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CLINICAL REPORT

Real-life Data on Patient Characteristics, Cost and Effectiveness of Field-directed Treatment for Actinic Keratoses: An Observational Study

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Actinic keratoses (AK) occur frequently; however, real-life clinical data on personalized treatment choice and costs are scarce. This multicentre one-year observational study investigated patient-characteristics, cost and effectiveness of methylaminolaevulinate photodynamic therapy (MAL-PDT), imiquimod (IMI) and 5-fluorouracil (5-FU) in patients with AKs on the face/scalp. A total of 104 patients preferred MAL-PDT, 106 preferred IMI and 110 preferred 5-FU. At baseline, significant differences between treatment groups were found; most patients were severely affected (mean 32.5 AK in PDT-group, 20.2 in IMI-group, 22.8 in 5-FU-group). A mean reduction in lesions of 81% after MAL-PDT, 82% after IMI and 88% after 5-FU was found after one year. Annual costs were €1,950 for MAL-PDT, €877 for IMI and €738 for 5-FU. These results show that, compared with clinical trials, in the real-life clinical setting AK patients are usually more severely affected and treatment costs are much higher. Furthermore, patient characteristics are important factors in treatment choice. Key words: actinic keratoses; treatment; cost; effectiveness; patient characteristics.

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Actinic keratoses (AKs) are chronically recurrent premalignant lesions that occur mainly on chronically sun-exposed skin in Caucasians. In a recent study conducted in the Netherlands, a prevalence of AKs of 49% in men and 28% in women was found in a cohort of the general population aged 45 years or above (1). Studies performed in other countries also show that AK frequently occurs in the elderly population (2, 3). Because of the potential of AK to develop into squamous cell carcinoma (SCC), treatment is recommended. Given the high incidence of AKs and their predominant occurrence in the head and neck region, a cost-effective therapy with good cosmetic results is needed.

Treatment can be directed at individual lesions, and cryotherapy is the most common treatment used. For patients with multiple AKs and in field cancerization, a field-directed approach is considered more appropriate, e.g. photodynamic therapy (PDT), imiquimod cream (IMI) or 5-fluorouracil cream (5-FU) (4). Within the group of field-directed treatments no specific patient characteristics to guide treatment choice have been defined.

Although personalized medicine and costs are nowadays of great importance in treatment choice, only a few studies on the cost of field-directed treatments have been published (5–7). Most of these studies are based on the results of randomized controlled trials (RCTs), in which selected patients with few AKs are treated and treatment choice is based on randomization. It is also known that patients in RCTs do not provide an adequate reflection of real-life clinical practice (8). The present study aimed to investigate whether patient characteristics play a directive in treatment choice in methylaminolaevulinate (MAL)-PDT, IMI and 5-FU in real-life practice in patients with AKs on the face and/or scalp. Furthermore, data on the cost and effectiveness of these treatment modalities were collected.

MATERIALS AND METHODS

Study design

Multicentre, 1-year observational study, conducted in 2 general and 2 university hospitals in the Netherlands.

Patients

Patients of 18 years and older, with a clinical diagnosis of AKs on the face and/or scalp region, suitable for field-directed treatment (AK in close proximity from each other), were included in the period October 2009 to June 2011. Patients were excluded in case of pregnancy, breast-feeding or contra-indications to field therapy. The study was approved by the local ethics committee of all participating institutions. All patients gave written consent to participate in the study.

Treatment modalities

Treatment choice between MAL-PDT, IMI and 5-FU was based on patients' preference (after explanation on the treatment options) in combination with the clinical appearance of AKs. The use of treatment was standardized in the participating hospitals.

PDT. During one week prior to PDT, patients were pre-treated with a keratolytic ointment (10% salicylic acid in petrolatum) to remove hyperkeratosis. On the PDT day (at the day-care centre), remaining hyperkeratoses were carefully removed by curettage and the skin was wiped with alcohol. In addition, a thin layer (approximately 1 mm) MAL cream (Metvix[®]; Galderma) was applied on the treatment area, and covered with an occlusive dressing and tinfoil to prevent influence of light. After 3 h the dressing and cream were removed and the skin was illuminated with a red light (632 nm, 37 J/cm²) from a light-emitting diode light source (Akti-lite[®]). Three months after PDT, clearance of AKs was assessed. In case of remaining AKs, additional treatment could be performed.

