Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies

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Summary

Background Photodynamic therapy (PDT) is increasingly used for treatment of actinic keratoses (AKs) but is a cumbersome procedure. A thin self-adhesive patch (PD P 506 A) containing 5-aminolaevulinic acid (5-ALA) was developed to facilitate PDT.

Objectives To investigate efficacy and safety of the patch in comparison with placebo–PDT (superiority design, observer-blinded; study AK 03) and standard therapy, cryosurgery (noninferiority design, open; study AK 04).

Methods Two separate confirmatory randomized parallel-group phase III studies were set up. In total, 449 patients with up to eight mild to moderate AK study lesions located on the head were treated in 29 German study centres (study AK 03: 103 patients; study AK 04: 346 patients).

Results Twelve weeks after treatment, 5-ALA patch–PDT proved to be superior to placebo–PDT ($P < 0{\cdot}001$) and cryosurgery ($P = 0{\cdot}007$). Efficacy rates on a lesion basis were 82% (AK 03) and 89% (AK 04) for PDT, 77% for cryosurgery and 19% (AK 03) and 29% (AK 04) for placebo–PDT. Local reactions at the treatment site occurred in almost all patients treated with 5-ALA patch–PDT or cryosurgery. Headache was the only side-effect not related to the treatment site which occurred in more than one patient.

Conclusions PD P 506 A is an innovative, easy-to-handle 5-ALA patch for PDT of mild to moderate AK lesions. Compared with current PDT procedures, pretreatment (e.g. curettage) is not needed and handling is considerably facilitated. A single PDT treatment results in efficacy rates being statistically significantly superior to placebo and cryosurgery.

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Conflicts of interest
A.H. and R.-M.S. receive speaker honoraria from photonamic GmbH & Co. KG. C.O., A.C.E.M. and M.S. are employees of photonamic. M.B. is an employee of the company that was put in charge of data management and statistical issues. R.-M.S. was involved in inventing the product. The other authors have no conflict of interest to declare.

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Extensive sun exposure can lead to the development of actinic keratosis (AK) especially in subjects with fair skin. AKs are currently considered to be in situ squamous cell carcinomas (SCCs).[1,2] National and international guidelines recommend the treatment of AK upon diagnosis to prevent further progression into SCC.[3,4] In photodynamic therapy (PDT) of skin diseases, the photosensitizers most frequently used are 5-aminolaevulinic acid (5-ALA) or its ester methyl aminolaevulinate

(MAL). The effectiveness of topical 5-ALA–PDT in the treatment of AK and other superficial skin tumours has so far been proven in several studies.[5–7]

Current PDT procedures involve application of an alcoholic solution or a cream containing 5-ALA or MAL. A long incubation interval of the alcoholic solution, the need for ablation of scales and crusts prior to cream application and light protection after cream application with an occlusive and light-tight dressing make the procedure time consuming and complex for both patient and physician. In order to facilitate PDT and to shorten handling times, a self-adhesive, skin-coloured thin 5-ALA patch (product code PD P 506 A) was developed.[8] As the 5-ALA patch is intended to be applied directly to AK lesions, crust removal prior to application is not necessary. The patch delivers 5-ALA to the skin lesion and protects it from light at the same time.

The optimum application duration of the 5-ALA patch to mild to moderate[2] AK lesions of head and face has been investigated in two preceding studies. A fluorescence analysis study assessed the influence of patch application duration on the protoporphyrin IX (PpIX)-specific fluorescence in AK lesions.[8] It was shown that PpIX-specific fluorescence immediately after patch removal increased with increasing application duration to a maximum at 4 h application. Subsequently, a clinical dose-ranging study was performed. Four hours patch application followed by illumination of the treated area with red light (wavelength 630 ± 3 nm, 37 J cm^{-2}) led to a clearance rate of 86% on a lesion basis.[9] In the current paper, we report on two randomized confirmatory phase III studies which were set up to investigate further the efficacy and safety of 5-ALA patch–PDT in comparison with both placebo–PDT and cryosurgery as a standard therapy.[3,10] Other studies suggest comparable clearance rates of cryosurgery and PDT.[11–13]

Materials and methods

The studies were performed as two separate multicentre confirmatory randomized parallel-group comparisons. Prior to study start, the studies had been approved by the responsible ethics committees and the competent authority (BfArM, Germany). The investigations were carried out in accordance with the German Drug Law, national and international Good Clinical Practice guidelines and the Declaration of Helsinki.

