

Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up

E.H. Tschen, D.S. Wong,* D.M. Pariser,† F.E. Dunlap,‡ A. Houlihan§ and M.B. Ferdon¶ and the Phase IV ALA–PDT Actinic Keratosis Study Group¹

Academic Dermatology Associates, Albuquerque, NM, U.S.A.

*Dermatology Specialists, Vista, CA, U.S.A.

†Virginia Clinical Research Inc., Norfolk, VA, U.S.A.

‡Radiant Research, Tucson, AZ, U.S.A.

§DUSA Pharmaceuticals Inc., Valhalla, NY, U.S.A.

¶Therapeutics Inc., 9025 Balboa Avenue, Suite 100, San Diego, CA 92123, U.S.A.

Summary

Correspondence

Mary Beth Ferdon.

E-mail: mbferdon@therapeuticsinc.com

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Conflicts of interest

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¹Members of the Phase IV ALA–PDT Actinic Keratosis Study Group comprise: S. Bruce (Suzanne Bruce and Associates, Houston, TX, U.S.A.), M.T. Jarratt (DermResearch, Inc., Austin, TX, U.S.A.), R.W. Loss (Dermatology Associates of Rochester, P.C., Rochester, NY, U.S.A.), J. Weiss and J.S. Shavin (Gwinnett Clinical Research Center Inc., Snellville, GA, U.S.A.), A. Barba (International Dermatology Research, Inc., Miami, FL, U.S.A.), D.A. Zeide (Radiant Research, Lake Worth, FL, U.S.A.) and R.T. Brodell (Brodell Medical Inc., Warren, OH, U.S.A.).

Background Actinic keratoses (AKs) are the most common epithelial precancerous lesions, especially among individuals with light complexions. AKs are believed to progress to in situ squamous cell carcinoma (SCC) and potentially, to invasive SCC. AKs and invasive SCCs share certain histopathological features and both share genetic tumour markers and p53 mutations. Given these facts, the treatment and management of AKs are integral components to quality dermatological health care.

Objectives Topical aminolaevulinic acid-based photodynamic therapy (ALA–PDT) has been extensively studied over the last several years. This study seeks to characterize further the efficacy and safety of ALA–PDT by extending previous work to: (i) assess the long-term recurrence rate of AKs that have resolved after ALA–PDT; (ii) to characterize the histopathology of treated AK lesions that do not completely respond to ALA–PDT or recur in long-term follow up; (iii) to characterize the histopathology of untreated clinically diagnosed AK lesions in the study population at baseline; and (iv) to evaluate ALA–PDT in darker skin types than previously studied.

Methods Patients enrolled in this study had six to 12 discrete AK lesions, either on the face or the scalp. Individual AK lesions designated for treatment were graded as either grade 1 (lesions slightly palpable and more easily felt than seen) or grade 2 (moderately thick AKs, easily seen and felt). Patients with grade 3 (very thick and/or hyperkeratotic) lesions were excluded. For each subject, two lesions at baseline were randomized to biopsy, and were not followed as part of the study while the remaining lesions (target lesions) were treated with ALA–PDT (baseline and month 2, if required) and followed for 12 months.

Results Of the 110 patients enrolled, 101 completed the study. The target AK lesions in the per-protocol population clearing completely in the first and second months following a single ALA–PDT treatment (baseline) were 76% and 72%, respectively. Sixty per cent of the patients received a second ALA–PDT treatment, limited to the target AKs still present at month 2. The percentage of treated target lesions that cleared completely peaked at 86% at month 4 then decreased gradually over time to 78% at month 12. The overall recurrence rate for all lesions that were noted to be cleared at some visit during the 12-month period was 24%

(162/688). Of the 162 recurrent lesions 16 were lost to follow up, seven spontaneously cleared and 139 were biopsied. With respect to the lesions biopsied, 91% (127/139) were diagnosed histopathologically as AK, with the balance of lesions being SCC (nine of 139: 7%), basal cell carcinoma (one of 139: 0.7%) and other non-AK diagnoses (two of 139: 1%). The recurrence rate for histologically confirmed AKs was 19%. The clinical diagnosis of AK by investigators appeared to be accurate, with 91% (200/220) of the untreated clinically diagnosed AK lesions being histopathologically confirmed to be AK (AK, 142/220: 65%; advanced AK, 29/220: 13%; macular AK, 29/220: 13%). Despite concentrated efforts to recruit patients with Fitzpatrick skin types IV–VI, the distribution was as follows: I, 11%; II, 36%; III, 41%; IV, 11%; V, 2%. The demographics of this study population are typical of a patient population with AK.

