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ORIGINAL ARTICLE

Bath psoralen–UVA photochemotherapy for localized scleroderma: experience from a single institute

Felix Pavlotsky, Nicole Sakka, Alina Lozinski & Aviv Barzilai

Department of Dermatology, Psoriasis and Phototherapy Centre, Sheba Medical Centre, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Hashomer, Israel.

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Correspondence:
Dr Felix Pavlotsky, M.D., Department of Dermatology, Sheba Medical Centre, Tel Hashomer 52621, Israel.
Tel: +972 0 3 5302286
Fax: +972 0 3 5304910
e-mail: felixp@post.tau.ac.il

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None declared.

SUMMARY

Background
Localized scleroderma (LS) comprises a spectrum of sclerotic autoimmune diseases primarily affecting the dermis. Various treatment modalities have been recommended for the management of LS, but only a few studies exist regarding the efficacy of bath PUVA photochemotherapy in the treatment of LS.

Objectives
To evaluate the efficacy of bath PUVA photochemotherapy in the management of LS in a retrospective study.

Methods
Twenty-eight patients (23 women and five men) with a diagnosis of LS, confirmed by histology, were included in the study. Patients were treated with a thrice-weekly regimen of bath immersion in 0.2 mg/1 water solution of 8-methoxypsoralen, followed by irradiation with UVA.

Results
Eleven patients (39%) showed complete remission (complete softening of the sclerotic plaques with or without postinflammatory hyper- or hypopigmentation) after a mean of 71 treatments (range 33–170) and a mean cumulative dose of 115 J/cm^2 (range 11–232). Partial softening and regression of the sclerotic plaques was observed in 14 patients (50%). Three patients (10.7%) showed no effect, and in none of the patients was worsening noted during treatment.

Conclusions
In our experience, bath PUVA photochemotherapy is an effective and well-tolerated treatment option for LS and should be considered as one of the first-line treatment modalities.

Photodermatol Photoimmunol Photomed 2013; 29: 247–252

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Localized scleroderma (LS), also known as morphea, comprises a spectrum of chronic sclerotic autoimmune diseases that primarily affect the skin but can potentially involve the fat, fascia, muscles and bones. Unlike systemic sclerosis, LS does not involve internal organs, and transition from LS to systemic sclerosis does not occur. However, extracutaneous manifestations are not rare and include myalgia, arthralgia, fatigue and uveitis (1–3). LS is characterized by overproduction of collagen and increased extracellular matrix deposition (1, 2). Although the exact pathogenesis is still unknown, it has been hypothesized that certain stimuli may cause release of pro-inflammatory cytokines, resulting in dysregulation of the connective tissue metabolism (1, 2). LS has a female predominance of 4.2 : 1 (1–4) and clinically manifests as livid erythema with central hardening and centrifugal expansion.

LS can present with a variety of clinical subtypes, but a uniformly accepted classification does not exist. Based on clinical criteria, LS can be classified into plaque-type morphea (including guttate, bullous and keloidal), generalized morphea (defined as more than four indurated plaques larger than 3 cm), morphea profunda, linear morphea (including coup de sabre and progressive hemifacial atrophy), pansclerotic disabling morphea and mixed forms (4). Plaque-type morphea makes up the vast majority of adult diagnoses (1–3, 5).

Various treatments have been reported for the management of LS. These include corticosteroids, topically, intralesionally or orally; topical use of tacrolimus (6), calcipotriene (4) or imiquimod (7); and systemic administration of methotrexate (5), mycophenolate mofetil (8), calcitriol (4), D-penicillamine (9), infliximab (10) or cyclosporine (11). Among these treatments, only a few have been tested in randomized placebo- or standard treatment-controlled studies. Treatment with methotrexate combined with systemic corticosteroids has the most convincing data supporting it, with retrospective reviews reporting a success rate of 80% (12–15).

For patients with limited involvement, treatment with topical tacrolimus 0.1% is supported by a randomized placebo-controlled trial and has been found to be effective in decreasing skin thickness, dyspigmentation, induration, erythema, telangiectasia and atrophy when applied twice a day for 12 weeks (6). Noncontrolled prospective trials support the use of occluded calcipotriene (16), calcipotriol in combination with bethamethasone dipropionate (17), and imiquimod (18). D-penicillamine has been reported in case series to be an effective treatment for morphea but is rarely given because of unfavorable side effects (9). Mycophenolate mofetil has been retrospectively assessed as a treatment adjunct in children with morphea, in addition to methotrexate and systemic corticosteroids, and primary outcome measures showed clinical improvement (8).