Imiquimod. IMI (Aldara[®], MEDA) was used at home 3 times per week (Monday, Wednesday and Friday) for 4 consecutive weeks. Cream was applied prior to normal sleeping hours, and removed in the morning, after approximately 8 h. Sufficient cream was applied to cover the treatment area (never more than 1 sachet). In case of an intense local reaction, treatment was interrupted and continued after recovery. Four weeks after finishing treatment, clearance of AKs was assessed. In case of remaining AKs, additional treatment could be performed.

5-FU cream. A sufficient amount of 5-FU cream was applied at home, twice daily, to cover the treatment area, until erosions, redness and crusting occurred (duration 2–4 weeks). After 3 months, in case of remaining AKs, additional treatment could be performed.

Subsequent and concomitant treatment. In case of AKs remaining after finishing the initial treatment of choice, patients received subsequent treatment, which could be a treatment other than the initial treatment. Depending on the number of AKs and the patient's preference, this could be lesion-directed (cryotherapy) or field-directed therapy. In case side-effects occurred (e.g. itching, infections) patients received concomitant treatment, e.g. topical corticosteroids or antibiotics.

Design

All patients were included and followed by the same 2 investigators. Patients were included at baseline (M0), prior to the start of the treatment. Follow-up evaluation was scheduled at 3 months (M3) and 12 months (M12) after treatment start. If necessary, extra appointments were made at the outpatient clinic (e.g. in case of subsequent treatment). Patients treated with IMI were also seen at 8 weeks after treatment start to evaluate the effect of the treatment. Effectiveness of the treatment for study purpose was evaluated only at M3 and M12.

At baseline, the following data were collected: age, sex, race and Fitzpatrick skin type of the patient; location, number and severity of AKs (according to the Olsen classification), number of diagnostic biopsies, previous AK treatments, patients' medical history and medication use. Presence of hypopigmentation, hyperpigmentation, atrophy, erythema, induration, scar formation, hyperkeratosis, and desquamation of the treatment area were scored.

Outcomes

Subjects were evaluated at M3 and M12. The following information was recorded:

Effectiveness of treatment

- **Lesion response:** the total number of AKs was evaluated by inspection, palpation and photography of the treatment area. Lesion response was registered as complete in case of 100% clearance.
- **Cosmetic results:** cosmetic score was classified as excellent when there was no scarring, atrophy, or induration and no or slight occurrence of erythema or change in pigmentation.

Consumption of care and associated costs. All costs related to the treatment of AK in the face/scalp during one year were col-

lected. Total costs were calculated by multiplying every item with the unit costs. Standard unit costs as established by the National Healthcare Insurance Board of the Netherlands were used where possible, otherwise costs were gathered from the hospital administration, and converted to the 2011 price level (9). Where relevant, different costs were used for general hospitals and university hospitals (general hospital €66 for a consultation, university hospital €134) (10). MAL-PDT costs were based on the costs for day-care admission (€251) (10), costs for grams of MAL used (tube 2 g €272, weighed before and after treatment), standard materials used (e.g. occlusive dressing, light source), and the costs for personnel. IMI was prescribed per treatment cycle, including 12 sachets (€60). For 5-FU one tube for the whole treatment area could be used (€41). The cost of a diagnostic biopsy was €150, including costs for pathological evaluation.

Mean costs per patient were calculated over a one-year period for each treatment group. In addition, mean costs per individual AK lesion were calculated.

Analysis

Study size determination. A sample size calculation was performed in order to obtain a sufficiently precise estimate of the proportion of patients in remission at 1-year follow-up. This was based on the following assumptions: an overall remission percentage of 70% (86% for IMI, 57% for 5-FU and 88–89% for PDT) (11, 12) and a 2-sided 95% confidence interval with a maximum of 60–80%. This resulted in a sample size of 81 patients ($\alpha=0.05$) per treatment group. To control for possible loss to follow-up (LTFU), a minimum of 100 patients per treatment group was included.

