

Topical aminolaevulinic acid-based photodynamic therapy as a treatment option for psoriasis? Results of a randomized, observer-blinded study

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Summary

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Accepted for publication

1 May 2004

Key words:

aminolaevulinic acid, photodynamic therapy, psoriasis, visible light

Conflict of interest:

None declared.

Background Topical aminolaevulinic acid-based photodynamic therapy (ALA-PDT) has recently been tried in small open studies for several inflammatory dermatoses including psoriasis.

Objectives The purpose of this randomized, within patient comparison study was to investigate whether topical ALA-based PDT using a range of light doses can induce a satisfactory response in localized psoriasis.

Patients and methods Twenty-nine patients with chronic plaque type psoriasis were enrolled in the study. After keratolytic pretreatment three psoriatic plaques in each patient were randomly allocated to PDT with 1% ALA and a light dose of 5 J cm⁻², 10 J cm⁻² or 20 J cm⁻², respectively. Treatment was performed twice weekly until complete clearance or for a maximum of 12 irradiations. As a measure of clinical response the psoriasis severity index (PSI) of the three target plaques was assessed separately by an observer blinded to the treatment at baseline, before each PDT treatment and 3–4 days after the last irradiation.

Results Eight patients withdrew prematurely from the study. Keratolytic pretreatment alone reduced the baseline PSI in all three dose groups by about 25%. Subsequent PDT with 20 J cm⁻² resulted in a final reduction of PSI by 59%, PDT with the lower doses of 10 J cm⁻² and 5 J cm⁻² decreased the baseline PSI by 46% and 49%, respectively. The difference in clinical efficacy between 20 J cm⁻² and 10 J cm⁻² or 5 J cm⁻² was statistically significant ($P = 0.003$; $P = 0.02$), whereas no difference was found between 10 J cm⁻² and 5 J cm⁻² ($P = 0.4$). All patients reported some degree of PDT-induced stinging or burning during irradiation.

Conclusions The unsatisfactory clinical response and frequent occurrence of pain during and after irradiation renders topical ALA-based PDT an inadequate treatment option for psoriasis.

Psoriasis is a chronic recurring disease with a major impact on the patient's quality of life.¹ Dependent on the type and extent of psoriasis, a range of topical or systemic therapies are available to induce remission. In recent years topical aminolaevulinic acid-based photodynamic therapy (ALA-PDT) that was initially introduced in dermatology for the treatment of non-melanoma skin cancer has also been tried for psoriasis. In a small study on three patients with psoriasis equal clearance was observed with dithranol or PDT using 10% ALA and 25 J cm⁻² of red light.² Collins *et al.* determined the results of

a single treatment with 20% ALA followed by irradiation with 2–16 J cm⁻² of visible light at different dose rates in 20 patients with psoriasis.³ Of a total of 80 test sites, 14 (18%) cleared, six (8%) showed a partial response and 60 (75%) showed little or no improvement. Subsequently, the same group investigated the efficacy of multiple treatments with 20% ALA-PDT and a visible light dose of 8 J cm⁻² in a pilot study of 10 patients with psoriasis on 19 treatment sites.⁴ Four of 19 sites showed substantial or complete clearance, 10 had a partial response and five showed little or no

improvement. In addition to the low rate of clearance, many patients experienced considerable pain during treatment.

In principle, ALA-PDT, if effective and well tolerated, would be an interesting treatment option for localized psoriasis because it lacks long-term side-effects. We therefore performed a randomized, observer-blinded study on the efficacy and tolerability of ALA-PDT for psoriasis with a lower concentration of 1% ALA in combination with different light doses.

Materials and methods

Patients

The study was approved by the local Ethics Committee. Twenty-nine patients (14 male, 15 female) with generalized chronic plaque type psoriasis, who had been referred to our phototherapy unit for treatment, were enrolled consecutively in the study. The mean age of the patients was 45 years (range 22–86 years). Informed consent was obtained after providing detailed information on the purpose and design of the study. All patients had discontinued any systemic psoriasis treatment for at least 6 weeks and any topical psoriasis treatment for at least 2 weeks before entry to the study.

Treatment

The study was performed by three physicians. One physician (A.T.) recruited the patients and chose three comparable plaques that were designated plaques A, B and C. According to a computer-generated randomization list these plaques were then allocated blindly to one of the three irradiation doses. Treatment was performed by a second physician (S.R.) and all blinded assessments were done by a third physician who was unaware of the dose allocations (U.B-T.). Of the target plaques, 85% were located on the lower limbs (68% below and 17% at or above the knee), 7% on the upper limbs and 8% on the trunk. The median area of the surface of the plaques was 36.6 cm². The psoriasis severity index (PSI) was assessed separately for each target plaque by the blinded observer at baseline, before each PDT treatment and at the end of the study. PSI corresponds to the summed score for scaling, erythema and induration; the scores range between 0 and 3 (0 = none, 0.5 = very discrete, 1.0 = mild, 1.5 = mild-to-moderate, 2.0 = moderate, 2.5 = severe, 3.0 = very severe) with a maximum total score of 9.

