]) have been used, showing complete response in stage I CTCL in two patients.⁵¹ Preliminary evidence suggests that higher intensity irradiation may spare the epidermis and specifically target the dermal lymphocytic infiltrate,⁵² and that 10% ALA is less effective.⁵³ There are other isolated reports of the use of topical PDT in the treatment of mycosis fungoides at different body sites^{54–56} and, more recently, of successful clearance of tumour stage CTCL in one subject treated with topical ALA–PDT⁵⁷ using a 4-h ALA (20%) application and 20 J cm⁻² irradiation with the Waldmann PDT 1200[®] source at 20 mW cm⁻². Five treatments were performed over 12 weeks. However, in a study of 10 patients with CTCL (10 plaque lesions and two tumour lesions), although seven of nine plaque lesions clinically cleared and showed histological regression, neither tumour lesion responded. The PDT regimen involved a 5–6 h ALA (20%) application and irradiation at 88–180 J cm⁻² (Waldmann 1200[®], 600–730 nm, 20–265 mW cm⁻²) with a median number of two treatments (2–11).⁵⁸

Thus, there is sufficient evidence *in vitro* and in small studies, that specificity and efficacy of treatment may be possible in patch- and plaque-stage disease and possibly even tumour-stage disease, if combined with debulking. However, larger studies are required, and the optimal treatment regimen, with respect to ALA application time, light dosimetry, delivery and frequency of treatment, needs to be clarified.

What about the treatment of other skin diseases?

The literature relating to the use of topical ALA–PDT in the treatment of other skin diseases consists of small case series or isolated case reports and must therefore be interpreted with caution. Methodology has not been standardized and there are no comparative studies with proven therapies. Thus, although there is a fairly extensive literature, studies of adequate size and design are lacking, and much further research is required.

Case series

Actinic cheilitis and keratoacanthoma

In a study of three subjects, actinic cheilitis responded to ALA–PDT (20% ALA, 55 J cm⁻² slide projector) with clearance and a 3-h ALA application time.⁵⁹ No recurrence was seen at 12 months. Efficacy of topical

ALA–PDT (6–8 h ALA (20%), 630 nm dye laser, 100 mW cm⁻², 80 J cm⁻²) has also been reported in four cases of keratoacanthoma.⁷

Erythroplasia of Queyrat

Topical ALA–PDT has been used in the treatment of erythroplasia of Queyrat of the penis because of the similarities to Bowen's disease. In one study in four subjects, 20% ALA was applied for 3–4 h, followed by 630 nm laser light at a dose of 100 J cm⁻² or irradiation with a slide projector (400–700 nm) at 125 J cm⁻². All patients were treated with the use of local anaesthesia, and burning, dysuria and penile swelling occurred for up to 5 days after treatment. Two patients with limited disease had complete response, one with maintained remission at 36 months and the other with recurrence at 18 months. The remaining two subjects with more extensive disease showed significant improvement but required further treatment with destructive laser therapy. Thus, extensive erythroplasia of Queyrat appeared less responsive.⁶⁰

Of concern is a recent report in one patient of the development of an invasive well-differentiated squamous cell carcinoma of the penis arising at a site of erythroplasia of Queyrat that had received three treatments with ALA–PDT 4 months previously.⁶¹ Although this is likely to be a complication of the disease rather than the treatment, it does raise concerns about the use of PDT in the treatment of erythroplasia of Queyrat, and the efficacy of treatment appears to be inferior for penile intrapidermal carcinoma *in situ* compared with cutaneous Bowen's disease.

Lichen sclerosus

There are several reports of the use of topical PDT in the genital region, and in a pilot study in 12 subjects with vulval lichen sclerosus, application of 20% ALA solution for 4–5 h, followed by irradiation with an argon ion pulsed dye laser at 635 nm (40–70 mW cm⁻², 80 J cm⁻² to the whole vulva) showed symptomatic improvement with reduction in pruritus on a visual analogue scale, in 10 of the 12 subjects, with seven showing improvement for up to 6 months. The majority of patients received a single treatment only and the remainder two to three. However, no improvement in the clinical appearance of the disease was seen in 10 of the 12 women, eight of whom were postmenopausal with advanced disease. Two premenopausal women showed objective signs of improvement

of disease after three cycles of treatment.⁶² Therefore, there appears to be limited evidence of efficacy of topical ALA-PDT in lichen sclerosus, particularly in premenopausal women with limited disease, although further work is required to clarify this.