Conclusions ALA-PDT was shown to be an effective and safe therapy for the treatment of AKs of the face and scalp in skin types I–V, with an acceptable rate of recurrence over 12 months of histologically confirmed AKs of 19%. Phototoxicity reactions were all expected, nonserious and had essentially resolved after 1 month post-treatment independent of skin type.

Actinic keratoses (AKs) are the most common epithelial precancerous lesions among individuals with light complexions. AKs are believed to progress to *in situ* squamous cell carcinoma (SCC) and potentially, to invasive SCC in 12–13% of untreated patients.¹ AKs and invasive SCCs also share certain histopathological features in that both contain atypical keratinocytes with loss of polarity, nuclear pleomorphism, disordered polarity, and increased numbers of mitotic figures;^{2–4} both share genetic tumour markers and TP53 mutations.⁵ Current modalities of AK treatment include cryosurgery with liquid nitrogen, curettage, electrosurgery, excision, dermabrasion, laser surgery, imiquimod, diclofenac, 5-fluorouracil and photodynamic therapy (PDT) with topical aminolaevulinic acid (ALA) or its methyl ester, methylaminolaevulinic acid.

The basis of ALA-PDT therapy for benign and malignant epidermal abnormalities is the controlled, localized photoactivation of protoporphyrin IX (PpIX). Upon topical application, ALA is enzymatically converted to PpIX, which then accumulates in epidermal cells.⁶ Rapidly proliferating skin cells, such as those in AKs, appear to convert more ALA to PpIX than do normal epidermal cells.⁶ Topical ALA-induced PpIX photosensitization has been extensively studied over the last several years, and comprehensive reviews of the preclinical and clinical pharmacology and toxicology of topical ALA-PDT are available.^{7–9}

The ALA-PDT therapy utilized in the present study was the combination of Levulan® Kerastick® (DUSA, Wilmington, MA, U.S.A.), a proprietary 20% topical solution dosage form of ALA, followed by photoactivation by the BLU-U® Photodynamic Therapy Illuminator (DUSA). The objectives were to characterize further the efficacy and safety of ALA-PDT by extending previous work to: (i) assess the long-term recurrence rate of AKs that have resolved after ALA-PDT; (ii) to characterize the histopathology of treated AK lesions that do not completely respond to ALA-PDT or recur in long-term

follow up; (iii) to characterize the histopathology of untreated clinically diagnosed AK lesions in the study population at baseline; and (iv) to evaluate ALA-PDT in darker skin types than previously studied.

Materials and methods

Study design

This study was a multicentre (11 private practice clinics), open-label, phase IV study of patients with AKs on the face and scalp. The study was conducted in compliance with the U.S. Food and Drug Administration regulations relevant to Good Clinical Practices. By complying with these regulations, the ethical concepts described in the Declaration of Helsinki were met.

Patient selection

Patients enrolled in this study were required to be at least 18 years of age with six to 12 discrete AK lesions, either on the face or on the scalp. Women were to be postmenopausal, surgically sterile, or using a medically acceptable form of birth control. Women of child-bearing potential were also required to have a negative urine pregnancy test prior to initiation of study medication. Patients were excluded from the study if they had a history of cutaneous photosensitization or porphyria, hypersensitivity to porphyrins, or a photodermatosis. Individual AK lesions designated for treatment were graded as grade 1 (lesions slightly palpable and more easily felt than seen) or grade 2 (moderately thick AKs, easily seen and felt). Patients with very thick and/or hyperkeratotic (grade 3) lesions were excluded. Other exclusion criteria included use of photosensitizing drugs, known sensitivity to vehicle components, active infectious disease, pregnancy or lactation, use of

another investigational drug within the previous 30 days, prior treatment of lesions with PDT, or any medical condition which could preclude study participation or compliance.

