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CLINICAL REPORT

A Randomized Multicenter Study to Compare Two Treatment Regimens of Topical Methyl Aminolevulinate (Metvix®)-PDT in Actinic Keratosis of the Face and Scalp

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Photodynamic therapy (PDT) with topical methyl aminolevulinate (MAL) administered in two treatment sessions separated by 1 week is an effective treatment for actinic keratoses. This open prospective study compared the efficacy and safety of MAL-PDT given as a single treatment with two treatments of MAL-PDT 1 week apart. Two hundred and eleven patients with 413 thin to moderately thick actinic keratoses were randomized to either a single treatment with PDT using topical MAL (regimen I; $n=105$) or two treatments 1 week apart (regimen II; $n=106$). Each treatment involved surface debridement, application of Metvix® cream (160 mg/g) for 3 h, followed by illumination with red light using a light-emitting diode system (peak wavelength 634 ± 3 nm, light dose 37 J/cm^2). Thirty-seven lesions (19%) with a non-complete response 3 months after a single treatment were re-treated. All patients were followed up 3 months after the last treatment. A total of 400 lesions, 198 initially treated once and 202 treated twice, were evaluable. Complete response rate for thin lesions after a single treatment was 93% (95% CI=87–97%), which was similar to 89% (82–96%) after repeated treatment. Response rates were lower after single treatment of thicker lesions (70% (60–78%) vs 84% (77–91%)), but improved after repeated treatment (88% (82–94%)). The conclusion of this study is that single treatment with topical MAL-PDT is effective for thin actinic keratosis lesions; however, repeated treatment is recommended for thicker or non-responding lesions. ***Key words: actinic keratosis; clinical trial; methyl aminolevulinate; topical photodynamic therapy.***

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Actinic keratoses (AK) are the most common premalignant skin lesions, with a prevalence of 10% for individuals over 40 years in the UK (1). Histologically, AK lesions contain features of squamous cell carcinoma (SCC) and therefore have the potential to progress to malignant lesions (2, 3). Although some of the AK lesions can spontaneously disappear (4), there is still a risk of progression to invasive SCC (from 0.025 to 16% per year in different studies) (2). Early identification and treatment is therefore advisable. Moreover, because AK lesions are usually located in cosmetically sensitive areas such as the face, an effective treatment with good cosmesis is important.

Photodynamic therapy (PDT), a treatment modality involving the use of a photosensitizing agent, oxygen and light of a specific wavelength to cause cell death, is used in the treatment of a range of skin lesions, including AK (5–7). Compared with conventional treatments such as cryotherapy, this modality offers the advantage of better cosmesis, due to high relatively selective uptake of the photosensitizer by neoplastic cells.

Currently, both 5-aminolevulinate (ALA), and the methyl ester of ALA, methyl aminolevulinate (MAL, Metvix®), are available for use as photosensitizers. Topically applied MAL will generate the formation of photoactive phorphyrin in the skin lesion. Compared with ALA, MAL offers the advantages of improved lesion penetration due to enhanced lipophilicity (8, 9) and greater specificity for neoplastic cells (10). MAL-PDT has also been shown to be less painful than ALA-PDT when performed on tape-stripped normal skin (11). Clinical data from controlled prospective studies demonstrate that MAL-PDT administered in two treatment sessions separated by one week is an effective treatment for AK lesions with an excellent or good cosmetic outcome in >90% of patients (12, 13). Moreover this treatment regimen with MAL has shown to be superior to cryotherapy (13). Patient satisfaction with this treatment is also high, with data indicating that 75% of patients prefer this treatment modality (12, 14). The current study was conducted to investigate whether a more flexible treatment schedule involving a single treatment session with re-treatment of non-responding lesions would be as effective as a standard two-treatment one week apart schedule in patients with thin to moderately thick AK lesions.

MATERIALS AND METHODS

Between January and October 2002, males and females aged at least 18 years with up to 10 clinically diagnosed AK lesions on

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the face and/or scalp were recruited to this randomized, prospective study by the specialist dermatology clinics of 21 hospitals in Sweden. Only those patients with mild (grade 1) or moderately thick (grade 2) non-pigmented lesions, as defined by Olsen et al. (15) (grade 1=slightly palpable, better felt than seen, i.e. thin lesions; grade 2=easily palpable lesions) were included. Ethical approval for the study was obtained from the local ethics committee responsible for each centre. The study was conducted according to the Declaration of Helsinki and all patients signed a written informed consent before entry.