Study medication

The 5-ALA patch (PD P 506 A) is a skin-coloured, square, self-adhesive patch with rounded corners. One patch has a size of 4 cm^2 and contains 8 mg 5-ALA (present as 5-ALA hydrochloride). In their appearance, placebo patches were identical to PD P 506 A but did not contain 5-ALA.

Study treatment: photodynamic therapy

PDT was administered in a double-blind manner. Three to eight (AK 03) or four to eight (AK 04) patches of either PD P 506 A or placebo were applied per patient, each patch covering one AK lesion. Before application, no specific lesion preparation was performed. After 4 h application, the lesions were immediately illuminated with red light (37 J cm^{-2} at 630 ± 3 nm). All AK 03 centres used the Aktilite® CL 128 (PhotoCure ASA, Oslo, Norway) light-emitting diode light source. Alternatively, Omnilux® (Photo Therapeutics Limited, Altrincham, U.K.) was used by 11 centres in AK 04, with the same illumination parameters.

Study treatment: cryosurgery

Patients (only AK 04) were treated according to a standardized cryosurgery protocol. The open spraying procedure with liquid nitrogen in one cycle was used; all centres used nozzles of size C (Brymill Cryogenic Systems, Basingstoke, U.K.). After formation of an ice-ball of the required size, freeze time started. Freeze time was defined by the study protocol to lie between 5 and 10 s.[14]

Randomization

Patients were randomly allocated to one of the treatment arms on the day of study treatment. The randomization was stratified per centre.

Study population

Inclusion and exclusion criteria for both studies were virtually identical. After having given written informed consent, caucasian male and female patients with AK (skin type I–IV, age ≥ 18 years) were included into the study. Women of child-bearing potential were not eligible. The selected AK study lesions had to be of either mild or moderate grade as defined by Cockerell[2] with a maximum diameter of 1·8 cm and an interlesional distance of at least 1 cm. Exclusion criteria were non-response to previous PDT, dermatological conditions which could possibly influence the study aims, porphyria, clinically relevant immunosuppression or dementia, topical treatment being able to affect the response to study treatment in the 4 weeks prior to and during the study (for systemic retinoids 3 months prior to study start), urea- and salicylic acid-containing preparations 2 weeks prior to and during the study, treatment with cytostatics or radiation during the 3 months preceding study therapy as well as during the study, known intolerance to one or more ingredients of PD P 506 A or its placebo as well as known adverse reactions to cryosurgery (only AK 04).

Study plan

In study AK 03, treatment was always performed by a second investigator to guarantee an observer-blinded status. In both studies, a safety inspection was scheduled 1 day after study treatment. Treatment efficacy was evaluated 12 weeks after study therapy. Additionally, patients' and investigators'

assessment of the cosmetic outcome of cleared lesions ('excellent', 'good', 'fair' or 'poor'), and patients' overall satisfaction with the cosmetic outcome ('very satisfied', 'satisfied', 'poorly satisfied', 'not satisfied') were documented.

Efficacy assessments

Efficacy assessments were based on clinical diagnosis being regarded as usual procedure in dermatological practice.[15] Complete clinical clearance of an AK lesion was defined as: no visual evidence of persisting AK on treated surface; no evidence of adherent scaling plaques on treated skin surface when palpated; lesions no longer perceptible to touch; and slight pink or red foci might be visible at lesion sides.

Safety and tolerability assessments

For PDT, local reactions were documented during patch application, illumination and thereafter. For cryosurgery, local reactions were documented during the spraying procedure and thereafter. Patients were given a diary for the documentation of local reactions during the 4 weeks after therapy. For safety reasons, PDT patients were instructed to protect their study lesions from light for 48 h after therapy. To monitor hepatic aminotransferases (alanine aminotransferase and aspartate aminotransferase) and γ-glutamyltransferase, blood samples were taken at baseline prior to treatment and on the day after treatment. Adverse events (AEs) were documented at each study visit.

