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ORIGINAL PAPER

Photodynamic therapy: an innovative approach to the treatment of keloid disease evaluated using subjective and objective non-invasive tools

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Abstract Optimal management for keloid disease (KD) is ill defined, with surgical excision resulting in recurrence rates over 50 %. Photodynamic therapy (PDT) uses light to activate a photosensitiser localised in diseased tissues. Two recent case studies and in vitro studies on keloid-derived fibroblasts indicate potential use of PDT in treating KD. Therefore, we hypothesized that there may be a role for PDT in the treatment of KD. Twenty KD patients were divided into three groups; existing keloid scar, post-surgical debulking and post-total surgical excision. Patients underwent three treatments of PDT at weekly intervals. Methyl aminolevulinate photosensitiser applied 3 h prior to PDT, administered at 37 J/cm^2. Non-invasive measures provided quantitative data for pliability, haemoglobin, melanin, collagen and flux. Pain and pruritus scores were measured and patients' were monitored for KD recurrence. All patients had reduced pain and pruritus scores. Haemoglobin flux ($p = 0.032$), collagen ($p = 0.066$) and haemoglobin levels ($p = 0.060$) decreased from week 1 to 3 in all except one patient where measurements were taken and pliability increased significantly ($p = 0.001$). Increases in pliability were significantly related to decreases in flux ($p = 0.001$). Only one patient with a keloid in a stress-prone anatomical location experienced recurrence of KD. All other patients had no recurrence at 9-month follow-up. Minimal side effects were reported. In conclusion, PDT reduces scar formation in KD evidenced by decreased blood flow, increased pliability, decreased collagen and haemoglobin levels. These findings indicate potential utility of PDT in the treatment of KD.

Keywords Keloid disease · Photodynamic therapy · Scar treatments · Field therapy · Methyl aminolevulinic acid

Abbreviations

ALA	5-Aminolevulinic acid
ATP	Adenosine 5-triphosphate
FLPI	Full-field laser perfusion imaging
IL-1 alpha	Interleukin-1 alpha
KD	Keloid disease
MAL	Methyl aminolevulinic acid
MMP	Matrix metalloproteinase
PDT	Photodynamic therapy
PpIX	Protoporphyrin 9
SIAscopy	Spectrophotometric intracutaneous analysis
TNF-alpha	Tumour necrosis factor-alpha

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Introduction

Keloid disease (KD) presents a complex and clinically challenging problem [34]. Notwithstanding the physical morbidity of pain, intense pruritus, erythema and morphomechanical deformity associated with KD [23], they can invoke psychosocial symptoms including anxiety, low self-esteem and difficulty forming and maintaining relationships [5, 9–11, 30]. Treatments available for the management of KD are unsatisfactory, generating limited success [37, 39]. Existing therapies such as surgical excision and intralesional corticosteroid injections have high recurrence rates in excess of 50 % when used singularly in the treatment of KD [19, 20]. Indeed, keloid scars do not always respond satisfactorily to current treatment modalities, which are often ill defined with varying levels of success [18].

Photodynamic therapy (PDT) is an established mode of treatment for skin conditions such as Basel Cell Carcinoma, Actinic Keratosis and Bowens Disease [16]. This treatment uses a photosensitising agent, which, during an incubation period, converts into protoporphyrin 9 (PpIX) in the target cells [16]. The synthesis of PpIX is enhanced in tissue containing hyper-proliferative cells, partly due to the altered enzyme activity in haemosynthesis [16], thus highlighting a potential for use not only in malignant cells, but also in conditions which harbour cells displaying aggressive behaviour or similar bioenergetics as cancer cells. Although KD is a benign hyperproliferative disorder [38], it is clinically aggressive as it frequently recurs following treatment [4, 24, 25, 40]. In addition, keloid fibroblasts display bioenergetics of cancer cells [25, 31, 46]. There is suggestion that keloid fibroblasts rely on glycolysis due to the inhibitors of glycolysis significantly decreasing the rate of adenosine 5′-triphosphate (ATP) biosynthesis [46].

Once the incubation period is complete, light of a specific wavelength is directed onto the area to be treated, activating the PpIX and resulting in the formation of cytotoxic reactive oxygen species [13].

Photosensitising agents can be administered either systemically, by intravenous route, or by topical application to the area to be treated. As systematic photosensitisers induce a prolonged phototoxicity, topical preparations are preferable [8]. Topical formulations available are 5-aminolevulinic acid (ALA), and methyl aminolevulinic acid (MAL), an esterified form of ALA with lipophilic properties, giving increased penetration through cell membranes [36].

