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ORIGINAL ARTICLE

Intraindividual, right–left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities

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Abstract

Backround Actinic keratoses (AKs) are considered as *in situ* squamous cell carcinoma. Early and effective treatment is important.

Objective To compare the efficacy, cosmetic outcome and patient preference of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) with that of 5% imiquimod (IMIQ) cream in patients with AKs on the dorsa of hands and forearms.

Methods Subjects received two ALA-PDT treatment sessions and one or two courses of imiquimod (three times per week for 4 weeks each). Treatments were randomly allocated to alternate upper extremities. Assessments included lesion response one and six months after treatment, cosmetic outcome evaluated by the investigators and patients' preference 6 months after treatment. Efficacy end point included the individual AK lesion clearance rate.

Results Thirty patients with 256 lesions were included in the study. At the first follow-up, treatment with ALA-PDT resulted in significantly larger rate of cured lesions relative to 5% IMIQ cream (70.16% vs. 18.26%). At the second follow-up both treatments showed a high rate of cured lesions (65.32% for PDT vs. 55.65% for IMIQ cream). Response rates obtained in grade I lesions were higher for both treatments (71.64% for PDT vs. 72.13% for IMIQ), while treatment with PDT resulted in a significant larger rate of cured grade II lesions (57.89% for PDT vs. 37.03 for IMIQ).

Difference in cosmetic outcome was not statistically significant. Results for subject preference favoured ALA-PDT.

Conclusions Our study shows that ALA-PDT and 5% IMIQ cream are both attractive treatment options for upper extremities AKs with comparable efficacy and cosmetic outcomes.

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Keywords

actinic keratosis, extremities, imiquimod, photodynamic therapy, treatment

Conflicts of interest

None declared.

The term actinic keratosis refers to a sun-induced clinical erythematous lesion covered with scale. Histologically, it represents an intraepidermal malignant neoplasm with proliferation of atypical keratinocytes.[1] Epidemiological data show a significant prevalence of actinic keratoses among the Caucasian population. In Europe, a prevalence of 15% in men and 6% in women has been documented.[2] Rates of malignant transformation of actinic keratoses are considerable: approximately 10% of actinic keratoses in immunocompetent patients progress into invasive squamous cell carcinoma (SCC), while progression rates raise to 40% in immunocompromized patients.[3] Early identification and treatment are therefore advisable as it is impossible to predict which lesions may become invasive and develop into metastatic SCC. Moreover, an effective treatment that leads to good cosmesis is important because of the cosmetically sensitive sites of actinic keratoses' development.

Therapies established for the treatment of actinic keratoses include both ablative procedures (surgery, laser ablation, curettage, cryotherapy) and topical treatments [photodynamic therapy (PDT), 5-fluorouracil, diclofenac 3% gel, 5% imiquimod cream].

PDT is a non-invasive and precisely directed treatment. The procedure involves activation of a photosensitizing agent by visible light, with subsequent release of reactive oxygen species, which in turn produce local tissue destruction. PDT has the ability to treat large skin areas, while previous clinical studies showed

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that it provides high response rates and superior cosmetic outcome compared with conventional therapies.[4,5] Moreover, it has recently been recommended as first-line therapy in the international PDT guidelines for non-melanoma skin cancer.[6]

Imiquimod is a representative of a new class of Toll-like receptor 7 agonists which serve as immune response modifiers. It stimulates the immune response by induction, synthesis and release of cytokines that increases immunity at the cellular level inducing the indirect antiviral and anticancerous activity.[7] Several studies have shown that imiquimod is effective at treating clinical and subclinical actinic keratoses.[8,9]

The aim of our intraindividual (right–left) study was to compare the efficacy, tolerability, safety and cosmetic outcome of topical 5-aminolevulinic acid (5-ALA) PDT with that of 5% imiquimod cream in patients with actinic keratoses on the dorsa of hands and forearms, and to evaluate patient preference.

Patients and methods

Thirty patients (25 male, 5 female) with clinical diagnosis of non-hyperkeratotic grade I (mild) and grade II (moderate) actinic keratoses on the dorsa of hands and forearms were enrolled in this intraindividual (right–left) comparison study. The study was conducted between September 2007 and July 2008. Each patient had to have at least six comparable lesions of similar severity on both sides (at least three lesions on each side). Precise location of each lesion was recorded on an anatomical diagram and documented with digital photographs. Exclusion criteria were other dermatological diseases or conditions in the treatment or surrounding (3 cm distance) area, topical treatments for actinic keratoses on hands and forearms within the past 2 months, invasive tumours within the treated area. All patients gave written consent to participate after having received detailed information on the purpose and design of the study. The study was approved by the local ethics committee and was conducted in accordance with the latest revision of the Declaration of Helsinki.

