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Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data

R.-M. Szeimies, E. Stockfleth,* G. Popp,† F. Borrosch,‡ H. Brüning,§ R. Dominicus,¶ H. Mensing,**
U. Reinhold,†† K. Reich,‡‡ A.C.E. Moor,§§ M. Stocker,§§ C. Ortland,§§ M. Brunnert,¶¶ and A. Hauschild***

Department of Dermatology, Regensburg University Hospital, Franz Josef Strauss Allee 11, Regensburg, Germany
*Charité, Skin Cancer Center Charité Berlin, Chariteplatz 1, Berlin, Germany
†Hofackerstraße 19, Augsburg, Germany
‡Oyther Str. 24, Vechta, Germany
§Schönberger Str. 72–74, Kiel, Germany
¶Vollenstr. 8, Dülmen, Germany
**Dermatologisches Ambulatorium, Heegbarg 5, Hamburg, Germany
††Medical Centre Bonn, Friedensplatz 16, Bonn, Germany
‡‡SCIderm GmbH, Esplanade 6, Hamburg, Germany
§§photonamic GmbH & Co. KG, Theaterstr. 6, Wedel, Germany
¶¶M.A.R.C.O. Institute for Clinical Research and Statistics, Moskauer Str. 25, Düsseldorf, Germany
***Department of Dermatology, Venerology and Allergology, University of Kiel, Schittenhelmstr. 7, Kiel, Germany

Correspondence
Christoph Ortland.
E-mail: c.ortland@photonamic.de

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Summary

Background Photodynamic therapy with a self-adhesive 5-aminolaevulinic acid (5-ALA) patch shows high efficacy rates in the treatment of mild to moderate actinic keratosis (AK) in short term trials.

Objectives The purpose of the trial was to follow up patients after successful 5-ALA patch-PDT at 3 month intervals over a total period of 12 months. Patients who had received placebo-PDT or cryosurgery served for comparison.

Patients/methods Three months after therapy, 360 patients from two separate randomized parallel group phase III studies (one superiority trial vs. placebo-PDT, one noninferiority trial vs. cryosurgery) were suitable for the follow-up study. Patients had to show at least one successfully treated AK lesion after initial therapy. A total of 316 patients completed the follow-up.

Results Twelve months after a single treatment, 5-ALA patch-PDT still proved superior to placebo-PDT and cryosurgery ($P < 0{\cdot}001$ for all tests). On a lesion basis, efficacy rates were 63% and 79% for PDT, 63% for cryosurgery and 9% and 25% for placebo-PDT. Recurrence rates of patch-PDT proved superior to those of cryosurgery (per protocol set: $P = 0{\cdot}011$, full analysis set: $P = 0{\cdot}049$). While 31% of cryosurgery lesions were still hypopigmented after 1 year, the 5-ALA patch-PDT groups showed hypopigmentation in 0% (superiority trial) and 3% (noninferiority trial) of the treated lesions.

Conclusion Twelve months after a single 5-ALA patch-PDT the majority of lesions were still cleared with an excellent cosmetic outcome. 5-ALA patch-PDT proved to be superior to cryosurgery in the noninferiority study setting.

Actinic keratosis (AK) is the result of chronic sun exposure especially in subjects with fair skin. Because of the risk of progression to squamous cell carcinoma (SCC), treatment guidelines recommend therapy of AK upon diagnosis.[1,2] Photodynamic therapy (PDT) using 5-aminolaevulinic acid (5-ALA) or its ester methyl aminolaevulinate (MAL) has proved to be effective in treating AK.[3–10]

For facilitation of traditional PDT and a shortening of handling times, a self-adhesive, skin coloured 5-ALA patch (product code PD P 506 A; photonamic GmbH and Co. KG,

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Wedel, Germany) has been developed which combines the proven therapeutic effect of 5-ALA with a novel patch technology.[11–13] The 5-ALA patch is intended to be directly applied to AK lesions without prior crust removal by curettage. It delivers 5-ALA to the skin lesion and protects it from light during occlusion due to an aluminised backing. It is skin coloured, square and 4 cm^2 in size. The patch contains 8 mg 5-ALA (present as 5-ALA hydrochloride). As no additional occlusive dressings or bandaging are needed during the application time, the 5-ALA patch is very discreet and convenient for the patient.