Procedures

At the baseline visit for each patient, the history of significant medical and dermatological conditions, including past AK treatments and concomitant medications, were recorded. Dermatological examination and skin typing were also performed, with skin classification according to the Fitzpatrick six-point scale.¹⁰

Six to twelve AK lesions were identified as study lesions for each patient. After a patient's lesions were numbered and their locations recorded on an anatomical diagram and by digital photography, the investigator referred to the randomization schedule for the specific number of study lesions for that patient to obtain the numbers of the two lesions to be biopsied. The two lesions randomized to biopsy were not followed as part of the study while the remaining lesions (target lesions) were treated with ALA-PDT and followed for 12 months.

All biopsies were sent to a central histopathology laboratory for processing (Cockerell and Associates Dermatopathology Laboratory, Dallas, TX, U.S.A.). AKs were classified as: (i) macular AK, (ii) AK or (iii) advanced AK, and SCCs as (i) *in situ* or (ii) with superficial invasion. The classification system used was that described by Yantsos *et al.*¹¹ Briefly, an AK of the usual type was diagnosed if there was atypia of the basal layers of the epidermis involving less than two-thirds of the epidermal thickness, with overlying parakeratosis. Advanced AK was diagnosed if there was at least one of the following present: atypia of at least the lower two-thirds of the epidermis; extensive proliferation of atypical keratinocytes along adnexal structures; extension of buds of atypical keratinocytes into the superficial dermis; extensive acantholysis of atypical keratinocytes. Macular AK was diagnosed if there was slight atypia of the basal layer of the epidermis, with minimal or no overlying parakeratosis. As these histological changes are quite subtle, the diagnosis of macular AK required clinical-pathological correlation (i.e. a clinical impression of AK). Macular, usual type and advanced AK correspond to grades I, IIa and IIb, respectively, of keratinocytic intraepidermal neoplasia as defined in Yantsos *et al.*¹¹

Treatment administration

Prior to administering study medication, target lesions were graded and evaluated for PDT response-like characteristics (erythema, oedema, stinging/burning, hypo- and hyperpigmentation). Topical ALA solution, 20%, was then applied as a double coat to the target lesions using a patented Kerastick® applicator. Patients were instructed to avoid immersion of the target lesions in water, or exposure to bright light, sunscreen, cosmetics, moisturizers/emollients etc., prior to visible blue light treatment that was scheduled 14–18 h after ALA

application. After this incubation period, the ALA-treated lesions were rinsed gently with water, patted dry and exposed to 10 J cm⁻² of visible blue light (417 ± 4 nm peak) delivered at 10 mW cm⁻² from the BLU-U® Photodynamic Therapy Illuminator (DUSA).

Patients returned once monthly for follow-up visits over the next year. Any target lesions that remained at month 2 were retreated with ALA-PDT. Biopsies of all nonresponding lesions were taken at month 3. Biopsies of all lesions recurring after a complete response (CR) were taken at the visit when the recurrence of the lesion(s) was clinically confirmed. A recurrent lesion was defined as one that had resolved to grade 0 (no visible or palpable lesion) following PDT treatment, but subsequently returned to grade 1–3.

Safety assessments

Safety of ALA-PDT was assessed by expected PDT responses (including erythema, oedema, pigmentation changes and stinging/burning) and adverse events. The severity of erythema and oedema was recorded in terms of the percentage of target lesions with these signs. These responses were recorded on PDT treatment days prior to drug application, prior to light exposure and immediately after light exposure. Stinging and burning were assessed at these time points as well as during light exposure at 1, 6 and 11 min. Pigmentation changes were recorded for each lesion prior to each light treatment and at each follow-up visit.

Efficacy assessments

At each visit, the investigator assessed lesions for clearance or recurrence. Photographs of the target lesions were taken at baseline (prior to treatment), months 3 and 12.

Analysis populations

The intent-to-treat (ITT) population included all patients who were randomized and received study medication and light treatment at baseline. A last-observation-carried-forward analysis was used for dropouts or missing data for the efficacy variables.