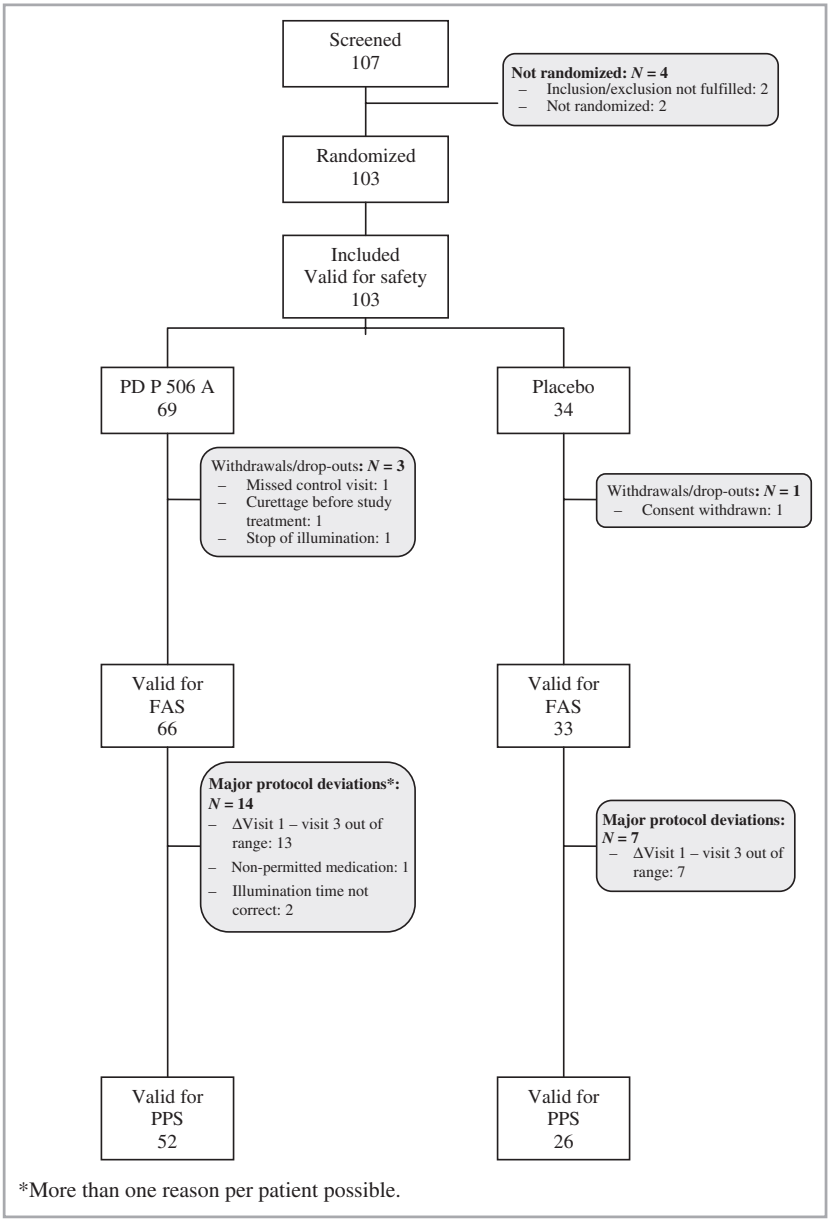

Fig 1. Flow chart for disposition of patients in clinical study AK 03. FAS, full analysis set; PPS, per protocol set.

Biometric approach

The primary parameter of both studies was the complete clinical clearance rate (CCCR) 12 weeks after PDT. CCCR was analysed on AK study lesion basis. For that reason, a repeated-measurement design for the binary outcome of clearance of three (AK 03) or four (AK 04) to eight AK lesions was chosen. For the correlated binary outcome the method general estimating equation was used to fit a regression model with treatment and centre as fixed factor.

AK 03 was intended as a test for superiority of PDT vs. placebo. Primary analysis was done on the full analysis set (FAS) (based on the intent-to-treat principle). AK 04 was designed as a test for noninferiority of PDT vs. cryosurgery. Based on published data for cryosurgery,[14] a compete clearance rate of 75% with cryosurgery was assumed. The equivalence delta was set to 12%. A procedure of ordered testing controlled for the overall type I error rate, i.e. α adjustments for multiple testing were not required. The significance level was $\alpha = 2{\cdot}5\%$ (one-sided) for each of the two tests. Primary analyses were based on the per protocol set (PPS). The generalized regression model for correlated binary response was applied including all three treatments. An exploratory analysis was additionally performed analogously based on the FAS.

Results

Patients

In AK 03, 107 patients were screened. Of these, 103 patients with 587 AK study lesions were randomized and treated. Ninety-nine patients were included in the FAS and used for