Treatment protocol

Eligible patients received PDT treatment and treatment with imiquimod 5% cream randomly allocated to alternate upper extremities.

At baseline, all patients were treated with ALA-PDT. Lesions were prepared by gently removing crusts and by roughening their surface with a small curette. 20% 5-ALA (MEDAC Gmbh, Hamburg, Germany) was applied on the lesions as well as on 5 mm of normal surrounding skin and left under occlusion for 4 h. Immediately after removal of the dressing and the cream remnants, treatment area was illuminated with red light (570–670 nm) by a non-coherent light source (Waldmann PDT 1200, Waldmann-Medizin-Technik, Villingen-Schwenningen, Germany) at a light dose of 75 J/cm^2 and a fluence rate of 75 mW/cm^2. Because of the great size of the treatment area, two PDT sessions were performed on the same day; one illuminating the hand and lower third of the forearm and one illuminating the upper two thirds of the forearm. Each patient received two ALA-PDT sessions 15 days apart.

Treatment with imiquimod was based on the approved dosage regimen for the treatment of multiple actinic keratoses on the head.[10] At baseline visit, patients were instructed to apply imiquimod 5% cream once daily 3 days per week, just prior to their sleeping hours. Cream was left on the skin for at least 8 h. Patients applied 500 mg (two sachets) of cream, amount needed because of the size of the treatment area. Treatment started at the day of baseline visit, continued for 4 weeks (course 1) followed by a 4-week post-treatment period. Patients who had not cleared all their actinic keratosis lesions in the treatment area participated in a second 4-week treatment cycle (course 2).

After end of treatment and during follow-up period, no additional actinic keratosis treatment was allowed.

Response evaluation

All patients were evaluated at baseline and at 1 and 6 months after treatment. Patients who had not completely cleared all their actinic keratosis lesions after the course 1 post-treatment period with imiquimod cream underwent a second treatment cycle and returned for a final assessment 6 months after treatment. The same examiners counted and recorded the number and performed the clinical evaluation of lesions at baseline and at follow-up visits. Efficacy end point included the individual actinic keratosis lesion clearance rate.

Clinical lesion response was defined as complete response (CR; complete disappearance of the lesion) or as non-complete response (non-CR; incomplete disappearance of the lesion).

Cosmetic outcome was assessed by investigators at month 6 after treatment and was based on the amount of scarring, atrophy, induration, erythema and pigment change within the treated area in comparison with adjacent, untreated skin. It was graded as excellent (no erythema, change in pigmentation, scarring, atrophy or induration), good (slight to moderate erythema or change in pigmentation but no scarring, atrophy or induration), fair (slight scarring, atrophy or induration) and poor (moderate to extensive scarring, atrophy or induration).

At month 6, patients completed a questionnaire regarding their preference in treatment procedure, efficacy and treatment choice in case of new lesions.

Adverse events were noted at each visit, together with their severity, duration and need for additional therapy.

Statistical analysis

Lesion complete response was compared between the treatment groups using *t*-test and 95% confidence intervals (95% CI), assuming independency between lesions within patients. The number of lesions with excellent, good, fair or poor cosmetic outcome was compared between the two groups by means of the Mann-Whitney test.

Table 1 Patient demographics and lesion characteristics at baseline

		ALA-PDT	Imiquimod
Sex, *n* (%)			
Male	25 (83.33)		
Female	5 (16.66)		
Age (years)			
Mean ± SD (range)	63.8 ± 9.5 (49–79)		
Total lesions, *n* (%)	256 (100)	133 (52)	123 (48)
Severity, *n* (%)			
Grade I		72 (54.1)	66 (53.7)
Grade II		61 (45.9)	57 (46.3)

Results

In total, 30 patients were enrolled in the study. Patients were all white-skinned, while 83.33% (25 of 30) were male and 16.66% were (5 of 30) female. Their ages ranged from 49 to 78 years (mean ± SD, 63.8 ± 9.5). Distribution according to Fitzpatrick skin types was as follows: II, 30% (9 of 30); III, 56.6% (17 of 30); IV, 13.3% (4 of 30).