Extramammary Paget's disease

The literature relating to the use of topical ALA-PDT in the treatment of extramammary Paget's disease is not persuasive. In a retrospective analysis of 30 patients with extramammary Paget's disease treated with multiple treatments, including radiotherapy and chemotherapy, ALA-PDT (20% ALA for 24 h, 630 nm argon dye laser, 112 mW cm⁻², 200 J cm⁻²) appeared to be effective in two patients. However, PDT was studied in combination with other therapies, and the effect of PDT alone was unclear.⁶³ In a single case report in one subject with recurrent inoperable vulval extramammary Paget's disease after chemotherapy and electron beam therapy, residual disease was successfully treated with ALA-PDT. The first treatment was delivered using 20% ALA emulsion and 500 J cm⁻² (200 mW cm⁻²) of polychromatic visible light (filtered 1000 W halogen lamp, 600–700 nm). However, biopsy 5 days later showed residual disease and subsequent treatments were performed using intralesional injection of 10% ALA in saline and the same irradiation protocol. A total of 10 treatments given once to twice weekly eventually resulted in histological clearance to 7 mm.⁶⁴ In two further reports one patient with extramammary Paget's disease responded to systemic PDT (Photofrin®) with long-term remission⁶⁵ and one had relapsed after 4 years' follow-up.⁶⁶ However, the role of topical ALA-PDT as monotherapy in early limited Paget's disease of the vulva has not been studied.

Condylomata acuminata

Photosensitizer accumulation after ALA application to condylomata has been shown.⁶⁷ Using *in vivo* fluorescence imaging and microscopy, the optimal time for irradiation appears to be between 30 min and 3 h after each ALA application.^{67,68} In a study of the use of ALA-PDT in the treatment of condylomata acuminata in seven patients, 20% ALA was applied in combination with local anaesthetic in a gel base for 14 h and irradiation with an argon dye laser at 630 nm performed (75 or 150 mW cm⁻², 100 J cm⁻²). One patient developed very marked swelling of the penis

and two patients were withdrawn because of pain, which was a major limiting factor. However, the remaining four subjects showed response rates of 75–100%, although one patient developed recurrence at 4 weeks.⁶⁹ The optimal treatment regimen needs to be examined as side-effects may have been more prominent, because it would be anticipated from time-course studies^{67,68} that lesion specificity would not be maximal with a 14-h ALA application time and that normal tissue would also be sensitized.⁶⁹

Scleroderma

On the basis of the rationale that ALA-PDT has been shown to be effective in certain cases of chronic inflammatory skin disease, such as psoriasis and lichen sclerosus, a pilot study in five subjects examined the application of ALA-PDT to the treatment of scleroderma.⁷⁰ All patients had evidence of inflammatory progressive disease and lesions were treated with 3% ALA gel for 4 h and irradiation with incoherent light (Waldmann 1200®, 40 mW cm⁻², 12 J cm⁻²). Treatment was delivered 1–2 times weekly for 3–6 months. Improvement in clinical skin scores and quantitative durometry scores was seen in all subjects. Minimal side-effects occurred and recurrence was not observed for up to 2 years' follow-up. This is an interesting potential use for topical ALA-PDT, although the mechanism of action in the treatment of scleroderma remains unclear. Further studies are required to substantiate this observation.

Hirsutism

ALA-PDT was shown to be effective in the treatment of patients with hirsutism. Irradiation dose dependence was shown, with only 50% response at 100 J cm⁻² irradiation and 90% response using 200 J cm⁻² irradiation.⁷¹

Single case reports

The effective use of ALA-PDT (20% ALA for 4 h, 630 nm argon laser, 50 mW cm⁻², 50 plus 50 J cm⁻²) in the treatment of naevus sebaceous has been reported.⁷² However, 13 treatments, combined with curettage, were required. Final histological clearance demonstrated significant dermal fibrosis and ablation of the sebaceous glands and, as the former would not be expected with PDT, the role of PDT alone was unclear. Response of epidermodysplasia verruciformis

to ALA-PDT (6 h 20% ALA, Waldmann 1200[®], 160 mW cm⁻², 160 J cm⁻²) has been shown.⁷³ Interestingly, although clearance of forehead lesions was observed, recurrence occurred at 12 months and HPV8 persisted despite treatment. In a report of efficacy of ALA-PDT (4 h 20% ALA, Paterson-Whitehurst[®] broadband source peak at 630 nm, 50 mW cm⁻², 50 J cm⁻²) in the treatment of penile lichen planus,⁷⁴ the patient was originally diagnosed as erythroplasia of Queyrat and received two treatments with ALA-PDT with clearance. However, on review of histology, the diagnosis of lichen planus was made. No recurrence was observed at 6-month follow-up.