After screening, eligible patients were randomized to one of two treatment regimens: a single MAL-PDT treatment session with re-treatment if there was a non-complete response (i.e. incomplete disappearance of the lesion) after 3 months (regimen I), or two MAL-PDT treatment sessions separated by one week (regimen II). The randomization was performed after the patient was included in the study. After inclusion, the investigator opened a sealed envelope to find the randomization code. Before each treatment session, any crust or scale was removed and the lesion surface was scraped gently using a curette or scalpel blade. Local anaesthesia was not required for the debriding phase. A 1-mm thick layer of MAL cream (Metvix 160 mg/g; PhotoCure ASA, Oslo, Norway) was applied to each lesion and 5 mm of surrounding tissue and covered with an adhesive occlusive dressing (e.g. Tegaderm®, 3M) for 3 h. The dressing was then removed and the cream was washed off with 0.9% saline solution, immediately before illumination with red light using a light-emitting diode system (Aktilite® CL 16; peak wavelength 634±3 nm, light dose 37 J/cm^2, irradiance 50 mW/cm^2 at 50 mm distance to the skin surface with a maximum variation over the target area of ±10%). During illumination the patient wore protective eyewear. Local anaesthesia was used if needed.

All patients were followed up 3 months after the last treatment. Lesion response was assessed by the investigator at this visit as either complete (i.e. complete disappearance of the lesion) or non-complete. For each lesion that had responded completely, the following parameters were assessed and rated as none, slight or obvious: hypopigmentation, hyperpigmentation, scar formation and tissue defect. Previously treated patients rated overall satisfaction with the study treatment as better, equal or worse compared with prior treatment modalities.

Adverse events, including local phototoxicity reactions that normally occur after PDT, were recorded before and after illumination, and 3 months after the last treatment, assessing their severity as mild, moderate or severe. The clinician assessed the causal relationship of any adverse events to the study treatment as related, uncertain or not related.

Statistical analysis

Data were evaluated on a per protocol basis, including all eligible lesions with response evaluation within the relevant time windows (−2 to +4 weeks) for the scheduled 3-month post-treatment assessment. The lesion and patient complete response rate, i.e. the proportion of patients in whom all lesions showed a complete response, was calculated with 95% confidence intervals (CI) for each treatment group. The two-sided 95% Clopper-Pearson confidence interval for the proportions was used. The one-sided (upper limit) 97.5% confidence interval for difference in patient complete response rate between regimen II and regimen I was calculated by the Mantel-Haenszel method to account for centre differences. The lesion complete response rate was summarized by lesion location and grade using count and percentages of lesions. Cosmetic outcome was summarized for each parameter using count and percentages of lesions. All treated patients were evaluable for safety.

In the sample size calculation the patient complete response rate was assumed to be 90% for both treatment regimens. To demonstrate with 97.5% confidence (α=0.025) and a power of 90% that regimen I is no more than 15% inferior to regimen II we needed at least 105 patients in each treatment group (in total 210 patients).

RESULTS

A total of 211 Caucasian patients with 413 lesions were randomized and treated; 105 patients with 198 lesions were initially treated once (regimen I) and 106 patients with 215 lesions were treated twice with 1 week apart (regimen II). The baseline characteristics of the two treatment groups were similar (Table I). The majority of patients (76–83% in both groups) had one or two lesions. Overall, most lesions (90%) were located on the face, and about 50% of these lesions were thin (grade 1). A slightly higher proportion of patients allocated to regimen II than to regimen I had previously received treatment for AK, most commonly cryotherapy (Table I).

Six patients in the regimen II group were protocol violators; three of these were only treated once, two were lost to follow-up and one patient discontinued due to an adverse event (erythema) and was not evaluated for response. In total, 13 lesions in these 6 patients allocated to regimen II were excluded from analysis. Thus, efficacy analysis was based on 400 lesions, 198 treated with regimen I and 202 treated with regimen II.