The 30 patients had a total of 256 lesions. Baseline lesion characteristics were similar between the two treatment groups with 133 lesions on the ALA-PDT side and 123 lesions on the 5% imiquimod cream side. Both sides were well balanced in terms of number and severity of lesions. Overall, 84.96% (113 of 133) of lesions treated with ALA-PDT were prepared at baseline. Lesions not prepared were all grade I lesions.

Patient demographics and baseline lesion characteristics are summarized in Table 1.

Overall, 28 patients (93.33%) with 239 lesions completed the study. Two patients were lost to follow-up and were not included in the analysis. Of the 239 lesions included in the analysis, 124 were treated with PDT and 115 with imiquimod.

Clinical evaluation

At 1 month after PDT treatment cycle and at course 1 4-week post-treatment period with imiquimod, the overall lesion complete response rate was 70.16% for PDT and 18.26% for imiquimod cream ($P < 0.05$). When looking at lesion response for the subgroups based on lesion grade, higher response rate was achieved in grade I lesions treated with PDT (75% for PDT vs. 34.42% for imiquimod). The difference was statistically significant ($P < 0.05$) with a 95% CI between 64.6 and 85.3 for PDT and between 22.5 and 46.3 for imiquimod. No grade II lesions treated with imiquimod cream achieved clearance, while complete clearance rate achieved with PDT was 64.91% with 95% CI between 52.5 and 77.3.

Table 3 Overall cosmetic outcome

	ALA-PDT (*n* = 124)	Imiquimod (*n* = 115)
Excellent	105 (85%)	86 (75%)
Good	17 (14%)	23 (20%)
Fair	1 (1%)	6 (5%)
Poor	0 (0%)	0 (0%)

At month 6, both treatments showed a significant reduction from baseline in lesion count. The overall lesion complete response was 65.32% for PDT (95% CI, 56.9–73.7%) vs. 55.65% for imiquimod cream (95% CI, 46.6–64.7%), difference that was not statistically significant ($P > 0.05$) The observed treatment difference was not similar for mild and moderate thickness lesions. Response rates obtained in grade I lesions were 71.6% (95% CI, 60.8–82.4%) and 72.13% (95% CI, 60.9–83.4%) for PDT and imiquimod cream respectively ($P > 0.05$). On the contrary, around 20% difference between treatments was observed in grade II lesions with response rates at 57.8% (95% CI, 45.15–70.7%) for PDT and 37% (95% CI, 24.15–49.9%) for imiquimod cream, a difference that was statistically significant ($P < 0.05$). Overall and by-grade lesion response is summarized in Table 2.

Cosmetic outcome

At month 6, the investigator-assessed cosmetic outcome showed no significant difference between the two groups. In the PDT group, 80% of the lesions had an excellent cosmetic outcome compared with 75% of those treated with imiquimod cream. Good, fair and poor outcome was observed in 19, 1% and 0% lesions treated with PDT and in 20, 5% and 0% lesions treated with imiquimod cream, respectively. Difference in cosmetic outcome between the two groups was not statistically significant ($P = 0.065$).

Cosmetic outcome assessed by the investigators can be seen in Table 3.

Patient preference

Results from patient questionnaire showed that patients preferred PDT regarding the procedure (69% vs. 31%). Despite response

Table 2 Overall and by grade lesion response 1 and 6 months after treatment

	1 month ALA-PDT	Imiquimod	6 months ALA-PDT	Imiquimod
Overall lesion response	87/124 (70.16%)	21/115 (18.26%)	81/124 (65.32%)	64/115 (55.65%)
Grade I lesion response	50/67 (75%)	21/61 (34.42%)	48/67 (71.64%)	44/61 (72.13%)
Grade II lesion response	37/57 (64.91%)	0/54 (0%)	33/57 (57.89%)	20/54 (37.03%)

rates, only 55% of the patients favoured PDT in terms of efficacy vs. 45% who favoured imiquimod cream. Finally, if they had to be treated again, 70% of them would prefer PDT vs. 30% of them who would prefer imiquimod cream.

Adverse events

No unexpected safety issues occurred in the study population until end of the follow-up period. The most commonly reported adverse events were expected, were specifically related to the type of therapeutic procedure and were mild to moderate and transient in nature. No patient discontinued the study due to adverse events.