The potential of PDT on scar tissue has been previously investigated both in vitro and in three published case reports. Chiu et al. [15] used Raft co-culture systems, whereby keratinocytes were layered on top of fibroblasts embedded in a collagen matrix. Following ALA-PDT, collagen density and contraction were found to have decreased, the greatest decreases occurring in an in vitro keloid tissue model [15]. Karrer et al. [27] looked at the effect of PDT upon five patients with localised scleroderma, a cutaneous fibrotic disorder, characterised by increased dermal collagen accumulation. In all patients, the sclerosis was found to have regressed markedly following a course of treatment that lasted between 3 and 6 months. Mendoza et al. [33] evaluated the cytotoxic effect of PDT using MAL and ALA on KD fibroblasts in various lesional sites and compared this with normal skin fibroblasts. They showed that the outcome is dependent upon the photosensitiser precursor, fluence and location of fibroblasts in the lesion. Furthermore, Li et al. [32] investigated the effects of ALA-PDT on hypertrophic scarring and showed that hypertrophic scar-derived fibroblasts effectively accumulate PpIX post-treatment. Campbell et al. [14] conducted a case series looking at the effect of MAL-PDT in two patients with longstanding hypertrophic scarring. In both cases, a reduction in symptoms and an improvement in skin flexibility were noted. Additionally, Bruscino et al. [12] reported positive effects of MA-PDT in a patient with hypertrophic scarring and demonstrated this significantly softened the scar. Nie et al. [35] also reported a positive effect of PDT in a patient with a persistent keloid which had not responded to a number of routine therapies. Following five MAL-PDT sessions, scar colour had improved and the keloid had reduced in size, become flatter, with reduced erythema in the surrounding margin.

In view of the above findings, we therefore hypothesised that there may be a role for PDT in patients with KD and our aim was to investigate the effect of PDT on specific, objectively measurable outcomes such as tissue pliability, haemoglobin flux and collagen values.

Materials and methods

Consecutive patients undergoing routine clinic visit and keloid management were selected for PDT (Fig. 1). The inclusion criteria included patients with a confirmed diagnosis of KD by clinical and histological confirmation and patients over the age of 16 years. The exclusion criteria included anyone who was pregnant, nursing mothers and patients reporting hypersensitivity to the photosensitising cream or any of its components were automatically excluded. Eligible candidates were given a detailed information sheet regarding PDT prior to commencing treatment.

The timing of PDT in relation to keloid formation or growth varied for each patient. This treatment was used as an alternative to the use of corticosteroid injections.