Before PDT treatment a keratolytic pretreatment with 10% salicylic acid in white petrolatum was done in all patients until all scales were removed or for a maximum period of 2 weeks. Thereafter, PDT was initiated using 1% ALA (Medac, Wedel, Germany) in an oil in water emulsion (Unguentum emulsificans aquosum cream according to the German pharmacopoeia) that was applied to each target plaque under occlusion for 4–6 h. Irradiation was done with a filtered metal halide lamp (600–740 nm, Waldmann PDT 1200) at 60 mW cm⁻² using a light dose of 5 J cm⁻², 10 J cm⁻² and 20 J cm⁻², respectively. Treatment was performed twice weekly until

complete clearance was obtained or for a maximum of 12 irradiations. The final assessment of the target plaques was done 3–4 days after the last treatment.

All but one patient had generalized psoriasis. Since PDT treatment was restricted to the three target plaques the remainder of the patients' body was treated with narrow-band UVB which has been shown not to exert any systemic therapeutic effect.⁵ The PDT-treated plaques were always shielded from narrow-band UVB exposure by UVB-impermeable rubber templates. For additional topical treatment only emollients were allowed.

Besides the PSI, therapeutic efficacy was also determined by the physician's global assessment score (complete response = 100% clearance, almost complete response = 90–99% reduction of PSI, substantial improvement = 75–89% reduction of PSI, moderate improvement = 50–74% reduction of PSI, slight improvement = 25–49% reduction of PSI, minimal improvement = 1–24% reduction of PSI, no improvement = PSI unchanged, worsening = increase in PSI) and the patient's self assessment score (marked improvement = 1, moderate improvement = 2, slight improvement = 3, no improvement = 4, worsening = 5). In addition, photographs were taken at baseline and at the end of the study.

Statistical analysis

A sample size of 21 evaluable patients was calculated to give 80% power to detect a difference of 2/3 of the standard deviation with an error probability of 5% between treatments with two different light doses. For the evaluation of treatment effects within individuals changes in PSI from the baseline values to the post-treatment values were calculated and compared within each patient and tested by t-test for a shift in location. The dose–response relation was analysed using a nonparametric Jonckheere-Terpstra test. Because of the explorative character of the analysis, no adjustment for multiple testing was done.

Results

Four patients withdrew prematurely from the study because they could no longer afford the additional time for PDT treatment. Two patients were excluded from evaluation because of poor compliance. One patient withdrew after six irradiations because of slow response to PDT treatment and another patient discontinued treatment after two irradiations because of marked pain during irradiation.

In the remaining 21 patients complete clearing was found in eight and substantial improvement in four of the 63 lesions. Twenty-one lesions showed a moderate and 28 a slight or minimal response. Two lesions revealed an increase in severity score (Table 1). Irradiation with 20 J cm⁻² led to complete clearing or more than 75% improvement in seven of 21 lesions compared with only two of 21 and three of 21 lesions after irradiation with 10 J cm⁻² and 5 J cm⁻². Clearing often started in the centre of the psoriatic plaques and

Table 1 Response to treatment of 63 plaques in 21 patients with psoriasis with topical aminolaevulinic acid and photodynamic therapy (ALA-PDT)

Response	5 J cm ⁻²	10 J cm ⁻²	20 J cm ⁻²	Total
Complete	2	2	4	8
Almost complete	0	0	0	0
Substantial	1	0	3	4
Moderate	6	6	9	21
Slight	8	10	2	20
Minimal	3	2	3	8
None/deterioration	1	1	0	2

Clinical response of the psoriatic target lesions to treatment with 1% ALA-PDT using three different light doses.

progressed in a centrifugal manner so that at the end of treatment some plaques showed complete resolution with the exception of a small rim of residual disease at the periphery of the lesion (Fig. 1a,b). Examination under Wood's light indicated that the latter was not due to insufficient porphyrin accumulation since significant fluorescence was also observed at the periphery of psoriatic plaques (Fig. 2a,b).