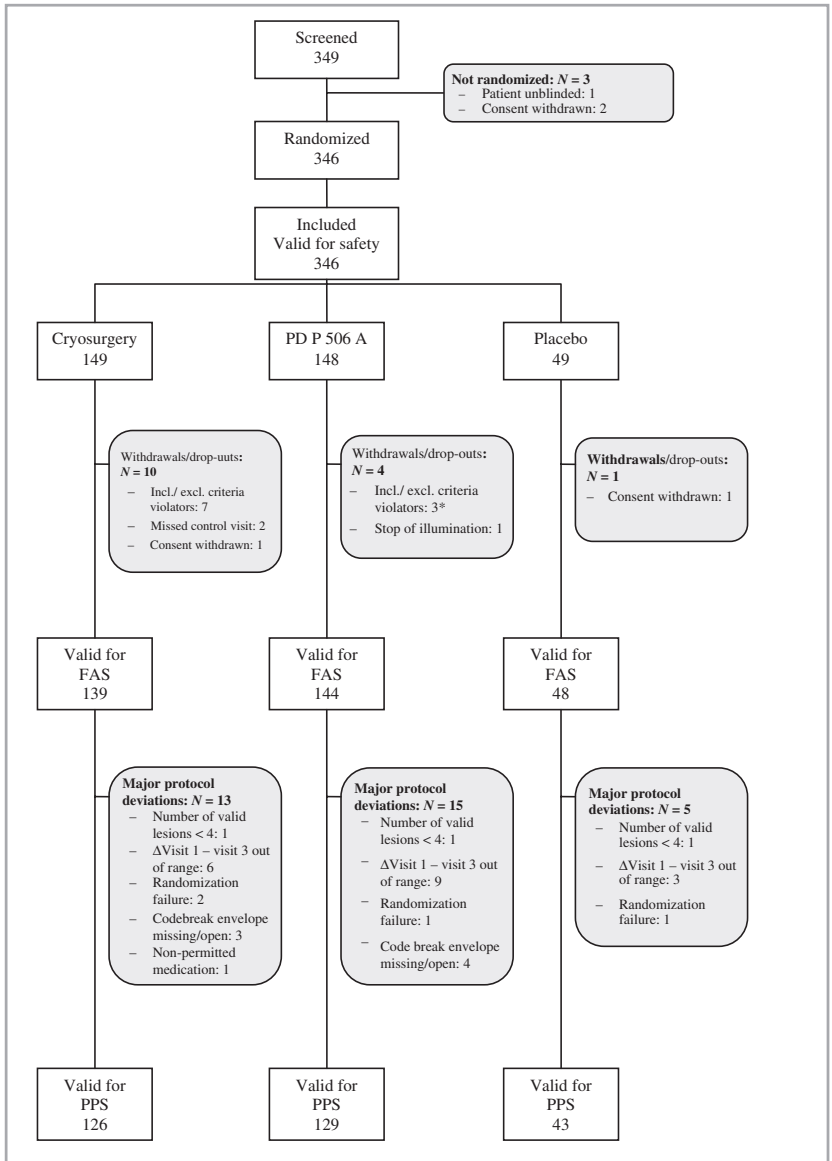

Fig 2. Flow chart for disposition of patients in clinical study AK 04. FAS, full analysis set; PPS, per protocol set.

Table 1 Summary of patient characteristics (safety samples)

	AK 03[a]		AK 04[b]		
Study arm	PD P 506 A (n = 69)	Placebo (n = 34)	PD P 506 A (n = 148)	Cryosurgery (n = 149)	Placebo (n = 49)
Gender, n (%)					
Male	58 (84)	26 (76)	104 (70)	104 (70)	40 (82)
Female	11 (16)	8 (24)	44 (30)	45 (30)	9 (18)
Age, years					
Mean ± SD	70·4 ± 8·32	71·4 ± 6·77	70·0 ± 8·32	70·6 ± 8·73	71·6 ± 7·54
Median (range)	69 (51–89)	70 (51–85)	69 (41–94)	70 (41–93)	70 (55–86)
No. of AK study lesions per patient					
Mean ± SD	5·8 ± 1·91	5·5 ± 1·91	5·8 ± 1·64	5·4 ± 1·57	5·9 ± 1·76
Median (range)	6 (3–8)	5 (3–8)	6 (1–8)	5 (2–8)	6 (2–8)
Skin type, n (%)					
I	5 (7)	4 (12)	32 (22)	22 (15)	9 (18)
II	57 (83)	28 (82)	92 (62)	105 (70)	30 (61)
III	7 (10)	2 (6)	24 (16)	20 (13)	8 (16)
IV	0 (0)	0 (0)	0 (0)	2 (1)	2 (4)

[a]Full analysis set; [b]per protocol set. AK, actinic keratosis.