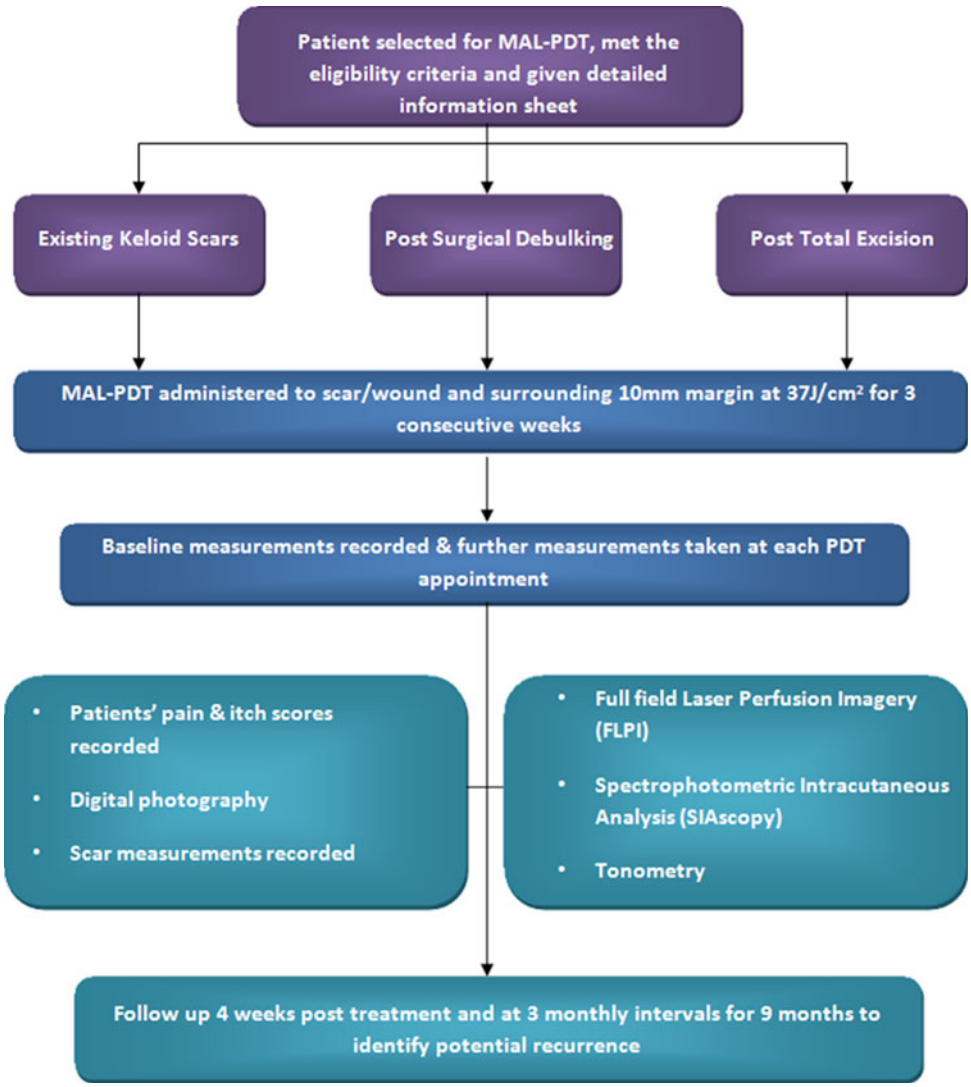

Fig. 1 Flowchart depicting the steps involved in the management of keloid scar patients with photodynamic therapy (PDT)

Patients presenting with a symptomatic keloid scar either had an existing keloid scar which then underwent treatment or were surgically debulked or excised where they had immediate PDT treatment.

All the scars were diagnosed as true keloids and this was histologically confirmed by an experienced dermatohistopathologist. Keloid cases ($n = 20$) were divided into three groups: (1) existing keloid scars (scar of no more than 2 mm in height), (2) post-surgical debulking (keloid scars of any size reduced/debulked to a keloid scar of at most a height of 2 mm) and (3) post-total surgical excision (of any size scar which was removed in total).

All non-invasive measures were performed at each visit prior to the application of MAL-PDT. Digital photography of the lesion to be treated was obtained for all patients at every session, as well as patient reported scar pain and pruritus scores. Further non-invasive objective data was obtained in all cases (subsets underwent different modalities of non-invasive objective scar assessment) of patients. Spectrophotometric intracutaneous analysis (SIAscopy) was done in ten patients, providing quantitative values of haemoglobin, melanin and collagen in the lesion. Full-field laser perfusion imagery (FLPI) was undertaken in ten patients, providing an indication of the mean blood flow in the area treated, the perfusion unit is expressed as 'flux'. Tissue pliability was measured using a tonometer, in patients with existing keloids and those who had undergone surgical debulking ($n = 16$).

Patients underwent three PDT treatments at weekly intervals. At each session, the lesion to be treated was cleaned with normal saline and overlying keratinised areas were removed using sterile gauze, to ensure best conditions for penetration. MAL photosensitiser was chosen for use as a previous case report had administered MAL to a keloid scar patient with good effect [35]. PDT was administered 3 h following application of MAL photosensitiser under occlusion, to the scar and its surrounding 10 mm margin. The inclusion of the 10 mm margin was based in previous

studies, which had identified the peripheral margin of a keloid scar as an active part of the lesion compared to the centre of the lesion [43, 45]. Irradiation was conducted using a red light with a wavelength of 630 nm and light dosage was administered at 37 J/cm^2. The particular light wavelength and fluence were based on a previous case report which showed positive effects with similar settings [35]. Following treatment, patients were reviewed in a specialist out-patient scar clinic 4 weeks post-treatment and at 3-month intervals for 9 months to identify potential recurrence as outlined in the flow chart.

Statistical analysis

The paired *t* test was used to assess changes from baseline to follow-up. Within-subject correlation analysis (over the three time points baseline, visit 2 and visit 3) was used to identify significant relationships between pliability and flux, collagen, melanin and haemoglobin, respectively. Between-subject correlation analysis was used to assess the relationship between changes in pliability and flux between specific visits.