The per-protocol (PP) population was a subset of the ITT population and included all patients who met the admission criteria; completed at least one follow-up visit; had target lesions of grade 1 or 2 at baseline; received light treatment within 13–19 h of ALA application; received the complete course of light treatment (1000 s); and did not use any excluded medications or treatments on the target lesions for the duration of the study. The PP analysis used observed values only. Patients whose visits fell outside predefined visit windows or had missing responses were excluded from that visit, but were included in the analysis of subsequent follow-up visits. The protocol specified that beginning with the month 3 visit, any nonresponding or recurring lesions were to be biopsied at the visit where the nonresponse or recurrence was

clinically confirmed. Either due to investigator discretion or patient request, biopsies were sometimes delayed. The PP analysis treated these lesions as 'not evaluable' at all visits following the visit that the biopsy was delayed.

The analyses of safety data and the assessment of recurrent and nonresponding lesions were based on the ITT population.

Statistical methods

AK lesion counts were performed at baseline and months 1–12. Lesion counts were evaluated as the percentage of individual lesions showing CR and the percentage of patients with 75% or greater reduction and 100% reduction in lesion counts compared with baseline. Recurrence rate of the lesions was determined at each visit subsequent to month 2 and biopsy results of nonresponding and recurring lesions were summarized.

Adverse events were tabulated by body system, severity and relationship to study drug. The number and percentage of lesions with PDT responses (erythema, oedema, changes in pigmentation) were tabulated for each visit as was the number and percentage of patients with stinging/burning.

Results

In total, 110 patients were enrolled in the study by 11 centres, with three to 20 patients per centre. Most were male (96/110: 87%) and white-skinned (104/110: 95%). Their ages ranged from 43 to 89 years (mean \pm SD 67.0 \pm 9.8). Despite concentrated efforts to recruit patients with Fitzpatrick skin types IV–VI, the distribution was as follows: I, 11%; II, 36%; III, 41%; IV, 11%; V, 2%. The demographics of this study population are typical of a patient population with AK.

The 110 patients had a total of 968 lesions; 220 lesions were biopsied at baseline and 748 target lesions were treated with ALA-PDT: 543 lesions on the face and 205 lesions on the scalp. The mean \pm SD number of lesions per patient was 6.8 \pm 2.1. Ninety-two per cent (101/110) of the patients completed the study. Nine patients discontinued either due to patient request or to therapeutic failure.

Six patients with a total of 43 lesions were excluded from all PP efficacy analyses due to PDT treatment occurring outside

the specified time window ($n = 1$), early termination of PDT treatment ($n = 2$) and application of ALA at an inappropriate visit ($n = 3$). The 104 patients in the PP population had a total of 705 target lesions. All of the excluded patients (five men and one woman) were white skinned, with lesions on the face, resulting in 500 (71%) lesions on the face and 205 (29%) lesions on the scalp. Ninety-eight of the patients in the PP population completed the study (see Fig. 1).

Baseline biopsied lesions

Most of the 220 lesions (two from each patient) biopsied at baseline were located on the face (156/220: 71%) with the remainder on the scalp (64/220: 29%). The clinical diagnosis of AK by investigators appeared to be accurate, with 91% (200/220) of the lesions being histopathologically confirmed to be AKs (AK, 142/220: 65%; advanced AK, 29/220: 13%; macular AK, 29/220: 13%). The remaining lesions included 5% (10/220) SCC (SCC in situ, 7/220: 3%; SCC with early invasion, 3/220: 1%), 0.5% (1/220) basal cell carcinoma (BCC) and 4% (9/220) benign non-AK diagnoses (Table 1). Three subjects had both baseline reference lesions diagnosed as SCC.

Efficacy

The percentages of the target AK lesions in the PP population that cleared completely in the first and second months following an initial single ALA-PDT treatment (baseline) were 76% (511/675) and 72% (476/661), respectively (Table 2). Sixty per cent (66/110) of all patients received a second ALA-PDT treatment, limited to those target AKs still present at month 2. The percentage of treated target lesions that cleared completely peaked at 86% (535/621) at month 4 then decreased gradually over time to 78% (458/585) at month 12 as detailed in Table 2. The percentage of the target lesions located on the face that cleared completely was higher than those of scalp lesions at all visits (Fig. 2).