The length of the application interval for the 5-ALA patch before illumination with red light has been evaluated in clinical studies.[12,13] Two randomized confirmatory phase III studies were conducted to compare the efficacy and safety of 5-ALA patch-PDT with that of placebo-PDT or cryosurgery. The results of the primary endpoint analyses of these trials which were collected 12 weeks after a single treatment have been reported in this journal.[14] Here we present the observations during an additional follow-up period of 9 months and report efficacy as well as the recurrence rates 12 months after a single PDT with the innovative 5-ALA patch.

Materials and methods

Data were collected during the follow-up period of two separate multicentre confirmatory randomized parallel group trials which were conducted in Germany. Ethics votes and approval by the regulatory body had been obtained prior to the start of the study. Both studies are registered at clinicaltrials.gov. The study methods as well as the results of the primary endpoints have been reported.[14] In the trials, patients had either been treated with 5-ALA patch-PDT, placebo patch-PDT or cryosurgery.[14]

For PDT, 5-ALA or placebo patches were applied to the lesions selected for study for 4 h without preparation of the lesions by, for instance, curettage. Placebo patches were of identical appearance to the 5-ALA patches but did not contain 5-ALA. A maximum of 8 AK lesions was treated per PDT session and patient. After patch removal, AK lesions were immediately illuminated with red light 37 J cm^{-2} at 630 ± 3 nm; Aktilite® CL 128 (Photocure ASA, Oslo, Norway) or Omnilux® (Photo Therapeutics Inc., CA, U.S.A.). Study lesions in the cryosurgery group were frozen using one cycle with the liquid nitrogen open spraying procedure for a maximum time of 10 s after ice ball formation. A mean freezing time of 7·3 ± 2 s was reported for the full analysis set. Again, a maximum of eight study lesions was treated.[14]

Study population

Patients were followed-up if they showed at least one AK study lesion successfully cleared 12 weeks after a single study treatment.[14]

Study plan

During follow-up, the efficacy of the study therapy was assessed at 3 month intervals. At these study visits, recurrent AK study lesions were treated with surgical techniques (cryosurgery, excision etc.). This form of therapy was used with the intention of avoiding an influence on the efficacy assessments of the study lesions that remained clear. Patients in which all study lesions were recurrent were withdrawn from the study. Concomitant medication and safety (adverse drug reactions) were documented at every visit. Furthermore, the cosmetic outcome ('excellent', 'good', 'fair' or 'poor') and pigmentation status of cleared lesions (normally pigmented, hyper- or hypopigmented) were recorded.

Efficacy assessments

Throughout the development program of the 5-ALA patch, complete clinical clearance of an AK lesion was defined as: (i) no visual evidence of a persisting AK on the treated surface; (ii) no evidence of adherent scaling plaques on the treated skin surface when palpated; (iii) lesions imperceptible to touch; and (iv) slight pink or red foci might be visible at lesion sites.

Biometrical approach

According to the original study plans, both studies were analysed separately without pooling of data. In order to test for differences in overall clearance rates between the treatment groups, the log-rank test (PROC LIFETEST) was applied for analyses on a lesion as well as on a patient basis. The recurrence rates were estimated based on the life-table approach for grouped data which adequately takes dropouts (i.e. 'censored' observations) into account. Recurrence rates were estimated by treatment group and subgroups (i.e. centre, gender, skin type, lesion diameter, lesion grade, localisation of lesion). In analogy, a patient-based evaluation with all cleared lesions per patient was performed.

