International Journal of Dermatology

Pharmacology and therapeutics

Effectiveness of medium-dose ultraviolet A1 phototherapy in localized scleroderma

Ozlem Su[1], MD, Nahide Onsun[1], MD, Hulya Kapran Onay[2], MD, Yeliz Erdemoglu[1], MD, Dilek Biyik Ozkaya[1], MD, Filiz Cebeci[1], MD, and Adnan Somay[3], MD

[1]Department of Dermatology, Bezmialem Vakif University, Faculty of Medicine, [2]Neoson Imaging Center, Radiology, and [3]Department of Pathology, Vakif Gureba Teaching and Research Hospital, Istanbul, Turkey

Correspondence
Ozlem Su, MD
Sıgırtmac Sok. No. 21 B blok d. 7
Osmaniye
Bakirkoy
Istanbul
Turkey
E-mail: ozlemsu@atlas.net.tr

Conflicts of interest: None.

Abstract

Background Recently, ultraviolet (UV) A1 phototherapy has been suggested as an effective treatment for localized scleroderma (LS); however, the optimal dose of UVA1 still has not been determined.

Objective We aimed to evaluate the therapeutic effectiveness of medium-dose (30 J/cm^2) UVA1 phototherapy and to show that 13 MHz ultrasound is a valuable tool for assessing the results of UVA1 phototherapy in LS.

Methods Thirty-five patients with LS were treated with medium-dose (30 J/cm^2) UVA1. In total, 30–45 treatments and 900–1350 J/cm^2 cumulative UVA1 doses were evaluated by clinical scoring in all patients. In 14 patients, skin thickness was also determined by 13 MHz ultrasound examination.

Results In all patients, medium-dose UVA1 therapy softened sclerotic plaques, and marked clinical improvement was observed in 29 of 35 (82. 85%) patients. Ultrasound measurements showed that skin thickness was significantly reduced. No side effects were observed during or after treatment.

Conclusion Medium-dose UVA1 phototherapy is a highly effective, safe, and well-tolerated therapeutic modality for treatment of all types of LS. A 13 MHz ultrasound probe may be used for evaluating UVA1 phototherapy results.

Introduction

Localized scleroderma, or morphea, is a connective tissue disorder characterized by thickening and sclerosis of the skin. A recent classification has grouped localized scleroderma into five subtypes: circumscribed morphea, linear scleroderma (LS), generalized morphea, pansclerotic morphea, and a mixed subtype, when a combination of two or more of the previous subtypes is present.[1] When LS involves the face, it is called "en coup de sabre" (ECDS). A particularly rare subtype of localized scleroderma is bullous morphea.[2] The most common circumscribed morphea (plaque type) is characterized by single or multiple, circumscribed, ivory-white, indurated, sometimes confluent plaques, which may be up to 20 cm in diameter.[3] During the active stages, lesions frequently expand with a violaceous border, the so-called lilac ring (inflammatory halo).[4] Histopathological examination of morphea during the active inflammatory stages in a peripheral violaceous border shows a rather marked inflammatory cell infiltrate, particularly in the reticular dermis. In late sclerotic stages, as seen in the central well-developed lesions, the inflammatory cell infiltrate largely disappears, and dermal collagen bundles appear thick and coarse and replace areas of subcutaneous fat.[5] Rarely, morphea and lichen sclerosis et atrophicus (LSA) occur simultaneously in the same patient.[6]

Although the disease has a benign course, the lesions are cosmetically disfiguring and may cause psychological distress. Moreover, it sometimes progresses and may involve underlying tissues of the skin (fat, fascia, and muscle). This may lead to muscle atrophy, flexion contractures if localized over the joints, and poorly healing ulcerations that can cause significant morbidities.[7,8]

The pathogenesis of scleroderma has not been completely delineated, but three processes have been demonstrated: disturbance of collagen metabolism,[9] vascular alteration,[10] and autoimmune activity.[11] Fibrosis in scleroderma is preceded by a T-helper lymphocytic infiltrate with subsequent collagen deposition and an increased synthesis of type I and type III collagen. In fibroblasts from sclerotic skin lesions, increased collagen expression was associated with decreased collagenase I expression, which may be important in collagen accumulation.[10]