The percentage of lesions that cleared completely differed by < 10% across skin types at each visit following the second treatment. Clearance rates of skin types I and II slightly exceeded those of types III and IV beginning at month 6.

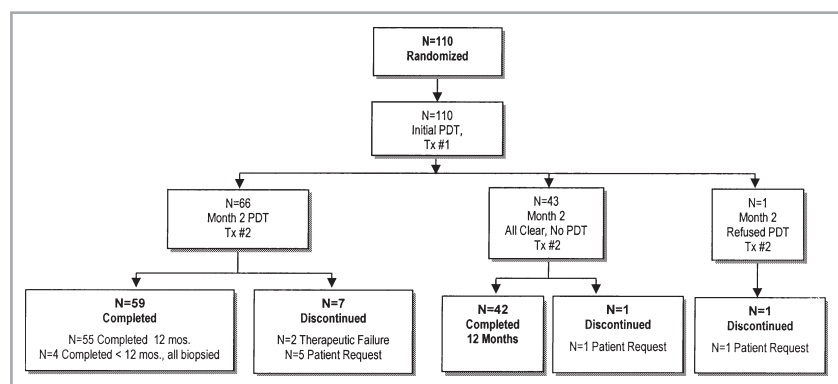


Fig 1. Subject enrolment flow chart. PDT, photodynamic therapy; Tx, treatment.

Table 1 Baseline reference lesion and target lesion disposition/histopathology

	Biopsied lesions, n (percentage of row total)									
	AK				SCC					
	AK	Advanced	Macular	Total	In situ	Sup Inv ^a	Total	BCC	Other	Total
Nontreated baseline reference lesions	142 (65)	29 (13)	29 (13)	200 (91)	7 (3)	3 (1)	10 (5)	1 (1)	9 (4)	220
Nonresponding target lesions	27 (53)	6 (12)	13 (26)	46 (90)	1 (2)	1 (2)	2 (4)	1 (2)	2 (4)	51
Recurrent target lesions	82 (59)	33 (24)	12 (9)	127 (91)	7 (5)	2 (1)	9 (7)	1 (1)	2 (1)	139
Total treated target lesions ^b	106 (57)	38 (21)	24 (13)	168 (91)	8 (4)	3 (2)	11 (6)	2 (1)	4 (2)	185

AK, actinic keratosis; SCC, squamous cell carcinoma; BCC, basal cell carcinoma. ^aSuperficial invasion. ^bFive AKs [two face: AK (n = 1) and macular AK (n = 1) and three scalp: AK (n = 2) and advanced AK (n = 1)] counted as recurrent and nonresponder included once in totals (see text for explanation).

Visit	Percentage of lesions cleared	Percentage of patients with 75% of the lesions cleared	Percentage of patients with 100% of the lesions cleared
Month 1	75.7 (511/675)	66.0 (66/100)	47.0 (47/100)
Month 2	72.0 (476/661)	59.6 (59/99)	41.4 (41/99)
Month 3	86.0 (573/666)	79.0 (79/100)	67.0 (67/100)
Month 4	86.2 (535/621)	81.1 (77/95)	62.1 (59/95)
Month 5	85.3 (505/592)	79.6 (74/93)	60.2 (56/93)
Month 6	85.9 (531/618)	80.6 (79/98)	59.2 (58/98)
Month 7	85.1 (525/617)	79.6 (78/98)	58.2 (57/98)
Month 8	82.8 (497/600)	76.0 (73/96)	53.1 (51/96)
Month 9	80.7 (484/600)	75.0 (72/96)	49.0 (47/96)
Month 10	82.3 (461/560)	77.8 (70/90)	51.1 (46/90)
Month 11	80.1 (442/552)	75.0 (66/88)	50.0 (44/88)
Month 12	78.3 (458/585)	72.0 (67/93)	39.8 (37/93)

Per-protocol analysis used observed values only. Patients whose visits fell outside predefined visit windows or had missing responses were excluded from a particular visit.