Table 2 Summary of the characteristics of actinic keratosis study lesions (primary efficacy samples)

	AK 03[a]		AK 04[b]		
Study arm	PD P 506 A (n = 384)	Placebo (n = 179)	PD P 506 A (n = 750)	Cryosurgery (n = 692)	Placebo (n = 259)
Localization, n (%)					
Forehead	228 (59)	65 (36)	300 (40)	326 (47)	146 (56)
Scalp	83 (22)	64 (36)	235 (31)	204 (29)	59 (23)
Cheek	39 (10)	27 (15)	143 (19)	84 (12)	33 (13)
Nose	26 (7)	13 (7)	42 (6)	44 (6)	13 (5)
Ear	2 (1)	3 (2)	9 (1)	9 (1)	4 (2)
Other	6 (2)	7 (4)	21 (3)	25 (4)	4 (2)
Severity, n (%)					
Mild	170 (44)	77 (43)	318 (42)	310 (45)	118 (46)
Moderate	214 (56)	102 (57)	432 (58)	382 (55)	141 (54)
Diameter, cm					
Mean ± SD	0·97 ± 0·28	0·98 ± 0·31	1·01 ± 0·35	0·97 ± 0·32	1·04 ± 0·33
Median (range)	0·9 (0·4–1·8)	0·9 (0·4–1·8)	1·0 (0·1–1·8)	0·9 (0·3–1·8)	1·0 (0·4–1·8)

[a]Full analysis set; [b]per protocol set.

primary efficacy assessment (Fig. 1). In AK 04, 349 patients with 1950 AK study lesions were screened. At randomization, 149 patients were allocated to the cryosurgery group, 148 to the PD P 506 A-PDT group and 49 to the group receiving placebo–PDT (Fig. 2). For patient and lesion characteristics, see Tables 1 and 2.

Study treatment

Duration of patch application and illumination was comparable between placebo and 5-ALA patch patients. In AK 04, the mean ± SD freezing time after ice ball formation was 7·3 ± 2·0 s without any difference in procedure for mild and moderate grade lesions.

Efficacy

In the placebo comparison study AK 03, the CCCR on a lesion basis for 5-ALA patch–PDT was 82% (316/384) as compared with 19% (34/179) for placebo–PDT (Fig. 3a). PDT with the 5-ALA patch was concluded to be superior to placebo–PDT, with high statistical significance ($P < 0·0001$). No gender-specific differences were apparent in the PD P 506 A group.

The CCCRs on a lesion basis in AK 04 were 89% (664/750) for 5-ALA patch–PDT, 77% (530/692) for cryosurgery and 29% (75/259) for placebo–PDT (Fig. 3a). PDT was concluded to be superior to placebo–PDT ($P < 0·001$). Furthermore, superiority of PDT over cryosurgery was concluded

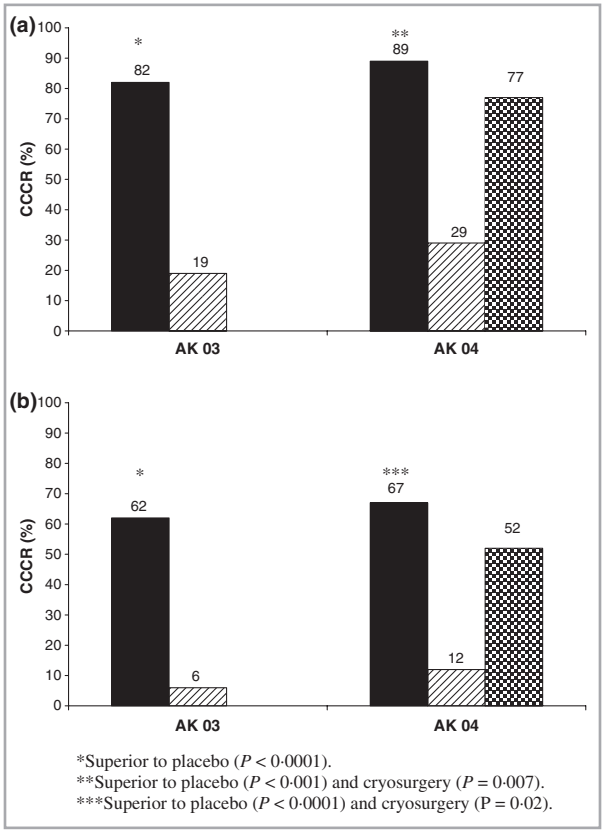

Fig 3. Complete clinical clearance rates (CCCRs) on lesion (a) and patient basis (b) 12 weeks after PD P 506 A–photodynamic therapy (PDT) (filled bars), placebo–PDT (dashed bars) or cryosurgery (dotted bars).