Statistical methods. Data were collected in a web application (Trial Registry Information and Administration System). For further analysis, data were entered into Statistical Package for Social Science (SPSS 20.0, IBM Corp, Armonk, NY, USA). Descriptive statistics and crosstabs (χ^2 , Fisher's exact test) were performed to analyse the differences between the study groups at baseline. *p*-values < 0.05 were considered statistically significant in the comparison between baseline characteristics. Based on the observational design of the study, and the fact that our goal was to describe real-life data rather than comparing effectiveness between groups, follow-up results were only described per treatment group. All patients were analysed according to the intention-to-treat (ITT) principle.

RESULTS

Study population

As this study had an observational design, most patients with field AK were willing to participate, thus the outpatient clinic population was well represented. Treatment choice was based on the patient's preference and the clinical appearance of the AK; no randomization was performed. A total of 320 patients was included in the study: 104 patients were initially treated with MAL-PDT, 106 with IMI and 110 with 5-FU (Fig. S1¹). In one of the general hospitals no PDT was performed.

Five patients withdrew from the study directly after inclusion. Ninety-three patients who were treated with MAL-PDT, 101 patients who were treated with IMI, and 98 who were treated with 5-FU attended the M3

¹<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2216>

visit (Fig. S1¹). At M12, 17 more patients were LTFU (PDT 3, IMI 5 and 5-FU 9 patients).

As may be expected in case of a naturalistic study, statistically significant differences were found between the baseline characteristics of the treatment groups (Table I). Patients treated with MAL-PDT had significantly more AKs, a larger affected area (face in addition to scalp), and more previous AK treatments. Those treated with IMI were the youngest and had the lowest number of AKs. Patients treated with 5-FU had the worst baseline cosmetic scores.

Lesion response

The mean percentage of lesion reduction, absolute number of lesion reduction, and total number of full responders after 3 months (M3) and 12 months (M12) are shown in Table II. Patients treated with MAL-PDT showed the highest absolute number of lesion reduction. Patients treated with 5-FU demonstrated the highest percentage of lesion reduction and the highest number of full responders at both M3 and M12.

Cosmetic results

At M12, 65.6% of patients treated with MAL-PDT, 64.9% of patients treated with IMI, and 54.9% of patients treated with 5-FU had an excellent cosmetic outcome.

Consumption of care and costs

An overview of subsequent treatments is shown in Table III. Patients initially treated with MAL-PDT had

Table II. Lesion reduction of actinic keratoses in patients treated with methylaminolaevulinate photodynamic therapy (MAL-PDT), imiquimod cream (IMI) and 5-fluorouracil cream (5-FU)

	MAL-PDT	IMI	5-FU
Number of lesion reduction at:			
M3, absolute numbers (SD)	23.90 (14.6)	15.70 (13.0)	19.66 (13.8)
M12, absolute numbers (SD)	25.81 (16.3)	15.14 (11.9)	19.34 (13.6)
Mean percentage of lesion reduction at:			
M3, % (SD)	79.39 (22.3)	80.00 (24.7)	89.53 (18.9)
M12, % (SD)	81.12 (22.4)	81.65 (23.4)	88.45 (15.8)
Total number of full responders at:			
M3, n (%)	24 (25.8)	34 (34.0)	52 (54.2)
M12, n (%)	19 (20.7)	35 (36.1)	37 (41.1)

SD: standard deviation; M3: 3 months after treatment; M12: 12 months after treatment.

Table I. Baseline characteristics of patients treated with methylaminolaevulinate photodynamic therapy (MAL-PDT), imiquimod cream (IMI) and 5-fluorouracil cream (5-FU)