Results

Patients

After having been treated in two separate randomized parallel group phase III studies, 360 patients were eligible for the follow-up period of a maximum of 9 months (i.e. 12 months after a single treatment). These patients had a total of 1619 cleared AK study lesions. Three hundred and sixteen patients completed the follow-up (Table 1). The reason for withdrawal or drop-out was 'no cleared study lesions' in most cases (n = 21), i.e. all treated lesions of these patients recurred. Other reasons for drop-out included unauthorized medication (n = 8), missed control visits (n = 7), withdrawal of consent (n = 5), death (n = 2) and lack of effect (n = 1).

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Table 1 Disposition of patients during follow-up period. Numbers in parentheses indicate the number of patients showing at respective follow-up visit and are only given if different from the total number of patients under observation

	No. of patients			
Visit	1	2	3	4
Follow-up period (months)	Start	3	6	9
Time after initial treatment (months)	3	6	9	12
Superiority study				
5-ALA patch-PDT	64	62 (61)	54 (51)	53
Placebo PDT	12	12	11	10
Non-inferiority study				
5-ALA patch-PDT	132	131	126 (125)	121
Cryosurgery	130	130	121 (120)	113
Placebo PDT	22	19	19 (18)	19
Total	360	354	331	316

Efficacy

One year after a single therapy, the overall clearance rates were still high for the active treatment arms of both studies (Fig. 1). The 5-ALA patch-PDT proved statistically significantly superior to cryosurgery as well as to placebo-PDT [$P < 0{\cdot}001$ for all tests, both studies, full analysis set (FAS) and per protocol set (PPS)].

In the noninferiority study, the recurrence rates after 12 months were 11% for the 5-ALA patch-PDT, 18% for cryosurgery and 15% for the placebo-PDT. In the superiority study, the observed recurrence rates were 24% for the 5-ALA patch-PDT and 53% for the placebo-PDT. The recurrence rate for the 5-ALA patch-PDT was found to be better than that of cryosurgery ($P = 0{\cdot}011$ for the PPS) and ($P = 0{\cdot}049$ for the FAS). The results of subgroup analyses showed that there was no single influential factor on the results.

In the noninferiority study, 50% of the patients originally treated with the 5-ALA patch and 37% of the patients in the cryosurgery group were still completely free from recurrence at Visit 4. In the superiority trial, the corresponding figure for the 5-ALA patch-PDT group was 32%.

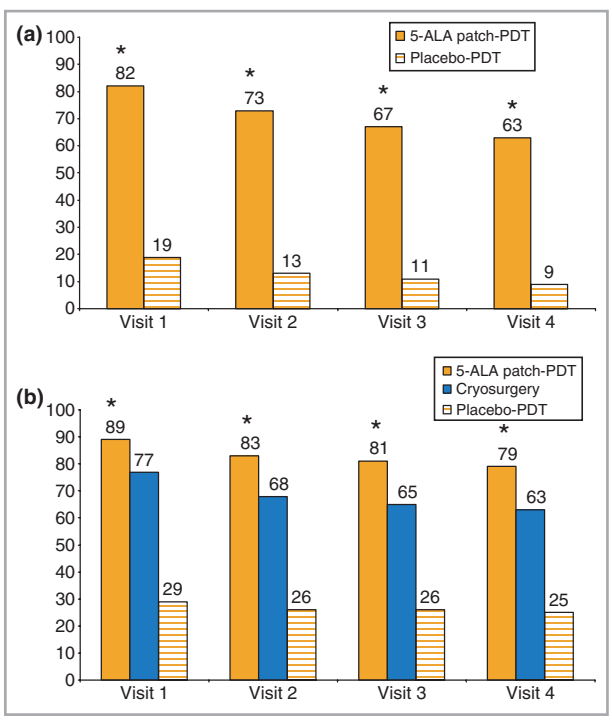

Fig 1. Overall clearance rates on a lesion basis at beginning of the follow-up period up to 12 months after a single therapy (Visit 1 indicating start of the follow-up period. Visits 2–4 were performed at intervals of 3 months). (a) Results of superiority study where 5-ALA patch-PDT was tested against placebo-PDT (*$P < 0{\cdot}001$ vs. placebo-PDT). (b) Results of noninferiority study on the comparison of 5-ALA patch-PDT vs. cryosurgery and placebo-PDT (*$P < 0{\cdot}001$ vs. cryosurgery and placebo-PDT).