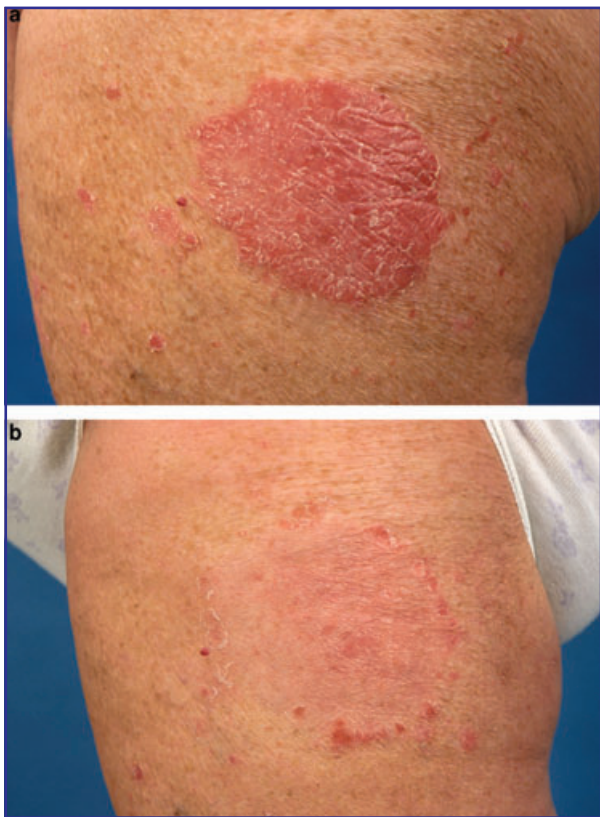


Fig 1. (a) Psoriatic plaque on the right thigh before topical aminolaevulinic acid-based photodynamic therapy. (b) The same plaque after eight treatments with 20 J cm⁻² showing complete clearance with the exception of a small rim of residual disease at the periphery of the lesion.



Fig 2. (a) Psoriatic plaque on the elbow prior to aminolaevulinic acid (ALA) application. (b) Fluorescence image of the same plaque as in (a) under Wood's light examination at 4 h after occlusion with 1% ALA.

The mean change in PSI is shown in Figure 3. Keratolytic pretreatment alone reduced the baseline PSI in all three dose groups by about 25%. Subsequent PDT with 20 J cm⁻² resulted in a final reduction of PSI by 59%, whereas PDT with the lower doses of 10 J cm⁻² and 5 J cm⁻² decreased the PSI by 46% and 49%, respectively. The difference in clinical efficacy between 20 J cm⁻² and 10 J cm⁻² or 5 J cm⁻² was statistically significant ($P = 0.003$, $P = 0.02$), whereas no difference was found between 10 J cm⁻² and 5 J cm⁻² ($P = 0.4$). During PDT treatment all severity parameters (scaling, erythema and induration) showed a similar reduction in intensity. At the final visit 3–4 days after the last irradiation a slight deterioration was observed that was mostly due to increased scaling. The latter was probably caused by the fact that at this visit there was no preceding occlusion with the ALA cream and thus a lack of desquamation effect.

The median physician's assessment score was moderate improvement, the median patient's assessment score was slight improvement.

All patients reported some degree of PDT-associated stinging or burning during the irradiation that in some cases lasted up to several hours after treatment. In eight patients the pain was so intense that treatment had to be interrupted on one or several occasions. This side-effect was more

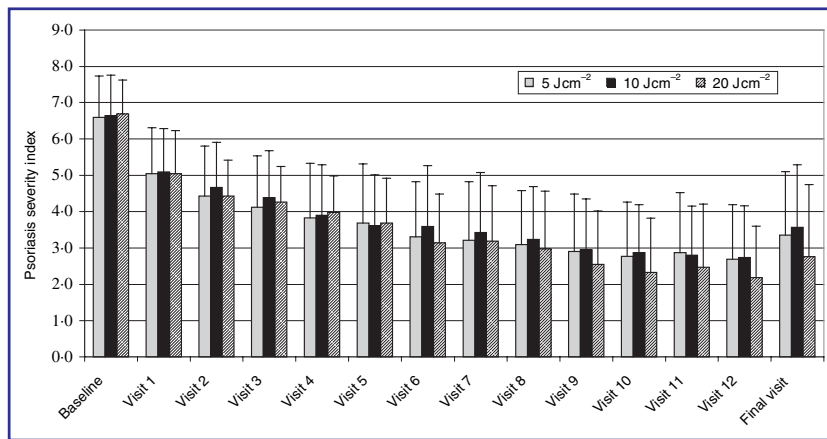


Fig 3. Decrease in mean psoriasis severity index during 1% topical aminolaevulinic acid-based photodynamic therapy with three different light doses.

pronounced in the initial phase of PDT treatment and was clearly dose-dependent as it occurred in only one of 21 of the lesions irradiated with 5 J cm⁻² as opposed to five of 21 of the lesions treated with 10 J cm⁻² and seven of 21 of the lesions treated with 20 J cm⁻². However, only one patient withdrew from the study because of unbearable pain during irradiation. Mild to moderate pigmentation was seen in all PDT-treated lesions.