Results

Demographic data

Of the 20 patients studied, 5 were male and 15 were female. 12 patients were of Caucasian ethnicity, whilst the following 8 patients were either Asian (Indian sub-continent origin) ($n = 3$), black Caribbean ($n = 2$), or of mixed ethnicity ($n = 3$). Ten patients treated had existing keloid lesions, whilst ten were post-surgical. Of the post-surgical patients, six were post-surgical debulking and four were post-total surgical excision. The majority of patients ($n = 10$) presented with sternal scars, the remaining presented with scars to the neck/scalp ($n = 4$), abdomen ($n = 2$), shoulder ($n = 2$), ear ($n = 1$) and hand ($n = 1$). The two main causes of scars were previous surgery ($n = 8$) and acne/spot ($n = 7$) (Online Resource 1).

Scar pain and pruritus scores

At every treatment visit, prior to administration of PDT, patients were asked to score their current symptoms of pain and pruritus, on a ten-point scale, with 0 being no pain/pruritus and 10 being the most pain/pruritus imaginable. Mean scores of both symptoms indicate that the patients studied experienced low levels of both pain (baseline mean score 1.3) and pruritus (baseline mean score 1.95). By the third treatment, both pain and pruritus scores had reduced by 77 %. The mean pain score had reduced to 0.3 ($p = 0.013$) and the mean pruritus score had reduced to 0.45 ($p = 0.003$).

Haemoglobin flux levels

At each visit, haemoglobin flux was measured in a subset of ten patients prior to commencing MAL-PDT treatment, using the FLPI. Our results show that flux significantly decreased from a mean of 297 to a mean of 156 ($p = 0.032$), with an average percentage decrease of 29 %. Nine out of the ten patients showed a decrease. The FLPI generated images depicting flux levels within the measured area (Fig. 2a). In one patient, flux levels increased, and this can also be seen clearly in the images taken by the device (Fig. 2b). This patient had a total surgical excision of a keloid on the lateral aspect of her shoulder, and was demonstrating signs of recurrence before the completion of her PDT treatment. There was a great variation between flux decreases, with existing keloid scar patients demonstrating the greatest response out of the three groups in terms of flux reduction (Online Resource 2) (Table 1a).

Pliability values

At each visit scar pliability was measured in all patients who had existing scars or who had undergone surgical debulking ($n = 16$) prior to commencing MAL-PDT treatment. Pliability significantly increased for the 16 patients where measurements were taken, from a mean of 3.3 in week 1 to 4.1 in week 3 ($p < 0.001$), an average percentage increase of 28 % (Table 1b).

Collagen levels

At each visit, collagen levels were measured in a subset of ten patients, using SIAscopy prior to commencing MAL-PDT treatment. Levels were found to have decreased in nine of ten patients—once again the case of recurrence being the exception. The average percentage decrease in collagen levels in ten patients was 25 %, from a mean level of 734 in week 1 to a mean level of 520 week 3 ($p = 0.066$). Images were produced by the device, which not only demonstrated the reduction in collagen, but also the reduction in scar colour (Table 1c; Fig. 3).

Melanin levels

At each visit, melanin levels were also measured in ten patients using SIAscopy prior to commencing MAL-PDT. There were no significant differences found from week 1 to week 3 (Fig. 3). Mean values changed from 142 in week 1 to 212 in week 3 ($p = 0.15$) (Table 1d).