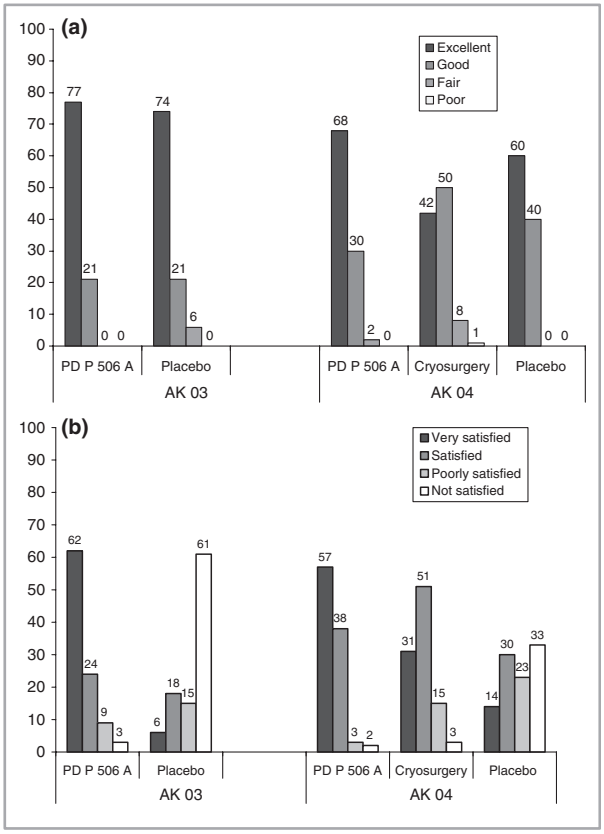

Fig 4. Cosmetic outcome and satisfaction with overall cosmetic result. (a) Cosmetic outcome of cleared lesions 12 weeks after therapy (patients' assessment). (b) Overall satisfaction with cosmetic outcome of treatment (patients' assessment).

(P = 0·007) as the lower limit of the one-sided 97·5% confidence interval [0·1691–∞] exceeded zero. As in AK 03, no gender-specific differences were apparent in the 5-ALA patch group. No differences between light sources Omnilux® and Aktilite® 128 CL were detected in the 5-ALA patch group where clearance rates were 87% (Omnilux®) and 90% (Aktilite® 128 CL).

Patients with all their study lesions cleared were regarded as completely cleared. Clearance rates on a patient basis were 67% (86/129) in AK 04 and 62% (41/66) in AK 03. The corresponding figure for cryosurgery was 52% (66/126). Placebo–PDT yielded clearance rates on a patient basis of 12% (5/43; AK 04) and 6% (2/33; AK 03) (Fig. 3b). Again it was demonstrated that 5-ALA patch–PDT shows statistically significantly higher efficacy rates than cryosurgery (P = 0·02) and placebo–PDT (P < 0·0001 in both studies).

Cosmetic outcome

There was no apparent difference between the cosmetic assessment of PDT- or placebo-treated lesions that were assessed 'cleared' (P = 0·36 for patients' assessment, P = 0·54 for investigators' assessment; PPS). However, patients' assessment of the cosmetic outcome of cryosurgery-treated lesions in AK 04 was statistically significantly less favourable (P < 0·001; PPS and FAS) (Fig. 4a).

Patient satisfaction with the overall cosmetic outcome of the treatment shows differences between the three treatment arms. These were descriptively analysed in AK 04 and are statistically significantly different for the comparisons of 5-ALA patch vs. placebo and 5-ALA patch vs. cryosurgery (P < 0·0001; PPS and FAS) (Fig. 4b).

Hypo- or hyperpigmentation has been reported to occur after PDT as well as after cryosurgery.[16,17] Twelve weeks after therapy, hypopigmentation was observed in 33% of the lesions treated with cryosurgery. In contrast, PDT-treated AK lesions were normally pigmented in the vast majority of cases (91% in AK 03, 88% in AK 04). No case of hyperpigmentation after PDT was observed in AK 03 while in AK 04, 9% of the patch–PDT-treated lesions were hyperpigmented. Under placebo, hypopigmentation was documented for 12% of the lesions in AK 03, while hyperpigmented lesions were documented in 4% of the cases in AK 04. These observations were tested statistically: pigmentation status was different between 5-ALA patch–PDT and cryosurgery (P < 0·001 for both analyses; PPS and FAS) while there were no statistical differences between 5-ALA patch–PDT and placebo (P = 0·87 PPS; P = 0·95 FAS).