Table 2 Percentage of lesions cleared and percentage of patients with 75% and 100% of lesions cleared (per-protocol population)

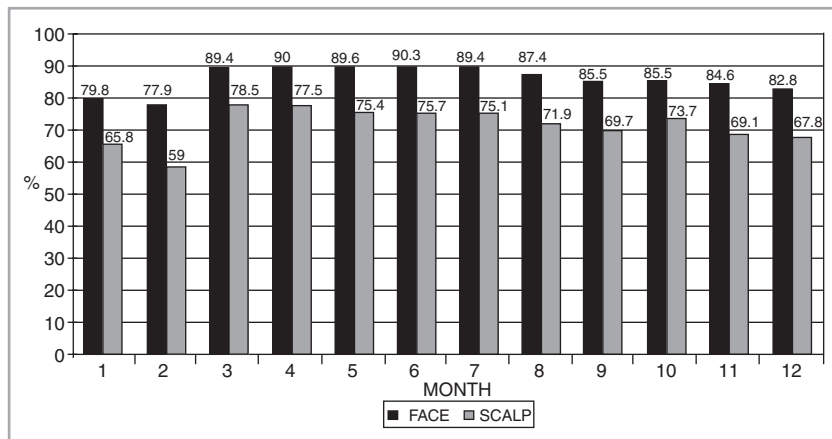


Fig 2. Actinic keratosis (AK) lesion complete response by lesion location (per-protocol population).

Complete clearing of all lesions after two ALA-PDT treatments was noted in the two patients with skin type V, but this reflects the responses of only a very limited number of lesions (n = 10). Throughout the study period, the percentage of AK lesions that cleared completely was very similar for the grade 1 and grade 2 lesions.

Following the second PDT treatment (month 2), the greatest percentage of patients in the PP population who experienced complete clearing of 75% or more of the target lesions was approximately 80% through month 7 and this decreased to 72% (67/93) at month 12 (Table 2).

Table 3 Disposition of nonresponding/recurrent lesions (intent-to-treat population)

Initial response	Biopsied	Not biopsied per protocol			Total
		CR/Stay CR	CR/Recurrence	LTF	
CR/Recurrence	134	7	–	16	157
Nonresponder	46	3	5 ^a	12	66
Total	180	10	5 ^a	28	223

CR/Stay CR, lesions cleared and stayed clear; CR/Recurrence, lesions cleared and then recurred; LTF, lost to follow up. ^aLesions were biopsied; total 185 lesions biopsied.

The percentage of patients in the PP population with complete clearing of 100% of the target lesions following the second ALA-PDT treatment ranged from a high of 67% (67/100) at month 3 to a low of 40% (37/93) at month 12 with interim clearance rates between 49% and 62%.

Recurrent and nonresponding lesions

The 223 lesions that were either nonresponders ($n = 66$) or recurred ($n = 157$) should have been biopsied at the visit they were clinically noted. These lesions were widely distributed between anatomical locations both on the face and on the scalp. The 43 lesions that were not biopsied when clinically confirmed as nonresponding or recurrent were subsequently lost to follow up (LTF) ($n = 28$), cleared and stayed clear ($n = 10$), or cleared and then recurred and were biopsied ($n = 5$). The remaining 180 lesions were biopsied PP.

As shown in Table 3, five of the 66 nonresponding lesions became clear, subsequently recurred and were biopsied (all confirmed AKs). Including these five lesions with the recurring lesions ($n = 157$) gives a total of 162 lesions that recurred.

In addition to the nonresponding/recurrent lesions, there were 523 lesions that cleared and remained clear throughout the study (durable CRs). Therefore, in all, there were 688 lesions (523 durable CRs + 157 CRs that recurred + 8 nonresponders that became CR) that showed CR at some visit during the study.

The overall recurrence rate was 24% (162/688). Sixteen of the recurrent lesions were LTF, seven cleared and stayed clear, and 139 were biopsied. Most (127/139: 91%) of these lesions were diagnosed histopathologically as AK (Table 1). The remaining diagnoses were SCC (nine of 139: 7%), BCC (one of 139: 0.7%) and other non-AK diagnoses (two of 139: 1%). Reducing the number of lesions that were CR at some visit ($n = 688$) by the lesions with non-AK diagnosis ($n = 12$), LTF ($n = 16$) and lesions that subsequently cleared and remained clear ($n = 7$), the recurrence rate for confirmed AKs was 19% (127/653).