Cosmetic outcome

During the follow-up period of the cryosurgery comparison study, the cosmetic outcome of cleared AK lesions was consistently highly rated (Table 2a). At all follow-up visits, the results for 5-ALA patch-PDT were better than those for cryosurgery ($P < 0{\cdot}001$). On the other hand there was no detectable difference between 5-ALA patch-PDT and placebo-PDT in the assessment of cosmetic results (Table 2b).

Furthermore, the pigmentation status differed markedly between the 5-ALA patch-PDT and cryosurgery (Fig. 2). One year after therapy, 94% (noninferiority study) and 100% (superiority study) of 5-ALA patch treated lesions were normally pigmented. After cryosurgery, only 68% of the lesions showed normal pigmentation one year after therapy. This difference is statistically significant with $P < 0{\cdot}001$.

Safety and tolerability

No adverse reaction related to the initial study treatment was observed during the follow-up period.

Discussion

A single course of 5-ALA patch-PDT has proved to be effective[13,14] and better than standard and placebo treatment[14] in short term studies with lesion clearance rates between 82% and 89%. This excellent efficacy of 5-ALA patch-PDT is linked to a convenient and easy way of treating AK; no curettage is necessary before applying the 5-ALA patch. The study results show that the thicker, moderate AK lesions respond as well to the 5-ALA patch PDT as mild AK lesions.[14] It is hypothesized that the reason for this is the rapid flux of 5-ALA from the patch during the occlusion period. Recent publications from other groups suggest that surface preparation does not affect the generation of fluorescence or the clinical results in AK[15] or basal cell carcinoma and Bowen's disease,[16] which further supports our approach. Due to its light impermeable backing

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Table 2a Cryosurgery comparison: frequency table for cosmetic outcome on lesion basis at visits 2, 3 and 4 (Per-protocol-set, n = 298). Results given for investigators' assessment

			Cosmetic outcome (Investigator's assessment)			
			Excellent	Good	Fair	Poor
Visit	Treatment group	No. of lesions	n (%)	n (%)	n (%)	n (%)
2	Cryosurgery	464	235 (51)	194 (42)	33 (7)	2 (0)
	5-ALA patch	590	461 (78)	124 (21)	5 (1)	0 (0)
	Placebo	60	47 (78)	13 (22)	0 (0)	0 (0)
3	Cryosurgery	436	215 (49)	187 (43)	30 (7)	4 (1)
	5-ALA patch	531	439 (83)	89 (17)	3 (1)	0 (0)
	Placebo	55	49 (89)	6 (11)	0 (0)	0 (0)
4	Cryosurgery	395	210 (53)	147 (37)	35 (9)	3 (1)
	5-ALA patch	515	422 (82)	91 (18)	2 (0)	0 (0)
	Placebo	52	47 (90)	5 (10)	0 (0)	0 (0)

Table 2b Statistical results of two-sided Wilcoxon test

		Cosmetic outcome (Investigator's assessment)	
		Full analysis set	Per protocol set
Visit	Comparison		
2	5-ALA patch vs. cryosurgery	< 0·001	< 0·001
	5-ALA patch vs. placebo	0·415	0·485
3	5-ALA patch vs. cryosurgery	< 0·001	< 0·001
	5-ALA patch vs. placebo	0·837	0·918
4	5-ALA patch vs. cryosurgery	< 0·001	< 0·001
	5-ALA patch vs. placebo	0·674	0·752