PDT reactions recorded during light treatment were stinging (83.3%), burning (100%) and pain (100%). Pain management included the use of a fan or of cooling sprays in patients who felt intense pain and discomfort. Local phototoxic reactions included moderate erythema (100%), oedema (66.6%) and blistering (26.6%). These reactions were well tolerated, did not demand additional treatment and resolved within 7–15 days without further complications.

The most frequently reported adverse events in the imiquimod cream group were application site reactions. Application site itching, burning and pain were reported by 21.4%, 10.7% and 3.5% of the patients accordingly.

Local skin reactions in the treatment area were mild to moderate and were well tolerated. They were more intense during course 1 than during course 2 and included erythema (92.8%), crusting (10.7%), scaling (10.7%), erosions/ulcerations (7.1%), and oedema (7.1%).

Infections in the treatment area were not observed.

Discussion

Actinic keratoses are among the most common cutaneous malignancies and are classified as an early *in situ* squamous cell carcinoma with reported progression rates of up to 20% over 10 years.[1] It is therefore recommended that all actinic keratoses are treated to prevent possible invasion.

There are numerous previous studies demonstrating the efficacy of PDT and imiquimod 5% cream in treating non-hyperkeratotic actinic keratoses.[11–18] However, we believe this is the first study comparing the efficacy of ALA-PDT vs. imiquimod 5% cream on multiple actinic keratoses located on sites other than the face and scalp (i.e. the upper extremities).

Based on the clinical assessment, ALA-PDT treatment provided 6 months after treatment resulted in a complete clearance rate of 65.32%. Response was best in grade I lesions with a complete clearance rate at 71.6%, while grade II lesions achieved a complete clearance rate of 57.8%.

Previous studies have shown complete response rates of 71–91% for lesions on the face or scalp given a single PDT with topical ALA.[11,12] With repeated PDT treatment – as was the case in our study – higher response rates can be achieved. actinic keratoses of the extremities may be more resistant than that of the face and scalp. One possible explanation for this increased resistance could be the lack of pilosebaceous units in these areas, as the presence of pilosebaceous units could lead to a better absorption of the prodrug and to a better response. Compared with studies with topical MAL-PDT in AK of extremities, our study demonstrated lower complete clearance rates. In a previous prospective randomized study, the authors demonstrated that two MAL-PDT sessions lead to complete response in 76% of actinic keratoses on the extremities 3 months after the initial treatment.[4] In a more recent multicentre intraindividual study for multiple actinic keratoses of the extremities, MAL-PDT provided 6 months after treatment resulted in a mean percentage reduction of 78% in lesion count, while 72% of the cured lesions had been treated only once.[15] In both studies, response was best in thin non-hyperkeratotic lesions, which is consistent with our results. However, in a study with 110 patients and a total of 968 lesions on the face and scalp treated with ALA-PDT, the percentage of lesions clearing completely was similar in grade I and grade II actinic keratoses.[16]

The drop in response rate from 70.16% to 65.32% at 1- and 6-month follow-up examination can be interpreted as an apparent rather then real complete resolution of some actinic keratoses. Residual malignant cells that are still in the epidermis, but not apparent by visual inspection, will continue to proliferate and result in a clinical recurrence at a later follow-up examination.[14]

Clearance rates obtained with imiquimod 5% cream in our study after the first course of treatment were lower compared with previous studies conducted on multiple actinic keratoses of the face and scalp.[17,18] However, the overall complete clearance rate raised from 18.26% to 34.42% when only grade I lesions' response was estimated. Clearance rates for individual actinic keratosis lesions on the head after one treatment course were 64.6% in a previous multicentre study;[18] however, baseline numbers of grade I and grade II lesions are not mentioned. A further increase in efficacy was demonstrated in our study after the second course of treatment, resulting in an overall complete clearance rate of 55.65%. This percentage rose to 72.13% after clinical assessment of grade I lesions only. In the above-mentioned study,[18] individual lesion clearance rates after a second course treatment reached 85.4%, while in a study conducted by Jorizo[17] *et al.*, the individual lesion clearance rate after two treatment courses was 74.4%. Again, clearance rates are not mentioned separately for grade I and grade II lesions.

Possible explanations for the higher response rates observed in treatment of actinic keratoses on the face and scalp with imiquimod cream might be the greater number of pilosebaceous units as well as the increased area vasculature that promote drug absorption and lead to a better result.

The excellent cosmetic outcome of both therapies is consistent with previous findings and may favour the use of PDT or imiquimod 5% cream over larger areas, which is useful considering the widespread nature of actinic keratoses in many patients.[15,19]

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