Clinically, 9% (66/748) of the target AK lesions did not respond to ALA-PDT by month 3. Twelve of the nonresponding lesions were LTF, three cleared and stayed clear, and 51 were biopsied. Ninety per cent (46/51) were diagnosed as AK, 4% (2/51) SCC, 2% (1/51) BCC and 4% (2/51) cicatrix (Table 1). Excluding the 15 lesions that were not biopsied

and the five with non-AK diagnoses, the nonresponse rate for confirmed AKs was 6% (46/728).

Six per cent (11/185) of the lesions that were biopsied during the trial [recurrent ($n = 9$) and nonresponding ($n = 2$) lesions] were histopathologically diagnosed as SCC (SCC in situ, SCC with superficial invasion). There was little difference between the incidence of SCC at baseline (10/220: 5%) and subsequent to PDT, implying that there were no cancer-promoting effects of the therapy.

Safety results

Expected photodynamic therapy responses

The incidence of erythema increased from 73% (80/110) at baseline to 95% (105/110) immediately after light treatment. The percentage of patients with erythema observed at all subsequent follow-up visits (except for month 2 retreatment) was less than that seen at baseline.

The rate of oedema increased from 15% (16/110) at baseline to 79% (87/110) immediately after light treatment. Oedema in the treated lesions was virtually absent after month 3.

The incidence of hypopigmentation in the target lesions at baseline was low (57/748: 8%) and mostly of minimal severity. The percentage of lesions with hypopigmentation remained low throughout the course of the study, ranging from 3% at months 1 (20/748) and 2 (19/747) to 8% (41/505) at month 12. Five per cent (36/691) of lesions that had no hypopigmentation at baseline were hypopigmented at the last study visit, while 81% (46/57) of lesions that were hypopigmented at baseline were normal at the last study visit.

Hyperpigmentation was recorded for 27% (205/748) of lesions at baseline and was minimal for the majority of cases. The percentage of lesions with hyperpigmentation decreased after the first treatment and remained low throughout the course of the study, ranging from 7% (49/746) at month 1 to 13% (65/513) at month 11. Four per cent (24/543) of lesions that were not hyperpigmented at baseline were hyperpigmented at the last study visit, while 69% (142/205) of lesions that were hyperpigmented at baseline were normal at end of study. Neither hypo- nor hyperpigmentation varied with skin type. Pigmentation effects were not a result of treatment and in fact, most pre-existing hypo- and hyperpigmentation appeared to resolve by the end of the study.

The rate of stinging/burning increased from 16% (18/110) at baseline to 64% (70/110) following Levulan® application and prior to light treatment. The incidence peaked at 6 and 11 min following initiation of light treatment, with 96% (104/108) experiencing stinging/burning at those time points, with approximately 10% reporting the intensity as severe. The stinging/burning rates at subsequent visits were less than that observed at baseline. Only two patients discontinued light treatment due to discomfort; one after 2 min due to severe burning and the other after 3 min due to pain. Pain management could have been used during the light treatment at the investigator's discretion. Pain management may have included the use of a fan, cooling sprays and/or oral non-narcotic pain medication. Topical pain medications were prohibited. Fifty-six per cent (62/110) of patients utilized a fan alone during initial treatment to minimize potential discomfort, while 35% (39/110) did not employ any type of pain management. During and after treatment, the percentage of patients reporting moderate to severe pain was the same or greater for patients who used a fan compared with patients who used no form of pain management.

Other PDT responses recorded during the study included pruritus (17/110: 16%) and wealing (10/110: 9%), while blistering, crusting, pain, tingling and vesiculation were reported in < 5% of the patients.

In summary, the PDT reactions were all expected and had mainly disappeared by month 1 of the study. Safety results were consistent for all skin types enrolled in the study.

Adverse events

Of the 110 patients enrolled in the study, 89 (81%) reported a total of 285 adverse events (excluding the PDT responses discussed above). Most events (263/285: 92%) were of mild or moderate severity and were considered by the investigator to be unrelated to treatment.