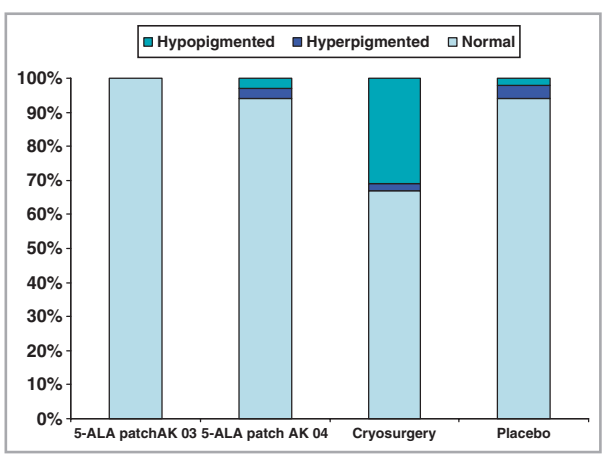

Fig 2. Pigmentation status of cleared lesions 12 months after single treatment. Data for placebo-PDT in the superiority study not shown as number of lesions was too small. AK 03 = study code of superiority study; AK 04 = study code of noninferiority study.

the patch also serves as light protection so that additional bandages or occlusive dressings are not needed. This makes the treatment simple, convenient and discreet for the patient.

In the follow-up study presented here, we show that the treatment effect is maintained over 12 months with up to half of the treated patients being completely lesion free. Remarkably, the high efficacy rates in our studies were obtained after a single PDT without prior crust removal from the study lesions. In contrast, traditional 5-ALA-PDT or MAL-PDT is often repeated after 2–3 months in case the lesions have not been cleared,[3–8] and removal of crusts is recommended before applying MAL cream.[6–10] Published 12 month data on the use of 5-ALA-PDT in mild to moderate AK are comparable with our data with efficacy rates of 78% and recurrence rates of 24%. However, in that study AK lesions were treated a second time if not successfully removed after the first PDT.[4]

The clearance rates observed in our noninferiority study are slightly better than those of the superiority study. Nevertheless, the 5-ALA patch-PDT shows superiority over placebo 1 year after a single therapy in both studies. However, the results after placebo-PDT differ between the studies with relatively high clearance rates in the noninferiority study. This difference might be explained by the low absolute number of lesions treated with placebo which had cleared 12 weeks after treatment, thus being eligible for follow-up.

Twelve weeks after study treatment, a considerable proportion of successfully treated AK lesions showed hypopigmentation in the cryosurgery arm.[14] Interestingly, this frequency was maintained over the follow-up period. On the other hand, the vast majority of PDT treated lesions was normally pigmented 1 year after therapy. This supports reports that hyperpigmentation after PDT is a transient phenomenon[17] and that, in contrast, hypopigmentation after cryosurgery results from injury of the epidermis and thus represents a form of scarring.[18] This is also reflected in investigators' and patients' assessment of the cosmetic result of the therapy. Here, 5-ALA patch PDT gets significantly better results than cryosurgery at 12 weeks[14] as well as 12 months after treatment.

Conclusion

Photodynamic therapy cannot only be considerably facilitated by application of the 5-ALA patch but also shows excellent

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and maintained efficacy over at least one year. High clearance rates and an excellent cosmetic effect as well as the absence of altered pigmentation after PDT proved to be superior as compared with cryosurgery.

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Conflicts of interest

RMS has received honoraria for participation in advisory boards from Galderma, Intendis and Peplin; has received honoraria and travel support as a speaker for Almirall-Hermal, Galderma, Intendis and photonamic and was involved in inventing the product. AH and ES are members of the advisory board of Intendis. AH received speakers' honoraria from photonamic and Intendis. ACEM, CO and MS are employees of photonamic. MB is an employee of the company in charge of data management and statistical issues (M.A.R.C.O.).

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