	MAL-PDT (n=104)	IMI (n=106)	5-FU (n=110)	p-value
Sex (male), n (%)	74 (71.2)	72 (67.9)	92 (83.6)	0.020
Age, mean ± SD	70.4 ± 8.1	68.5 ± 9.2	73.2 ± 8.1	0.000
Skin type (Fitzpatrick), n (%)				0.004
Type 1	35 (34)	27 (25.7)	13 (11.8)	
Type 2	62 (60.2)	69 (65.7)	87 (79.1)	
Type 3	6 (5.8)	9 (8.6)	10 (9.1)	
History, n (%)				
Bowen's disease (≥1)	23 (22.1)	7 (6.6)	18 (16.4)	0.006
Basal cell carcinoma (≥1)	39 (37.5)	25 (23.6)	34 (30.9)	0.091
Squamous cell carcinoma (≥1)	15 (14.4)	9 (8.5)	24 (21.8)	0.023
AK – Olsen (grade), n (%)				0.079
1	71 (68.3)	60 (56.6)	64 (58.2)	
2	31 (29.8)	40 (37.7)	35 (31.8)	
3	2 (1.9)	6 (5.7)	11 (10.0)	
AK location, n (%)				0.000
Scalp	22 (21.2)	36 (34.0)	48 (43.6)	
Face	54 (51.9)	63 (59.4)	56 (50.9)	
Face and scalp	28 (26.9)	7 (6.6)	6 (5.5)	
AK				
Lesions, n, mean ± SD	32.48 ± 18.38	20.22 ± 16.00	22.78 ± 15.67	0.000
Lesions/size area, mm, mean ± SD	0.15 ± 0.06	0.14 ± 0.10	0.11 ± 0.06	0.000
Previous treatment, n (%)	62 (59.6)	45 (42.5)	61 (55.5)	0.034
Cosmetic score, mean ± SD	4.47 ± 2.64	4.29 ± 2.24	5.37 ± 2.74	0.005
Co-morbidity, mean ± SD	2.21 ± 1.81	1.76 ± 1.56	1.70 ± 1.44	0.097

SD: standard deviation; AK: actinic keratoses.

the highest number of subsequent treatments. In only a few patients was a second cycle with PDT or IMI, as prescribed in the treatment protocol, performed. Since most often only a few isolated AK lesions remained, patients were almost always subsequently treated with cryotherapy. Two patients (MAL-PDT and IMI group) were subsequently treated with CO₂ laser (not mentioned in the table).

An overview of treatment costs per patient is shown in Table IV. The mean cost per individual AK lesion was €87 (range €9.9–698.3) for MAL-PDT, €71 (range €16.0–527.5) for IMI, and €55 (range €11.2–380.0) for treatment with 5-FU.

DISCUSSION

The present study demonstrates which treatment patients with multiple AKs currently receive in real-life clinical

Table III. Number of subsequent treatments during 1-year follow-up

	MAL-PDT n=91 n (%)	IMI n=96 n (%)	5-FU n=92 n (%)
Cryotherapy*	71 (78.0)	68 (70.8)	55 (59.8)
5-FU*	8 (8.8)	3 (3.1)	12 (13.0)
IMI*	5 (5.5)	13 (13.5)	2 (2.2)
MAL-PDT*	11 (12.1)	2 (2.1)	1 (1.1)
Total*	75 (82.4)	71 (74.0)	61 (66.3)

*Percentage per treatment group.

MAL-PDT: methylaminolaevulinate photodynamic therapy; IMI: imiquimod cream; 5-FU: 5-fluorouracil cream.

Table IV. Costs (€) per treatment group; methylaminolaevulinate photodynamic therapy (MAL-PDT), imiquimod cream (IMI), and 5-fluorouracil cream (5-FU)

	MAL-PDT Mean ± SD (range)	IMI Mean ± SD (range)	5-FU Mean ± SD (range)
Outpatient clinic visits	754.31 ± 275.58 (198.99–1,604.40)	627.55 ± 26.36 (265.32–1,203.30)	590.74 ± 27.54 (198.99–1,337.0)
Biopsies	22.80 ± 9.54 (0.0–781.7)	12.26 ± 6.04 (0.0–469.02)	21.67 ± 6.97 (0.0–312.68)
Treatment	984.11 ± 56.60 (0.0–2,704.41)	99.50 ± 4.50 (59.59–238.36)	41.14 ± 0.0 (41.14–41.14)
Concomitant treatment	4.73 ± 1.13 (0.0–47.69)	2.34 ± 0.51 (0.0–24.40)	2.55 ± 0.43 (0.0–24.50)
Subsequent treatment	180.83 ± 25.30 (0.0–1,432.38)	130.48 ± 22.60 (0.0–1550.25)	79.98 ± 10.03 (0.0–538.58)
Total	1,949.90 ± 75.52 (534.34–4,127.83)	877.17 ± 43.49 (329.98–3,332.72)	738.41 ± 34.29 (306.46–1,875.20)

situations, how these patients fare in terms of lesion load and cosmetic outcome, and what costs are incurred.