Most lesions (92% allocated to regimen I and 93% allocated to regimen II) were prepared prior to

Table I. *Patient and lesion characteristics at baseline, all treated patients*

	Regimen I*	Regimen II*
No. of patients	105	106
Male:female; *n*	41:64	41:65
Age in years; mean (SD)	69 (10)	68 (11)
Skin type (*n*)		
I	7	8
II	59	58
III	27	31
IV/V	12	9
Prior treatment for actinic keratosis	46	59
Cryotherapy	38	48
Total no. of lesions	198	215
Facial lesions	184	189†
Thin	93	89
Moderate	91	95
Scalp lesions	14	26
Thin	6	6
Moderate	8	20
Lesion diameter (mm); mean (SD)	10.0 (9.1)	9.6 (7.0)

*Regimen I, a single MAL-PDT treatment session; regimen II, two MAL-PDT treatment sessions separated by 1 week.
†Lesion parameters are missing for five lesions in regimen II.

Table II. *Summary of treatment information, all treated patients*

	Regimen I* (n=105)	Regimen II* (n=106)
No. of treatments	235	420
Prior lesion preparation; *n* (%)	217 (92)	389 (93)
Metvix application time (hh:mm)†	3:07 (0:12)	3:05 (0:12)
Illumination time (mm:ss)†	8:01 (0:02)	8:01 (0:02)

*Regimen I, a single MAL-PDT treatment session; regimen II, two MAL-PDT treatment sessions separated by 1 week.
†Mean (SD).

illumination. The treatment procedure used in each group was similar. Overall, the mean period of application of the cream was about 3 h and mean illumination time was about 8 min (Table II).

Efficacy

The overall lesion complete response rate after a single treatment with MAL-PDT was similar to that observed with regimen II (81% vs 87%). A further 22 lesions in the regimen I group showed a complete response after retreatment 3 months after the initial treatment (overall response rate 92%). Although the single- and two-treatment schedules appeared to be similarly effective for thin lesions (93% vs 89%), lesion complete response rates were lower in moderately thick lesions treated once rather than twice (70% vs 84%), although the rate subsequently improved after repeated treatment (88%) (Table III). Overall, patient complete response rates were similar: 89% (95% CI 81–94%) with regimen I (including repeated treatment) and 80% (71–87%) with regimen II. The upper 97.5% confidence limit for the difference between the two treatment regimens was 0.2%, which clearly shows that regimen I was non-inferior to regimen II. Cosmetic outcome with respect to hypopigmentation, hyperpigmentation, scar formation and tissue defect was assessed for each of the parameters as excellent in >75% of the lesions in each treatment group (Fig. 1). The most common aberration was hyperpigmentation, which was slight in 16% (58) of the lesions, and obvious in 1% (5) of the lesions.

Patient satisfaction with MAL-PDT was higher than with previous treatments. Compared with all previous treatments, MAL-PDT was rated better in 68% (41/60) of the cases in the regimen I group and 55% (44/80) of the cases in the regimen II group. Overall, MAL-PDT was rated better than cryotherapy in 66% (25/38) of the cases in regimen I and 58% (28/48) of the cases in regimen II.

Safety

Adverse events were reported for 95 (45%) patients, 42 allocated to regimen I and 53 allocated to regimen II. Not surprisingly, the total number of adverse events in regimen II was about twice that observed in regimen I (134 vs 66 and 95 vs 54, respectively). However, there was no evidence of any cumulative local phototoxicity following repeated MAL-PDT; in regimen II, 76 local events were reported after the first treatment and 46 local events were reported after re-treatment.

The profile of treatment-related local adverse events was not unexpected for this treatment modality, with burning sensation of the skin, skin pain and erythema most commonly reported (Table IV). Most local adverse events were of mild to moderate intensity and of relatively short duration; the median duration of burning sensation and pain was <1 day, and the median duration of erythema was 5 days with regimen I and 2 days with regimen II. One patient allocated to regimen II discontinued treatment due to moderate erythema; the event subsequently resolved completely.

DISCUSSION

The results of the current study demonstrate that in patients with thin AK lesions, a single treatment with

Table III. *Number (%) of lesions with complete response (CR) 3 months after last treatment, summarized by lesion thickness and location, all evaluable patients*

	Total		CR/no. of lesions	
	No. of lesions	CR; *n* (%)	Face	Scalp
Regimen I (single treatment only)	198	161 (81)	151/184 (82)	10/14 (71)
Thin	99	92 (93)	86/93 (92)	6/6 (100)
Moderate	99	69 (70)	65/91 (71)	4/8 (50)
Regimen I (including repeated treatment)	198	183 (92)	171/184 (93)	12/14 (86)
Thin	99	96 (97)	90/93 (97)	6/6 (100)
Moderate	99	87 (88)	81/91 (89)	6/8 (75)
Regimen II	202*	175 (87)	154/176 (88)	21/26 (81)
Thin	85	76 (89)	71/79 (90)	5/6 (83)
Moderate	113	95 (84)	79/93 (85)	16/20 (80)

*Lesion parameters are missing for four lesions in regimen II.