Phototherapy has been applied for a variety of sclerosing skin diseases (19, 20) such as eosinophilic fasciitis, chronic graft-vs.-host disease, lichen sclerosis et atrophicus and necrobiosis lipoidica, most probably because of its anti-inflammatory and antifibrotic effect. In LS, most studies have focused on treatment using the UVA range (320–400 nm), either oral/systemic psoralen–UVA (PUVA) or UVA-1 (21–31), mainly because of the deeper penetration into the dermis compared to UVB (280–320 nm). Oral PUVA may be associated with systemic side effects such as nausea, vomiting and cataract formation, as well as with increased risk of developing skin cancer (32). In bath PUVA, patients immerse in methoxypsoralen solution and then are exposed to UVA radiation. This treatment modality avoids the systemic side effects of oral PUVA. In this study, we summarize our experience of bath PUVA for the treatment of localized scleroderma.

MATERIALS AND METHODS

Study population

In this retrospective analysis, patients with localized scleroderma treated at the phototherapy unit in the Department of Dermatology at Sheba Medical Centre over a 7-year period (2005–2012) were included. The study was approved by Sheba Medical Centre's ethical committee.

The diagnosis of localized scleroderma was based on clinical examination and confirmed using standard histopathological criteria. Cutaneous biopsies were obtained from the center of a sclerotic lesion prior to initiation of treatment.

For all patients included in the study, complete disease history was obtained before initiation of phototherapy. Exclusion criteria were pregnancy or lactation, use of any immunosuppressive therapy within the last 4 weeks or any topical treatment within the last 2 weeks prior to initiation of treatment.

Study procedure

All patients underwent the same treatment procedure, involving bath immersion in 0.2 mg/l water solution of 8-methoxypsoralen for 20 min at a temperature that was convenient and tolerable to the patient. Immediately after the bath, the skin was dried and exposed to UVA radiation. UVA radiation was administered using a

Photodermatol Photoimmunol Photomed 2013; 29: 247–252

conventional PUVA cabinet (Waldmann, Villinger-Schweningen, Germany), in which the UVA bulbs emit light ranging from 320 to 410 nm. Treatment was administrated three times a week with an initial UVA dose of 0.3 J/cm^2, with subsequent increments of 0.3 J/cm^2 added every 2–3 treatments up to a maximum dose of 10.0 J/cm^2. All patients used protective eyewear during treatment, and the face and genital area were shielded. Emollients were applied after the irradiation.

Clinical assessment and end points

Patients were examined around every 10 treatments, and complete or partial response was defined as complete or partial softening, respectively, of the sclerotic plaques, with or without postinflammatory hyper- or hypopigmentation. Relapse was defined as the reappearance of new lesions and/or hardening of the previously treated sclerotic plaques.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 11.0) (SPSS Inc., Chicago, IL, USA). Number of exposures and cumulative dose are given as mean (range).

RESULTS

The clinical characteristics of the patients are described in Table 1. Twenty-eight patients were involved, five men and 23 women, with a mean age of 51 years (range 10–78). Among them, 21 patients were classified as having generalized, six as having localized and one as having pansclerotic morphea. Of the 21 patients with generalized morphea, one case was associated with lichen sclerosis et atrophicus, one with silicone implants and one with prior radiation exposure.

The mean number of treatments received was 56 (range 7–170) and the mean cumulative UVA dose was 116 J/cm^2. Complete response was seen in 11 patients (39%) after a mean of 71 exposures (range 33–170) and a mean cumulative dose of 115 J/cm^2 (range 11–232) (Figs 1–3). Fourteen patients (50%) showed partial improvement after a mean of 51 exposures (range 7–151) and a mean cumulative dose of 136 J/cm^2 (range 2.7–471), and three patients showed no clinical improvement. None of the patients worsened during treatment (Table 2).

Treatment was well tolerated in all patients, with some minor side effects reported: burning sensation (39%);

Table 1. Study population

Total number of patients	28
Gender	
Males	5
Females	23
Age (years)	
Mean	51
Range	10–78
Clinical presentation	
Generalized	21
Localized	6
Pansclerotic	1
Skin type	
I	3
II	12
III	5
IV	8

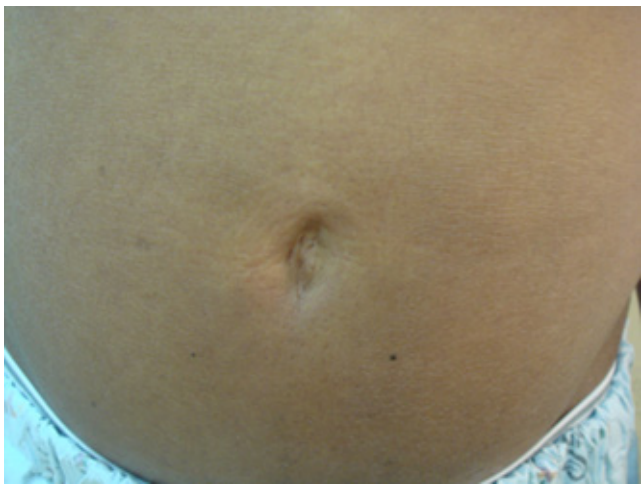

Fig. 1. Fifty-six-year-old patient with generalized morphea.