Contradictory evidence

An early report of the efficacy of PDT with topical haematoporphyrin derivative (0.5% for 2 h) and UVA irradiation (metal halide, 360–365 nm, 55 mW cm⁻², 4 J cm⁻², total 96–120 J cm⁻²), performed three times weekly in two subjects with alopecia areata, showed encouraging results. Hair growth occurred at 8–10 weeks after treatment and was maintained for up to 4 months.⁷⁵ More recently, in a study of six subjects with alopecia areata, the use of 5%, 10% and 20% ALA cream for 3 h and irradiation with polychromatic red light (600–700 nm), commencing at 10 J cm⁻² with 5 J cm⁻² increments, was examined.⁷⁶ No significant hair growth occurred after 20 twice-weekly treatment sessions. *In vivo* fluorescence spectroscopy in one patient showed an increase in PpIX fluorescence 3 h after application with subsequent photobleaching. However, fluorescence microscopy showed that this was not localized to the inflammatory infiltrate around the hair follicles. Thus, the most recent literature suggests that ALA-PDT is not effective in the treatment of alopecia areata, despite a multiple treatment regimen.

Further contradictory evidence relates to the use of topical ALA-PDT in the treatment of vulval intraepithelial neoplasia. Kurwa *et al.*⁷⁷ demonstrated a lack of response of VIN grade III to a single treatment with ALA-PDT (20% ALA for 4 h, Waldmann 1200[®] 580–740 nm, 50–104 mW cm⁻², 150 J cm⁻²). In a separate study, 52% of 25 patients with VIN grades I–III showed complete response after multiple treatments with ALA-PDT using a 635-nm laser at 100 J cm⁻².⁷⁸ However, only 27% of those with multifocal grades II and III disease showed a complete response. In a separate study of eight women with high-grade VIN, three (37%) showed clearance of disease and 16 of 18

showed some relief from vulval symptoms using a 4-h 20% ALA application time and a 630-nm nonlaser source.⁷⁹ Therapy was well tolerated, with only one subject noting significant discomfort. All women volunteered to be re-treated with PDT in preference to other therapies. Fehr *et al.* studied 15 patients with VIN III who were treated with ALA-PDT using 10% ALA applied for 2–3 h and laser irradiation (635 nm, 120 J cm⁻²).⁸⁰ Patients treated with laser ablation or surgery ($n = 57$) acted as controls. Eleven of the 15 subjects treated with PDT were histologically clear of disease at 8 weeks and three recurrences were seen in follow-up of up to 7 months. No significant difference was seen in the response between the small number of PDT-treated patients and the control patients. However, the presence of multifocal disease was a poor predictor of response to PDT. Recent data have indicated that the presence of HPV may also predict a poor response to PDT.⁸¹ Thus, topical ALA-PDT may have a role in the treatment of VIN, particularly localized disease of lower histological grade and using multiple treatments. However, further studies are required in view of the contradictory evidence to date.

Poor response to topical ALA-PDT

ALA-induced porphyrins have been shown to accumulate in amelanotic melanoma *in vivo*.^{82–84} However, poor light penetration in pigmented tumours is a major limiting factor, and *in vitro* studies have been performed to optimize therapy with the use of 1064-nm laser pretreatment to irradiate pigment prior to PDT therapy.⁸⁵ Clinical studies of the use of ALA-PDT in the treatment of melanoma are very limited but show poor response of both amelanotic and melanotic metastatic disease.⁸⁶

Up to 100% response can be achieved with systemic PDT⁸⁷ in the treatment of breast cancer cutaneous metastases, and indeed, tumour selectivity and inhibition of tumour growth with ALA-induced porphyrins and PDT has been shown in animals models.^{88–90} However, clinical studies have shown a poor response of cutaneous breast metastases to topical ALA-PDT, which is likely to be due to the depth of metastatic nodules.^{4,6} Interestingly, intraleisional injection of the chlorin (TPPS4) and subsequent irradiation of cutaneous breast metastases showed complete response in three of nine subjects, with partial response in four.⁹¹ Thus, although *in vitro* and animal studies support the theoretical use of PDT in the treatment of breast metastases,

clinical evidence to date indicates that ALA-PDT with current regimens is not effective and is likely to be due to poor photosensitizer and irradiation penetration. However, further studies to optimize photosensitizer and light delivery are warranted.

Conclusions

Topical ALA-PDT has been applied to several non-NMSC, with recalcitrant viral warts, acne, psoriasis and cutaneous T-cell lymphoma studied in most detail. The evidence is encouraging for the use of ALA-PDT in the treatment of selected cases of recalcitrant viral warts and acne. Preliminary studies in psoriasis have been disappointing because of lack of prediction of response to treatment and adverse effects, but further work is required to clarify optimal use of photosensitizers and treatment parameters, which may minimize these problems. The preliminary evidence for the use of PDT in the treatment of CTCL is encouraging for patch- and plaque-stage disease, and optimization of treatment regimens and comparisons with other proven therapies will be essential. Remaining evidence relating to the use of ALA-PDT in the treatment of other skin conditions is based on small case series, case reports and unpublished observations, for example, in tinea pedis and chondrodermatitis nodularis helioides. Larger trials of robust design are lacking and comparative studies with established treatment modalities are required, with standardization of methodology. The potential for ALA-PDT in the treatment of several skin conditions is promising, but rigorous trials must be performed prior to its acceptance as an alternative form of therapy.

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