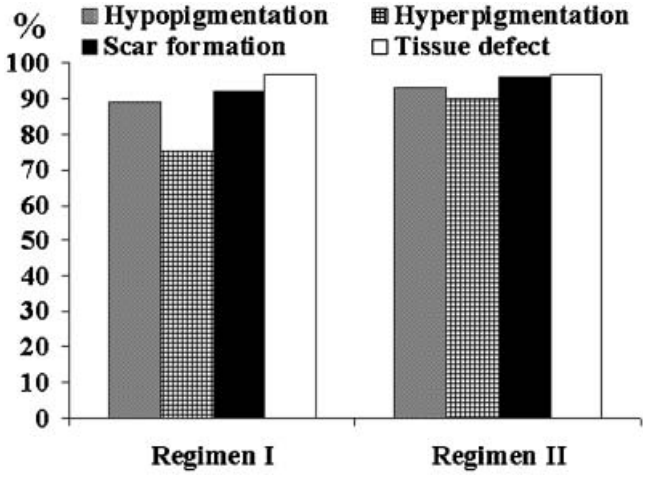

Fig. 1. Lesion cosmetic outcome for lesions in complete response. Percentage of lesions with excellent cosmetic results for hypopigmentation, hyperpigmentation, scar formation and tissue defect.

Table IV. *Number (%) of patients with common treatment-related local adverse events*, summarized by treatment regimen*

Event	Regimen I (n=105)	Regimen II (n=106)
Burning sensation of skin	16 (15)	20 (19)
Pain	9 (9)	19 (18)
Erythema	9 (9)	11 (10)
Oedema	2 (2)	10 (9)
Stinging skin	6 (6)	3 (3)
Pricking skin sensation	1 (1)	7 (7)

*Events considered related or with uncertain causality, as assessed by the investigator, and reported for at least 5% of patients.

MAL-PDT is as effective (93% complete response) as a two-treatment schedule (89% complete response). Almost all of the thin lesions with a non-complete response after initial treatment resolved after re-treatment (overall lesion complete response rate 97%). However, the results of the study do indicate that the two-treatment schedule is more appropriate for thicker (grade 2) AK lesions. Lesion complete response rates were 70% after single treatment but improved to 88% after re-treatment, comparable with that observed with the two-treatment schedule in this study (84%). Of course, one could also choose to treat only the non-responding thicker lesions again after 3 months, which could be a more cost-effective approach in practice. Other studies with the two-treatment schedule show overall lesion response rates of 89–91% (12, 13), which is comparable with this study of 87% complete response rate. Another study of single treatment with MAL-PDT (but with no possibility to re-treat if necessary) shows an overall lesion complete response rate of 70% (14) compared with 81% in this study. This could probably be explained by the fact that only 40% of the lesions were scraped before putting on the MAL cream in that study compared with 92% in this study.

Cosmetic outcome was generally excellent, and more patients preferred MAL-PDT to conventional therapy such as cryotherapy. The preference for MAL-PDT could of course be influenced by the fact that this was the most recent treatment for the patient. New clinical randomized studies will be needed to confirm this preference. The study also provided further evidence of the general tolerability of MAL-PDT. Local phototoxicity reactions, such as burning sensation of the skin, skin pain and erythema, were consistent with the known side effect profile for topical PDT.

Given the ever-increasing financial constraints that are affecting the health-care systems, a treatment that offers greater flexibility without loss of efficacy might add benefit. The results of this study have clearly shown that a single treatment with MAL-PDT is as effective in thin AK lesions as a two-treatment schedule. However, repeated treatment is more appropriate for lesions of moderate thickness (i.e. grade 2) or for lesions with a non-complete response after initial treatment. The single treatment schedule offers the additional advantages of improved patient convenience and acceptability, while at the same time reducing the use of health-care resources.

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