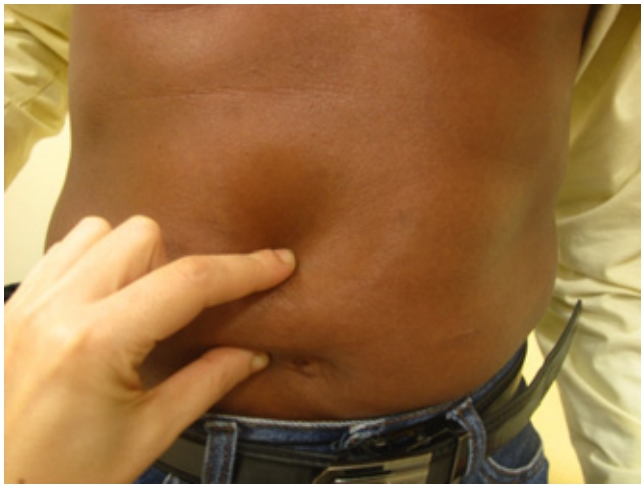

Fig. 2. Patient in Fig. 1 after 64 bath PUVA sessions, showing marked softening of the sclerotic plaque.

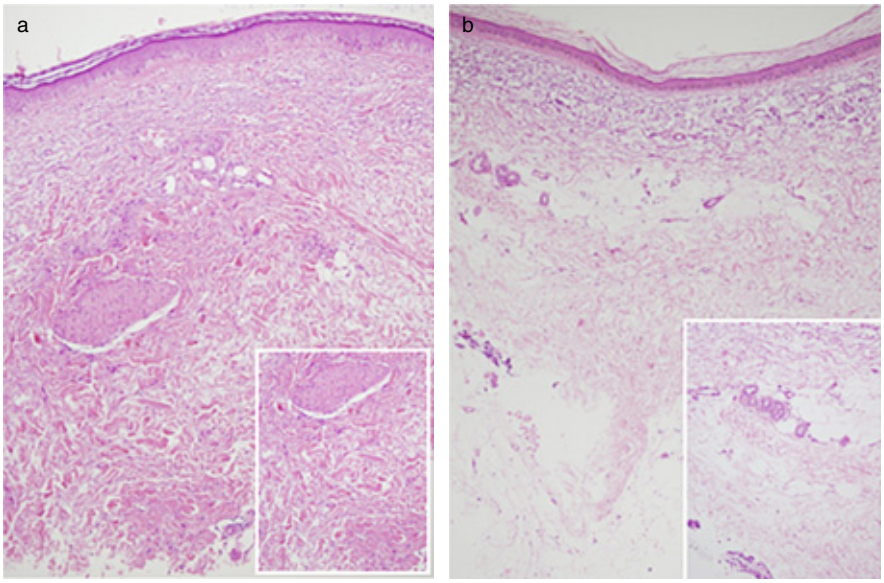

Fig. 3. (a) Biopsy specimen taken from a sclerotic lesion of right forearm before bath PUVA, showing features of mild solar elastosis with marked fibrosis in the reticular dermis and collagen bundles strangulating the erector pili muscle (hematoxylin–eosin stain, original magnification 40×, right corner 100×). (b) Biopsy specimen taken from the same lesion after 64 bath PUVA sessions, demonstrating evidence of atrophic epidermis with severe solar elastosis, edematous dermis with decreased-thickness collagen bundles and adnexa surrounded by adipose tissue (hematoxylin–eosin stain, original magnification 40×, right corner 400×).

Table 2. Clinical response to therapy

		Exposures (*n*)		Cumulative dose (J/cm^2)	
	Patients (*n*)	Mean	Range	Mean	Range
Complete response	11	71	33–170	115	11–232
Partial response	14	51	7–151	136	2.7–471
No effect	3	ND	ND	ND	ND

ND, no data.

pruritus (14%); recrudescence of herpes simplex, rosacea exacerbation and linear hyperpigmentation (one patient each). None of these adverse effects necessitated discontinuation of treatment. Nevertheless, 9 patients (32%) discontinued the course of treatment, mainly because of difficulty in maintaining the time-consuming thrice-weekly regimen.