Discussion

Up to the present only two small uncontrolled studies have addressed the efficacy of repetitive ALA-PDT for psoriasis.^{2,4} The present randomized, observer-blinded study was initiated to gain more information on the use and practicability of ALA-PDT for localized psoriasis.

Based on our own observations of very painful sensations during PDT of psoriasis with ALA concentrations of 10–20% and light doses of 5–20 J cm⁻² an ALA concentration of 1% was chosen for this trial. In addition, a pretreatment phase with 10% salicylic acid was included in our study protocol to facilitate the penetration of ALA into the psoriatic plaques.

Overall, the therapeutic outcome was unsatisfactory as complete clearance was observed in only eight of 63 treated lesions. Although the treatment response was variable and not predictable for a given patient, the best results were achieved with the highest light dose (Table 1). However, it does not seem feasible to increase efficacy further by simply increasing the irradiation since we observed a high rate of PDT-associated pain reactions that was clearly dose-associated.

Our results concur with a previous investigation on 10 patients and 19 treatment sites.⁴ In that study 20% ALA and a light dose of mostly 8 J cm⁻² delivered at a fixed dose rate of 15 mW cm⁻² was used. ALA-PDT was performed up to three times per week with a maximum of 12 treatments. One site responded with complete clearance and three further sites showed substantial clearing. Ten sites of 19 responded partially with a reduction of the clinical severity score between 30% and greater than 50%. Five patients reported substantial pain that increased with increasing magnitudes of the calculated photodynamic dose (the product of the initial

photosensitizer concentration and the percentage of photobleaching).

It is interesting to note that in our study two patients showed complete resolution of all target plaques irrespective of the light dose, whereas in another two patients clearance occurred only with 20 J cm⁻² but not after irradiation with 10 J cm⁻² or 5 J cm⁻². This finding indicates that the light dose is not the only factor determining the response of psoriasis to ALA-PDT. The concentration of ALA-induced protoporphyrin IX (PpIX) in lesional psoriatic skin might be equally important for the therapeutic outcome. By monitoring laser-induced fluorescence emission, large variations in PpIX levels were observed within different plaques of the same patient as well as between plaques of different patients after topical application of ALA.⁶ We also noted nonhomogeneous fluorescence indicative of ALA-induced porphyrins in the ALA-treated target lesions by visual assessment under Wood's light (Fig. 2a,b). Likewise, irregular or absent fluorescence was reported to occur in 20–40% of psoriatic lesions after occlusion with 20% ALA for 6 h.⁷ In agreement with these findings, both varying levels and distribution patterns of PpIX fluorescence were found in biopsy sections of psoriatic plaques.⁴ The reason for the great variation in PpIX accumulation in psoriatic plaques is poorly understood. Different expression of hyperkeratosis in lesional skin acting as a barrier against ALA penetration might contribute to nonhomogeneous accumulation of porphyrins.⁷ However, the matter is more complex as approximately half of untreated psoriatic plaques show distinct red autofluorescence caused by elevated levels of PpIX in the stratum corneum that is absent in the nonlesional skin of patients with psoriasis or in the skin of patients with other dermatological diseases. The origin of PpIX in psoriatic plaques remains unknown.⁸

In our study we often observed a characteristic pattern of clearance with resolution starting in the centre and subsequently spreading to the periphery of the plaques (Fig. 1a,b). This concurs with a previous observation of relapse starting from the edge of psoriatic plaques after PDT treatment.³ Lower PpIX accumulation due to a lesser amount of topically applied ALA at the margin of the lesions is unlikely to be the reason for this phenomenon, since the

ALA-treated area always included 1 cm of surrounding non-lesional skin. In addition, Wood's light examination did not reveal lower fluorescence intensity at the periphery of ALA-treated plaques. Alternatively, one might hypothesize that the centrifugal pattern of resolution merely reflects increased disease activity at the outer edge of the plaques which is not sufficiently suppressed by the PDT treatment.

In conclusion, the use of 1% ALA-PDT in combination with light doses ranging from 5 to 20 J cm⁻² was investigated for chronic localized plaque type psoriasis. An unsatisfactory clinical response, a slow pace of improvement and the frequent occurrence of pain during and after irradiation renders topical ALA-based PDT an inadequate treatment option for psoriasis. Alternative photodynamic regimens such as systemic ALA in combination with blue light or systemically administered verteporfin in combination with red light might provide better therapeutic results.^{9,10} However, the effectiveness of such alternative approaches has yet to be substantiated by controlled studies in larger series of patients.

Acknowledgments

This study was supported by a financial grant from Photonamic GmbH & Co. KG, Wedel, Germany.

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