Table 3 Adverse reactions at the treatment site during illumination (photodynamic therapy) or cryosurgery (safety samples) and on day 1 after therapy (safety samples)

Study arm	PD P 506 A (AK 03) (n = 69)	PD P 506 A (AK 04) (n = 148)	Total PD P 506 A (n = 217)	Total placebo (n = 83)	Cryosurgery (n = 149)
During illumination or cryosurgery					
Any finding, n (%)	68 (99)	147 (99)	215 (99)	22 (27)	124 (83)
Erythema	56 (81)	127 (86)	183 (84)	12 (14)	102 (68)
Irritation	61 (88)	126 (85)	187 (86)	8 (10)	80 (54)
Pain	30 (43)	52 (35)	82 (38)	–	63 (42)
Pruritus	4 (6)	22 (15)	26 (12)	9 (11)	7 (5)
Vesicles	–	–	–	–	8 (5)
Cold feeling	–	–	–	–	2 (1)
Discomfort	–	1 (1)	1 (0)	1 (1)	–
Oedema	–	1 (1)	1 (0)	–	–
Swelling	–	1 (1)	1 (0)	–	–
On day 1 after therapy					
Any finding, n (%)	66 (96)	147 (99)	213 (98)	16 (19)	146 (98)
Erythema	65 (94)	144 (97)	209 (96)	13 (16)	130 (87)
Vesicles	3 (4)	7 (5)	10 (5)	–	86 (58)
Irritation	22 (32)	55 (37)	77 (35)	–	15 (10)
Pruritus	13 (19)	26 (18)	39 (18)	5 (6)	18 (12)
Scab	12 (17)	15 (10)	27 (12)	1 (1)	23 (15)
Exfoliation	14 (20)	17 (11)	31 (14)	–	13 (9)
Pain	12 (17)	17 (11)	29 (13)	–	11 (7)
Oedema	1 (1)	2 (1)	3 (1)	–	2 (1)
Swelling	–	1 (1)	1 (0)	–	3 (2)
Erosion	2 (3)	–	2 (1)	–	–
Discharge	1 (1)	–	1 (0)	–	1 (1)
Bleeding	–	–	–	–	1 (1)
Discomfort	–	1 (1)	1 (0)	–	–
Infection	–	1 (1)	1 (0)	–	–
Pustules	–	1 (1)	1 (0)	–	–

Safety and tolerability

In AK 03, only one AE was rated by the investigator as related to study therapy (transient discoloration of the skin in the 5-ALA patch group). In AK 04, 3% in each of the active treatment arms and 2% in the placebo arm reported an AE related to the study therapy. These included eyelid oedema, face oedema, swollen face and headache in the cryosurgery group, headache, pyoderma and emotional distress in the 5-ALA patch–PDT group and the feeling of heat in the placebo group. The only adverse reaction which was documented for more than one patient was headache, with similar incidence for 5-ALA–PDT and cryosurgery. No serious AE was reported which was related to study therapy.

During 5-ALA patch application, local reactions (mainly itching) were observed in 34% (AK 04) and 42% (AK 03) of the patients. All reactions were of mild or moderate intensity. None of the events required intervention. Patients treated with placebo patches experienced fewer reactions at the application site (13%). Again, itching was most frequently mentioned. During subsequent illumination, phototoxic local reactions at one or more study lesions were observed in nearly all study patients (Table 3). Most were mild or moderate. Cooling of the study lesions during illumination as the only allowed relief was requested by 30% (AK 04) and 45% (AK 03) of the patients. Discomfort led to early stop of illumination in three 5-ALA patch-treated patients (one patient AK 03, two patients AK 04). Erythema was the local reaction reported most frequently. All reactions declined over time.

After cryosurgery, 83% of the patients experienced at least one local reaction at one of their study lesions during or immediately after therapy (Table 3). On day 1 after therapy, nearly all patients showed local reactions at the treatment site (Table 3). Most of the reactions were mild or moderate. Again, erythema was the most frequently reported local reaction; vesicles were another frequently mentioned reaction to cryosurgery.

Discussion

PDT is an efficacious but also time-consuming and labour-intensive treatment modality. Current treatment possibilities often require lesion preparation by curettage prior to cream application, occlusion of the treated area and light-protective

measures. The registered treatments need to be administered between 3 and 18 h prior to illumination.

Topical PDT shows excellent cosmetic results without leaving scars. To exploit these advantages further a way was sought to facilitate the procedure and to have a pharmaceutical form at hand which could be easily applied in daily practice. This led to the development of the thin 5-ALA patch, PD P 506 A. A fluorescence analysis had shown that the PpIX content in AK lesions is dependent on the application duration.[8] This finding was verified in a clinical dose-finding study which defined the 4 h application of the 5-ALA patch as optimal.[9] A further phase I study proved that simultaneous application of eight patches is very well tolerable locally and systemically.[8]

To confirm the results of the preceding phase I/II studies, two phase III studies were set up. In these, patch–PDT proved statistically significantly superior to standard treatment, cryosurgery, as well as to placebo–PDT.