Follow-up after cessation of therapy was available in 10 of 11 patients with complete response. In seven patients, no recurrence was observed after a mean follow-up period of 7 months (range 1–18 months). In three patients, relapse was reported. The elapsed times until recurrence were 6, 24 and 28 months.

DISCUSSION

The exact mechanism of action of ultraviolet radiation in the treatment of localized morphea remains obscure. Studies have demonstrated that UVA causes apoptosis of epidermal Langerhans cells and T-cells, reduces mast cells, increases synthesis of collagenases and decreases synthesis of collagen (8, 20, 33).

Kerscher *et al*. were the first to describe, in 1995, the use of UVA-1 phototherapy in the treatment of localized scleroderma (21). Stege *et al*. reported that high-dose UVA-1 therapy is effective for the treatment of localized scleroderma and is superior to low-dose UVA-1 therapy but

Photodermatol Photoimmunol Photomed 2013; 29: 247–252

theoretically carries an increased risk for carcinogenesis (23). Kreuter *et al*., in 2006, showed that there was no significant difference between medium-dose UVA-1 and low-dose UVA-1 (22). In addition, medium-dose UVA-1 was proven to be more effective than narrowband UVB. However, UVA-1 is not widely available in many dermatology centers and also requires specialized and expensive equipment, making UVA-1 less accessible to patients. This has led many clinicians to investigate the use of full-spectrum UVA (320–400 nm), which is widely available, in the treatment of LS, both with and without psoralen.

Usmani *et al*. reported the use of systemic administration of psoralen followed with UVA irradiation in 13 patients with LS (27). Eleven of 13 patients showed improvement of the skin after a mean of 26 exposures and a median cumulative dose of 135.0 J/cm^2, with nausea and gastrointestinal upset recorded as side effects. Several case reports and small studies using oral psoralen or low-dose broadband UVA have documented the benefit of full-spectrum UVA in the treatment of localized scleroderma (27–31). No randomized control studies of UVA-1 in comparison with full spectrum UVA have been performed so far.

PUVA bath therapy is a well-tolerated treatment and avoids the potential major side effects of systemic administration. In bath PUVA photochemotherapy, gastrointestinal side effects are not observed; compared with oral psoralen, there is a shorter duration of photosensitization and no necessity of eye protection. Bath PUVA photochemotherapy has been proven effective for LS, as demonstrated in several small studies (34–37). Kerscher *et al*. conducted the largest study of patients with LS treated with bath PUVA photochemotherapy, in which 13 of the 17 enrolled patients showed improvement or clearance of the sclerotic plaques within 3 months or less of treatment (34). Their study did not differentiate between complete and partial response to treatment. Clinical findings were confirmed by ultrasound and histological examination.

In this retrospective study, 28 patients with LS were treated with bath PUVA photochemotherapy. Eighty-nine per cent of the patients improved, showing regression or complete softening of the sclerotic plaques. Even though there is a tendency for scleroderma lesions to spontaneously resolve, as found in an epidemiological study by Peterson *et al*. (38), who reported that 50% of patients with localized scleroderma had a cutaneous softening or other evidence of disease resolution after 3.8 years, bath PUVA photochemotherapy was found to be effective. Bath PUVA treatment was well tolerated and adverse effects were found to be minimal and not necessitating discontinuation of treatment. Limitations of this study include the retrospective nature of the analysis, the relatively small number of patients and the lack of objective methods to evaluate therapeutic efficacy, such as ultrasonography or histological evaluation. Given the fact that scleroderma has low incidence and prevalence, our group of 28 LS patients treated with bath PUVA is the largest described so far. We used a much more convenient thrice-weekly treatment regimen than did other studies (a four-times-a-week treatment regimen was used in other studies) with a lower concentration of 8-methoxypsoralen, both of which led to minimal side effects. Total cumulative dose was higher than described in previous studies, because we were aiming for complete response. Outcome measurements assessing depth, hardness, elasticity and activity; ultrasound and histological assessments; and clinical scoring systems all exist, but there is no uniformly accepted outcome measurement, making it difficult to determine the efficacy of therapy in LS. Our assessment included clinical evaluation of improvement of the sclerotic plaques by a single observer by palpation. Improvement was supported by patients' subjective assessment, but this was not included as part of the response assessment criteria.

Although the effects of bath PUVA have been studied in only a small number of patients, its adjunctive use should be encouraged. In our experience, and concordantly with previous studies, we suggest that PUVA bath chemotherapy should be considered as a safe and beneficial treatment modality and regarded as one of the first-line approaches for treatment and management in selected patients with LS. Bath PUVA is a promising, beneficial and well-tolerated treatment in inducing softening of the sclerotic plaques in LS. However, because of the possibility of spontaneous regression in LS, further multicenter randomized controlled trials should be performed to assess treatment efficacy.

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