Thirteen patients reported 17 adverse events (excluding PDT responses) graded as possibly, probably or definitely related to treatment. These included pain associated with PDT ($n = 4$) and rash associated with PDT ($n = 4$), and single reports of facial oedema, headache, nausea, paraesthesia, rhinitis, crusting, dry skin and pruritus. A skin carcinoma unrelated to ALA-PDT was initially mistakenly reported as related to treatment by the investigator.

Discussion

This phase IV long-term follow-up multicentre study in 110 patients with nonhyperkeratotic AKs demonstrates the safety and efficacy of ALA-PDT as an effective topical treatment for nonhyperkeratotic AKs on the face and scalp. These results are consistent with those from two phase III multicentre trials with ALA-PDT¹² in which the percentage of patients who experienced more than 75% or greater clearing of AKs was 77% and 89%, respectively, at weeks 8 and 12 (compared with the 72% and 86% reported in this study). A high rate of lesion

response was noted, with only 28% and 9% of lesions not responding to one or two ALA-PDT treatments, respectively. The current study also demonstrates the utility of ALA-PDT treatment for AKs in producing long-term clearance of AK lesions following ALA-PDT, with about one-fifth of the AKs recurring during the 12-month study period.

The histopathology data from this study demonstrate that although AKs can usually be diagnosed on the basis of the clinical appearance, the physician may, on occasion, find it difficult to distinguish AKs from SCCs or other pathological lesions without performing a biopsy. It has been suggested that AKs are part of a continuum that begins with solar-induced neoplastic transformation of basal keratinocytes which eventually extend into the dermis and are then referred to as SCC. Yantsos *et al.*¹¹ have suggested that AKs or solar keratoses should be termed 'keratinocytic intraepidermal neoplasias' and classified in an analogous way to the well-established 'cervical intraepidermal neoplasias'.

The percentage of skin lesions clinically diagnosed as AK at baseline and histologically proven to be AK (200/220: 91%) was similar to the percentage of clinically appearing recurring AKs during the entire study (127/139: 91%). The percentages of lesions clinically diagnosed as AK but which proved upon biopsy to be SCC were also similar for baseline (10/220: 5%) and recurrent lesions (9/139: 7%). These data suggest that ALA-PDT spot treatment to AKs does not alter the incidence of nonmelanoma skin cancer (NMSC) in patients. Along these lines, animal model studies of ultraviolet (UV) carcinogenesis suggest that large-area topical ALA-PDT or systemic ALA-PDT dosing can delay the development of SCCs.^{13,14} Similarly, the results of two recently published small clinical trials^{15,16} suggest that large-area (full face) application of ALA-PDT in patients with AKs for as short a time as 1 h followed by photoactivation with blue light in a manner identical to that used in this study results in the resolution of AKs with an efficacy similar to that demonstrated in this and in the larger registration trials of this therapy.¹² Moreover, the authors demonstrated significant improvement in several parameters of photodamage in perilesional skin, including sallowness, mottled pigmentation, skin quality and Griffiths score.^{15,16} The results of these studies together with the finding that ALA-PDT can significantly delay UV carcinogenesis (in animal models) suggest that ALA-PDT does not alter the incidence of NMSC and that the therapy should be examined for its possible effect on reducing the rate of development of new AKs and possibly NMSCs. Additional studies are clearly needed to clarify these questions further.

In conclusion, ALA-PDT was shown to be an effective and safe therapy for the treatment of AKs of the face and scalp in skin types I–V, with more than 80% of the AK lesions clearing completely after two ALA-PDT treatments and an overall recurrence rate of any lesion of 24% (162/688) and a recurrence rate for confirmed AKs of 19% (127/653) over 12 months. The percentage of lesions clearing completely was similar in grade 1 and grade 2 AKs and in all the skin types studied (I–V). Phototoxicity reactions were all expected and

had essentially resolved after 1 month post-treatment independent of skin type. In addition, no pigmentation effects were appreciated during the study and if anything, a trend toward restoring the subject's normal skin colour was noted.

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