Clinical study AK 04 is the largest single PDT study for AK so far. It shows that a single PDT with the novel 5-ALA patch is able to achieve very high clearance rates. These results were confirmed in clinical study AK 03. The data compare favourably with a placebo-controlled clinical trial, in which Levulan® Kerastick® (DUSA Pharmaceuticals, Wilmington, MA, U.S.A.; 5-ALA in alcoholic solution) had reached a clearance rate of 66% on a lesion basis.[18] The lesion-based clearance rates for MAL–PDT with Metvix® (PhotoCure ASA) in two parallel-group studies were 68·7% and 91% after two MAL–PDT treatments with an interval of 1 week.[10,11] In a recent split-face study, MAL–PDT reached clearance rates of 86·9% on a lesion basis after a single session.[13] However, MAL–PDT always includes a step of lesion preparation, while the 5-ALA patch is applied directly to the AK lesion without curettage. Furthermore, both mild and moderate graded lesions have been shown to respond equally well to patch–PDT, which contrasts with both Levulan®–PDT and MAL–PDT.[5,11,12]

Cryosurgery was chosen as the comparator arm as it is one of the methods most widely used in Europe for the treatment of AK lesions.[3,10] Despite many literature reports, cryosurgery is not well standardized. Treatment protocols often depend on the personal experience of the treating physician. In 2004, a study was published where the influence of the freezing duration on the clearance rate was analysed.[14] For a freezing time of 5–10 s after ice ball formation and a single freeze-thaw cycle, a clearance rate of 75% after 3 months was reported. In AK 04, investigators had to treat patients according to this regimen. The fact that the lesions were frozen for a mean of 7·3 s shows that the requested freezing time was realistic. Furthermore, a comparison of literature data[14] with the results presented here shows a high grade of conformity. This demonstrates that standardization of cryosurgery is possible and reproducible.

One of the known advantages of PDT is the excellent cosmetic outcome. The present studies demonstrate that the cosmetic outcome of 5-ALA patch–PDT is superior to both cryosurgery and placebo. Hyperpigmentation of lesions, a potential complication after PDT, was rarely seen and was at a significantly lower rate than hypopigmentation observed after cryosurgery.

It is intended that PDT of AK induces phototoxic reactions at the treatment site.[5,11,12] Cryosurgery also causes local reactions at the treatment site.[17] In clinical study AK 04, pain during illumination in PDT did not differ from pain experienced during cryosurgery in frequency and severity. In the majority of patients, pain or irritation during illumination was graded as of mild or moderate intensity. In a total of 1·4% of the patients treated with patch–PDT in both clinical studies, illumination was stopped prematurely due to pain or burning. This is a similar magnitude as is reported for Levulan® and Metvix®.[5,12] Only one adverse reaction, headache, was observed in more than one patient. No influence on liver enzymes or other systemic adverse reactions were noted in the whole development programme.[8,9]

Usage of the 5-ALA patch will markedly improve handling of PDT. First, the patch is applied directly to mild to moderate AK lesions without preparing them by, for example, curettage, which is necessary when applying MAL–PDT.[13] Second, no occlusive dressing and further light protection have to be applied which again is the case when applying MAL or 5-ALA cream. Thus, the 5-ALA patch reduces the present multistep method of application of the photosensitizer's precursor to a simple one-step procedure. When taking off the patch, illumination can start immediately without lesion cleaning. In contrast, treated areas have to be rinsed with saline after application of MAL or 5-ALA in semiliquid formulations. Although the 5-ALA patches were administered by trained nurses or the investigators throughout the clinical study programme, the convenience of administration might make the patch suitable for self-application by the patient prior to illumination at the doctor's office.

In conclusion, a considerable facilitation in performance of PDT with the 5-ALA patch is accompanied by very good efficacy and excellent cosmetic results of a single PDT treatment. The reproducibility of the magnitude of the treatment effect and the comparability of the study data with literature data show that the effect is of clinical relevance. Furthermore, efficacy of PDT with the novel 5-ALA patch exceeded that of standard therapy, cryosurgery, in a statistically significant way, with better cosmetic results and no observed differences in tolerability. In these studies the 5-ALA patch was applied to isolated AK lesions. Due to the convincing efficacy and safety data, the possibility of larger patches to treat larger areas of AK (e.g. field cancerization) will be evaluated.

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