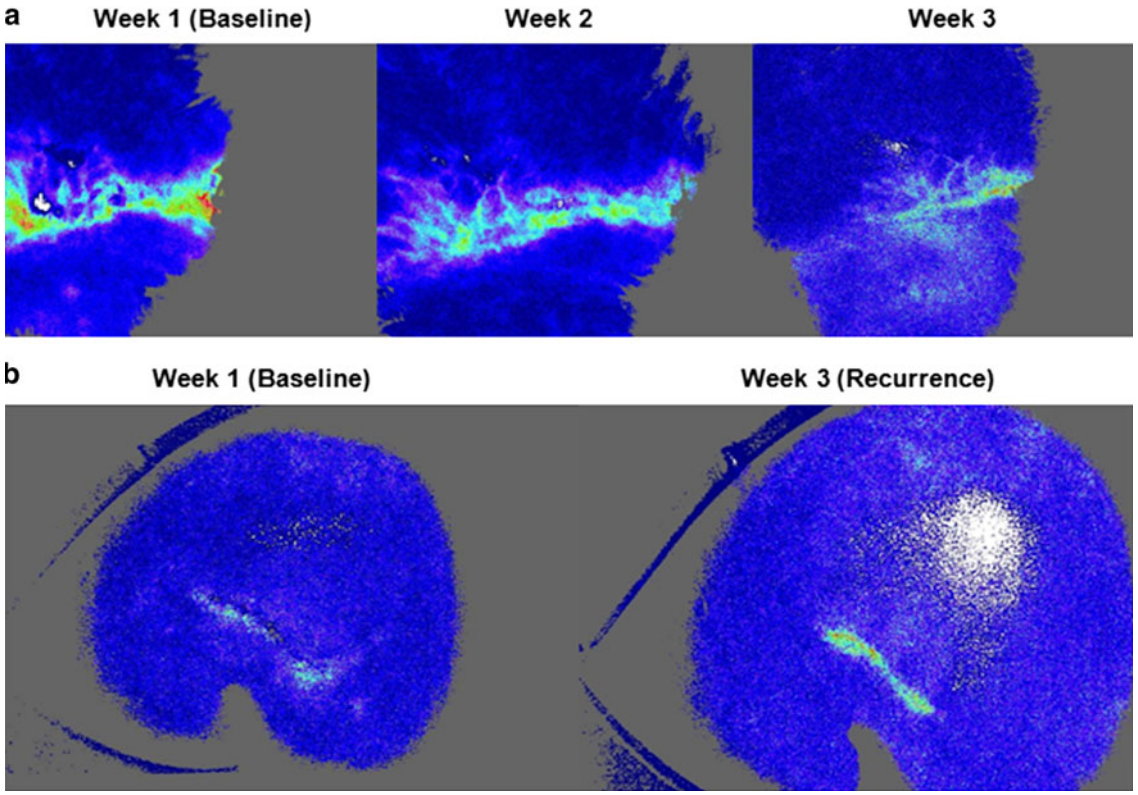

Fig. 2 **a** Full-field laser perfusion imaging showing a 35-year-old male with a sternal keloid scar which had undergone surgical debulking. The images show a 49.7 % decrease in haemoglobin flux from week 1 (baseline) to week 3 indicated by the reduction in colour at the scar site. **b** Full-field laser perfusion imagery showing a 43-year-old female with a keloid scar on her shoulder post-surgical excision. The images show an 84 % increase in haemoglobin flux from week 1 to week 3 as depicted by the increase in colour at the scar site

Haemoglobin levels

At each visit, haemoglobin levels were measured in a subset of ten patients using SIAscopy prior to commencing MAL-PDT. Haemoglobin levels were found to have decreased in nine out of the ten patients (Fig. 3). Overall, patients mean values changed from 307 to 229 ($p = 0.060$) (Table 1e).

Within-subject correlations over time

We found a statistically significant negative within-subject correlation between pliability and flux values (increases in pliability over time are matched with decreases in flux), but no such relationship existed between pliability changes and collagen, melanin or haemoglobin level changes.

Pliability versus flux ($n = 7$)	$r = -0.77; p = 0.001$*
Pliability versus collagen ($n = 8$)	$r = -0.17$; $p = 0.56$
Pliability versus melanin	$r = 0.28$; $p = 0.32$
Pliability versus haemoglobin	$r = -0.34$; $p = 0.24$

The significant finding for pliability versus flux was reflected, to some extent, by the simple negative correlations between the changes in pliability and flux between the time points. These simple correlations correspond to a less powerful analysis to that used to derive the within-subject correlations (which are based on all three time points).

Correlation on change baseline to visit 2	$r = -0.22$; $p = 0.63$
Correlation on change visit 2 to visit 3	$r = -0.76$; $p = 0.049$*
Correlation on change baseline to visit 3	$r = -0.54$; $p = 0.21$

Treatment side effects

Two side effects following treatment were reported by three patients. Inflammation was experienced by three patients following the first treatment, lasting, on average, 2 days. Two of these patients continued to experience inflammation for a short period of time following the subsequent two treatments, whilst one patient did not experience it following the third treatment. Pigmentation changes were noted in three patients. All three patients had a Fitzpatrick score of 3 or above. The patient with a Fitzpatrick score of 6 took the longest to resolve their symptoms following treatment (Online Resource 3).