Differences were found in patient characteristics between the treatment groups. Patients who were much more severely affected, with a number of AKs, who had had more previous treatments, and a higher overall number of previous skin tumours, were more often treated with MAL-PDT. We also noted more comorbidities in this patient group. The youngest patients, who were least severely affected by AKs and previous treatments, were more frequently treated with IMI. Male patients, those of older age, with more previous SCCs, and worse cosmetic scores at M0, were most often treated with 5-FU.

MAL-PDT is registered for AK treatment when other treatments are considered less appropriate. Therefore, it is not surprising that patients in the PDT group were more severely affected and had had more previous treatments. Compared with patients treated with IMI, the number of AKs was 60% higher in the PDT group, compared with patients treated with 5-FU, the number of AKs was 43% higher in the PDT group. It is well known that these AK fields (field cancerization) are more difficult to treat and have a higher potential for recurrence, and that multiple initial treatments are recommended in these patients (13–15). The higher number of previous treatments in the PDT patient group may thus be a consequence of rapid recurrences and/or therapy-resistant AK.

Another difference between PDT and the other treatments is that PDT is an in-hospital treatment. Patients who are unwilling or unable to treat themselves with IMI or 5-FU will choose PDT. This may explain the larger treatment area and the higher number of co-morbidities in the MAL-PDT group, since these might be patients who prefer more assistance with their treatment.

With respect to consumption of care, it was found that patients treated with MAL-PDT had more pre-treatment consultations. This may be because one of the university hospitals planned a standard pre-PDT visit for instructions. This is not standard in other hospitals.

Furthermore, treatment costs for MAL-PDT were the highest. This is mainly due to the high costs of MAL cream and costs related to day-care admission. In patients with large treatment areas, multiple appointments were necessary to treat all lesions.

The number of full responders in the present study is lower than in previous clinical trials (11, 16). This may be because there is a striking difference in the number of AKs at baseline (approximately 7 in previous studies, compared with approximately 25 in the present study). An earlier study from our group, in which patients with AK were treated with MAL-PDT, showed that patients in whom therapy failed, had significantly higher numbers of AK at baseline (13). This may have an important influence on overall efficacy. Furthermore, the follow-up period and treatment regimen were different from previous trials. The official treatment protocol for 5-FU prescribes a single treatment session, whereas for MAL-PDT and IMI an additional session after evaluation may be part of the initial treatment session. In our study it was found that, in clinical practice, cryotherapy is more often used as a subsequent treatment instead of an additional cycle of MAL-PDT or IMI.

Compared with previous studies of field-treatment for AK, different costs were found. In a study by Annemans et al. (5) cost per AK lesion after 6 months' follow-up and treatment with MAL-PDT was €58. Other studies performed were based on a decision analytical approach or assumptions on the number of treatments (6, 7). Except for Gold's study, in which a standard second treatment cycle was calculated, treatment costs in the literature were lower than the costs found in our study. Although the published studies were performed in other countries, additional factors may explain the differences in costs. Only one of these studies is observational, with a follow-up of only 6 months (5). In addition, a smaller spectrum of costs was included (e.g. no subsequent treatment, no treatment of recurrences). Moreover, patients in the present study were more severely affected.

The aim of our study was to assess the costs and effectiveness of the various treatment modalities as used in clinical practice for patients with multiple AK. The appropriate design for such a study is an observational longitudinal study, monitoring treatment effects and costs as they arise in practice. The disadvantage of such a design is that many patients received additional treatment for their AK, as AK is a chronic and recurrent disease, therefore the reduction in lesion number at M12 was influenced by subsequent treatments. However, our aim was not to demonstrate the efficacy of a single treatment modality alone.

Another limitation may be the fact that the number of AKs assessed at M3 and M12 were all AKs present in the treatment area, including new lesions. Other study designs mainly assessed the response and recurrences of specific lesions. However, to calculate the costs for

field-directed treatment in patients with multiple lesions, it is more appropriate to include all lesions appearing in the treatment area, since they all need treatment.

Conclusion

The present observational study shows that, in real-life clinical practice, patients with AK are more severely affected than patients in clinical trials and that the costs of field-directed treatment are much higher. This is caused mainly by the high number of AKs and the wider range of costs included in our study. New developments, e.g. daylight PDT for individual cases, may reduce these costs in the future.