Table 1 Mean measurements of haemoglobin flux, tissue pliability, collagen, melanin and haemoglobin during treatment

Groups	Number in each group (n)	Week 1	Week 2 (mean values)	Week 3
Haemoglobin flux[a]				
Group 1	4	410.9	284.5	132.0
Group 2	3	280.4	246.0	157.8
Group 3	3	161.6	194.9	185.5
All groups combined	10	296.9	242.5	155.8
Tissue pliability[b]				
Group 1	10	3.2	3.5	4.1
Group 2	6	3.5	3.8	4.2
Group 3	0	0	0	0
All groups combined	16	3.3	3.6	4.2
Collagen[c]				
Group 1	5	650.0	469.5	352.8
Group 2	3	715.8	385.3	492.4
Group 3	2	494.8	985.8	978.6
All groups combined	10	734.4	449.6	519.9
Melanin[d]				
Group 1	5	269.4	244.0	294.1
Group 2	3	367.2	126.2	423.9
Group 3	2	207.5	201.6	131.3
All groups combined	10	286.3	200.2	300.5
Haemoglobin[e]				
Group 1	5	303.2	129.2	186.0
Group 2	3	279.0	214.7	215.7
Group 3	2	367.0	349.8	355.4
All groups combined	10	306.7	199.0	228.8

[a] Mean haemoglobin flux measurements during treatment at week 1, week 2 and week 3 for each sub-group and all combined. These results show that flux decreased at an average of 29 % in all but one patient ($p = 0.032$)

[b] Mean tissue pliability measurements during treatment. Pliability was found to have increased in all 16 patients at an average of 28.0 % ($p = 0.001$)

[c] Mean collagen measurements during treatment. Collagen levels were found to have decreased in nine out of the ten patients, with the exception of one case who experienced disease recurrence. On average, collagen levels decreased by 24.6 %

[d] Mean melanin level measurements during treatment

[e] Mean haemoglobin level measurements during treatment. Haemoglobin levels were found to have decreased by 27.5 % in nine out of the ten patients

Group 1, existing keloid scars; Group 2, post-surgical debulked; Group 3, post-total surgical excision

Discussion

For the first time, this study presents promising results evaluated objectively and subjectively in a case series of KD patients benefiting from the anti-fibrotic effect of PDT. Our non-invasive yet objective tool measurements including FLPI, SIAscopy and tonometry provided objective sequential results pre- and post-PDT.

FLPI measurements showed a reduction in haemoglobin flux in all but one case where this device was used. SIAscopy demonstrated a degradation of collagen with tonometry results indicating that scar tissue became more pliable following treatment. The impact of PDT upon scar-related symptoms was measured with scores given subjectively by patients for both pain and pruritus at their baseline measurements and subsequent follow-up. The majority of patients experienced no significant side effects following treatment ($n = 17$). Inflammation following treatment was transitory, lasting an average of 2 days. Pigmentation changes, experienced by three patients, took up to 4 weeks to resolve. One patient whose symptoms took 6 weeks to resolve had a Fitzpatrick score of 6, indicating that caution may be required when using PDT in individuals with high Fitzpatrick scores.

Mechanism of action

The mechanism of action of PDT upon scar tissue is thought to be twofold [28]. In vitro studies have shown that ALA-PDT induced collagen-degrading matrix metalloproteinase (MMP)-1 and MMP-3 in dermal fibroblasts, whilst reducing collagen Type 1 mRNA expression [28]. However, although dermal fibroblasts are the cells responsible for collagen over-proliferation, the limited penetrative nature of PDT implies that the primary targets of light therapy are mainly the epidermal keratinocytes. The photosensitising cream can penetrate through the stratum corneum into the epidermal keratinocytes, where it can be converted into PpIX, whilst the basement membrane, between the keratinocytes and dermal fibroblasts, presents a barrier to deeper penetration, thus limiting absorption by dermal fibroblasts [29]. Karrer et al. [29] in 2004 conducted an experiment using in vitro fibroblasts and keratinocytes to evaluate the effect of ALA-PDT upon epidermal keratinocytes. Their findings suggest that ALA-PDT induces keratinocytes to produce interleukin-1 alpha (IL-1 alpha), a pro-inflammatory cytokine, and increase tumour necrosis factor-alpha (TNF-alpha). These cytokines, Karrer et al. [29] hypothesised, may influence dermal fibroblasts into producing increased amounts of the

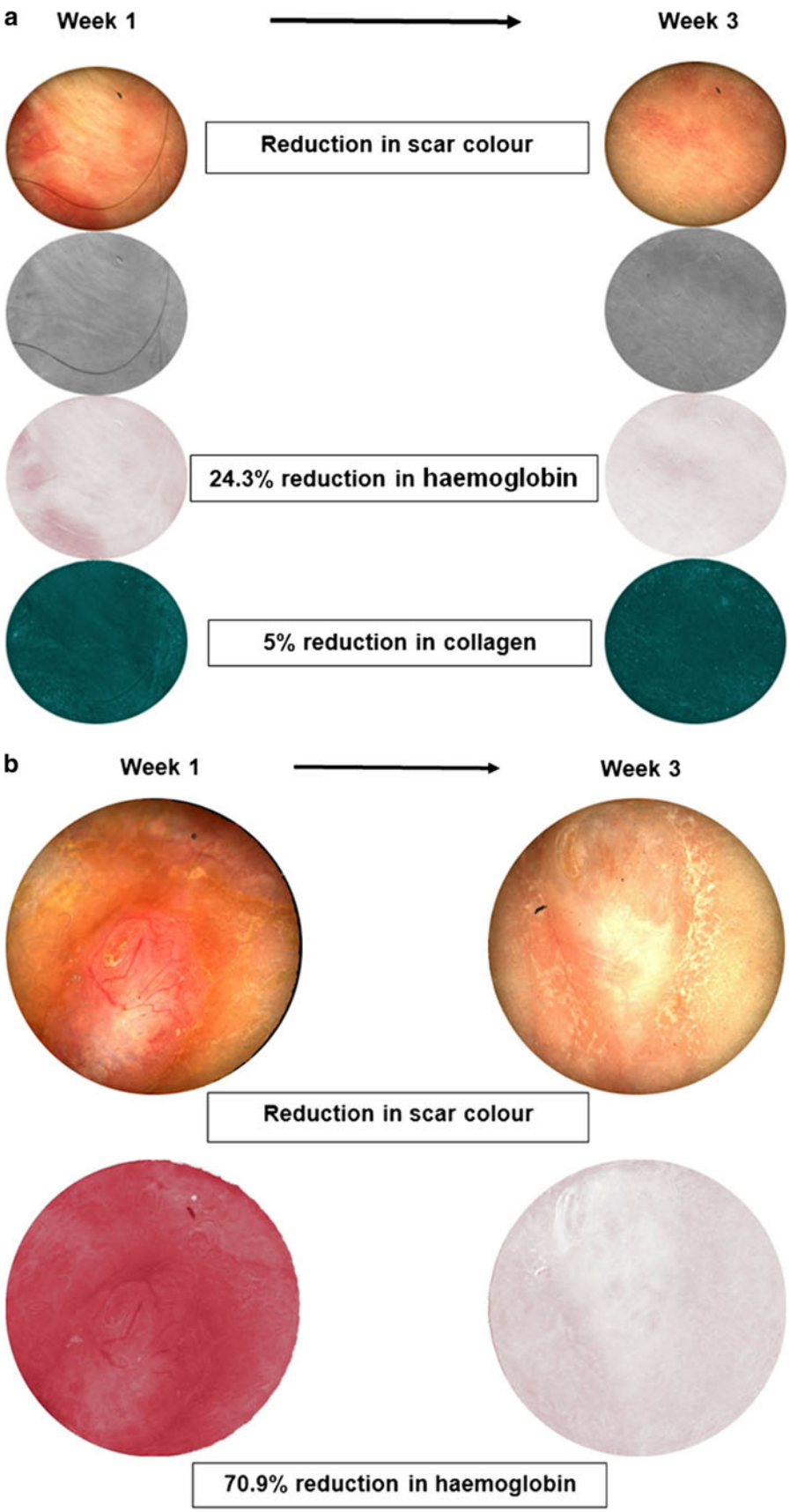

Fig. 3 **a** Spectrophotometric intracutaneous analysis images of a 20-year-old female with an existing keloid scar to her neck. The images show a reduction in scar colour, a 24.3 % reduction in haemoglobin levels and a 5 % reduction in collagen levels from week 1 to week 3 post-photodynamic therapy treatment. **b** Spectrophotometric intracutaneous analysis images of an 88-year-old female with an existing keloid scar to her hand. The images show a reduction in scar colour and a 70.9 % reduction in haemoglobin levels from week 1 to week 3 post-photodynamic therapy treatment

collagen-degrading proteins matrix metalloproteinase-1 (MMP-1) and matrix metalloproteinase-3 (MMP-3). This theory of twofold mechanism of action may explain our findings of decreased collagen values in the keloid lesions treated with PDT, as well as the increase in tissue pliability. However, there was no statistically significant finding between pliability and collagen values. This may be due to the SIAscopy device only providing a summation of the superficial levels of collagen and not a true measure of other components of the dermis. Pliability was measured with a tonometer which gives a precise measurement of pliability of a specific area of the keloid scar.