Since all treatments appeared to be effective in the different treatment groups, patient characteristics and costs could play an important part in treatment choice. Since, at present, MAL-PDT is regarded as a costly treatment, this therapy is preferred for specific cases, e.g. patients with extensive or therapy-resistant field cancerization, or who are not compliant or able to perform treatment at home. Otherwise, 5-FU appears to be the least costly treatment that is effective in cases of multiple AK.

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REFERENCES

1. Flohil SC, van der Leest RJ, Dowlathahi EA, Hofman A, de Vries E, Nijsten T. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. *J Invest Dermatol* 2013; 133: 1971–1978.
2. Memon AA, Tomenson JA, Bothwell J, Friedmann PS. Prevalence of solar damage and actinic keratosis in a Merseyside population. *Br J Dermatol* 2000; 142: 1154–1159.
3. Schaefer I, Augustin M, Spehr C, Reusch M, Kornek T. Prevalence and risk factors of actinic keratoses in Germany – analysis of multisource data. *J Eur Acad Dermatol Venereol* 2014; 28: 309–313.
4. Stockfleth E, Ferrandiz C, Grob JJ, Leigh I, Pehamberger H, Kerl H, European Skin A. Development of a treatment algorithm for actinic keratoses: a European consensus. *Eur J Dermatol* 2008; 18: 651–659.
5. Annemans L, Caekelbergh K, Roelandts R, Boonen H, Leys C, Nikkels AF, et al. Real-life practice study of the clinical outcome and cost-effectiveness of photodynamic therapy using methyl aminolevulinate (MAL-PDT) in the management of actinic keratosis and basal cell carcinoma. *Eur J Dermatol* 2008; 18: 539–546.
6. Gold MH. Pharmacoeconomic analysis of the treatment of multiple actinic keratoses. *J Drugs Dermatol* 2008; 7: 23–25.
7. Muston D, Downs A, Rives V. An economic evaluation of topical treatments for actinic keratosis. *J Dermatolog Treat* 2009; 20: 266–275.
8. Garcia-Doval I, Carretero G, Vanaclocha F, Ferrandiz C, Dauden E, Sanchez-Carazo JL, et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. *Arch Dermatol* 2012; 148: 463–470.
9. CBS Statline. [Accessed 2014 Sep 16]. Available from: <http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=71311ned&D1=0&D2=0&D3=12,38,51,64,77,90,103,116,129,142,155,168,181,194,219,232&HDR=T&STB=G2,G1&VW=T>.
10. Hakkaart-van Roijen L., Tan S.S., Bouwmans C.A.M. [Guideline for cost-effectiveness studies.] [Last viewed on 2014 Sep 16]. Available from: <http://www.zorginstituutnederland.nl/binaries/content/documents/zinlwww/documenten/publicaties/overige-publicaties/1007-handleiding-voor-kostenonderzoek/1007-handleiding-voor-kostenonderzoek/Handleiding+voor+kostenonderzoek.pdf> (in Dutch).
11. Krawtchenko N, Roewert-Huber J, Ulrich M, Mann I, Sterry W, Stockfleth E. A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. *Br J Dermatol* 2007; 157 Suppl 2: 34–40.
12. Tarstedt M, Rosdahl I, Berne B, Svanberg K, Wennberg AM. A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol* 2005; 85: 424–428.
13. Kleinpenning MM, van de Kerkhof PC, Gerritsen RM. The clinical efficacy of topical methyl-aminolevulinate photodynamic therapy in moderate to severe actinic keratoses of the face and scalp. *J Dermatolog Treat* 2010; 21: 252–257.
14. Wennberg AM, Stenquist B, Stockfleth E, Keohane S, Lear JT, Jemec G, et al. Photodynamic therapy with methyl aminolevulinate for prevention of new skin lesions in transplant recipients: a randomized study. *Transplantation* 2008; 86: 423–429.
15. Wulf HC, Pavel S, Stender I, Bakker-Wensveen CA. Topical photodynamic therapy for prevention of new skin lesions in renal transplant recipients. *Acta Derm Venereol* 2006; 86: 25–28.
16. Morton C, Campbell S, Gupta G, Keohane S, Lear J, Zaki I, et al. Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. *Br J Dermatol* 2006; 155: 1029–1036.