Field therapy

Slaughter et al. [42] first used the term 'field cancerisation' in 1953, when, by performing histological examinations of oral cancer tissue, they proposed that abnormal tissue surrounded the tumour itself and may account for further recurrences following surgery. It has been demonstrated that in basal cell carcinomas, the excision of such tumours should include at least 5 mm of the surrounding margin [21]. Further studies have identified that secondary primary tumours, even those more that 7 cm away from the original tumour, bear common clonal origins [41, 44], indicating that a large genetically altered field exists in the epithelium surrounding a primary tumour [7].

Keloid scars are benign hyperproliferative growths of dermal fibroblasts [22]. In vitro studies looking at keloid tissue have produced similar findings to those investigating cancer fields, in that they have identified the margin surrounding keloid scars to be highly active [43, 45]. In a recent study, Javad and Day [26] identified the presence of mitochondrial-associated proteins at the margins and highlighted that this is the most active part of the scar. There is a high rate of recurrence following surgical intervention of keloid scars [17]. Therefore, this could explain the high recurrence rate following intralesional surgical excision which leaves behind the active margin of the keloid scar. In our study, we applied this evidence by ensuring that the 10 mm margin surrounding the keloid scar was also treated with PDT. Furthermore, we investigated the potential of PDT as a field therapy option, by treating patients who had undergone total surgical excision of the scar. Three of the four patients treated in this way experienced no recurrence in their keloid at 9 months. The patient who experienced a recurrence, did so within 6 weeks of excision, as demonstrated by both her haemoglobin flux and collagen results. This patient, during follow-up consultation, stated that she had resumed her daily gym routine within a few days following surgery. It may be possible that the added mechanical stress of strenuous exercise had contributed to the recurrence, as mechanical stress in the early stages of healing is highly associated with abnormal scar formation in susceptible areas, such as the shoulder, which was the site of this patient's keloid [1, 2]. Further research will enable us to determine whether there is a role for PDT in field therapy of raised dermal scars. The initial results and underpinning theory suggest a potential benefit.

Future research

MAL-PDT is non-invasive, and our results demonstrate both a good cosmetic outcome with minimal side effects, particularly in comparison with other traditionally used treatments, such as steroid injections, which can invoke pigmentation changes and dermal atrophy. This is the first case series to date investigating the potential of PDT in keloid scars, and is the first to use non-invasive, objective measuring devices such as SIAscopy and FLPI imaging in order to provide quantifiable data on haemoglobin flux and collagen values. Whilst the results of this case series correspond with the previous published cases, there are clear differences in treatment regime. Longer term follow-ups with regular objective non-invasive methods are needed. Measurements taken following the second PDT treatment may be inadequate as the results may have been skewed by oedema and other acute tissue changes. Further research is required in order to determine an optimal treatment regime that is both effective and moreover, acceptable to patients.

PDT, with its incubation period and requirement for multiple treatment sessions, can be viewed as time-intensive in nature and may be particularly burdensome for some KD patients. New devices such as the portable PDT devices [3] could help to ease this treatment burden to some extent and therefore reduce any compliance issues, but this is yet to be clinically studied in KD. Systemic PDT could also be used in the treatment of KD, although there can be side effects such as sensitivity to light [6].

The range of size, severity and maturity of raised dermal scarring also raise questions regarding selection of appropriate patients for treatment. Given the limited penetration of PDT in its present form, clearly some pre-surgical keloid patients will be unsuitable for treatment, due to the volume of their keloid scar. Furthermore, it would be pertinent to assess whether response to treatment is affected by the anatomical site of the scar or how clinically aggressive the disease is in the individual patient. In addition, a longer term follow-up as well as histological evidence pre- and post-therapy may provide further clues to the utility of PDT in the management of KD.

In conclusion, we show for the first time in a unique case series that PDT can reduce scar formation in KD as evidenced by lack of recurrence and improvement in signs and symptoms as well as by decreased blood flow, increased

pliability and decreased collagen levels. The findings of this study may indicate potential utility of MAL-PDT as a field therapy, to treat and prevent recurrence of KD. MAL-PDT is a non-invasive treatment, which produces a good cosmetic outcome with minimal side effects. Further research will help evaluate the optimal PDT treatment regime in the management of this common, complex and clinically challenging problem.

Conflict of interest Galderma UK kindly provided the methyl aminolevulinate (MAL) photosensitiser for the purpose of this study but no funding was received.

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