Numerous therapeutic agents have been used, with limited success, including topical, intralesional, and systemic glucocorticoids, penicillin G, D-penicillamine, antimalarials, sulfasalazine, vitamin D analogs, vitamin E, imiquimod, topical tacrolimus, etretinate, potassium p-aminobenzate, griseofulvin, interferon gamma, methotrexate, cyclosporine, phototherapy, and extracorporeal photopheresis.[4,7,12,13]

Recently, different types of phototherapy, such as psoralen and ultraviolet (UV) A,[14] broadband UVA (320–400 nm),[15] and UVA1 (340–400 nm)[4,10,11] have been advocated as a new line of therapy, based on the finding that synthesis of collagenase can be directly stimulated in human skin fibroblasts by UVA radiation. Very promising results have notably been achieved with UVA1 phototherapy thus far, with low-dose (LD) and medium-dose (MD) UVA1 seeming to be as effective as high-dose (HD) UVA1, with a possible better risk–benefit ratio.[4,10,11,16] The optimal dose regarding therapeutic efficacy vs. possible side effects remains to be evaluated.

We aimed to evaluate the therapeutic effectiveness of MD (30 J/cm²) UVA1 phototherapy and to show that 13 MHz ultrasound is a valuable tool for the assessment of diagnosis and treatment results in LS.

Materials and methods

Patients

Thirty-five patients with localized scleroderma were selected for MD UVA1 phototherapy and were treated after informed consent at our dermatology clinic between April 2005 and June 2009. For each patient, a complete disease history was obtained before starting irradiation therapy. Laboratory examinations included complete blood cell count, liver and kidney parameters, rheumatoid factor, antinuclear antibodies, and serology for *Borrelia burgdorferi*. In all patients (27 female and 8 male; age 3.5–75 years), the diagnosis of LS was made on clinical and histopathological features. None of the patients had any evidence of systemic sclerosis or pseudoscleroderma. All patients had at least two clinically identical scleroderma lesions (mostly contralateral). All patients included in the study were Caucasian; 15 patients had skin type II, 15 had skin type III, and five had skin type IV according to Fitzpatrick's classification. Exclusion criteria were as follows: pregnancy or lactation, any internal immunomodulation or immunosuppressive therapy within the last four weeks, any topical therapy within the last two weeks other than the use of emollients, current use of potentially photosensitizing drugs, history of relevant cardiac/cardiovascular events, and a history of an autoimmune disease or neoplasm. Patients were classified to have plaque (n = 18), linear (n = 4), ECDS (n = 3), generalized morphea (n = 7), deep or pansclerotic (n = 1), and generalized associated with overlying LSA (n = 2) subtypes. Of 18 patients with plaque morphea, seven had late-stage sclerotic and 11 had active inflammatory lesions. One patient with linear morphea had upper limb involvement associated contractures. Four patients with generalized morphea presented with late-stage lesions. The remaining three patients with generalized morphea presented with active inflammatory lesions. The disease duration varied between three months and 55 years. Before treatment, skin biopsies were taken from lesional skin. Unfortunately, post-treatment histopathological examination was done on only four of these patients. Fourteen of 35 patients were evaluated by clinical score as well as by 13 MHz ultrasound.

Ultraviolet A1 equipment

The UVA1 irradiation equipment consisted of a Waldmann 7001 K cabin with Waldmann TL10R low-pressure lamps (Waldmann Gmblt, Schvenningen, Germany). These lamps generate UVA1 wavelengths in the 340–400 nm range. In addition, infrared irradiation is emitted, but this is filtered out by an acrylic glass screen. The UVA1 irradiation levels are approximately 35 mW/cm^2. A dose of 30 J/cm^2 is achieved in approximately 30 minutes.

Treatment

In all patients, total body UVA1 phototherapy (340–400 nm) was administered 3–5 times a week for 10–15 weeks, resulting in a total of 30–45 treatment sessions. Each treatment session consisted of an exposure of 30 J/cm^2 UVA1 per body half, resulting in a cumulative UVA1 dose of 900–1350 J/cm^2. During therapy, patients wore eye goggle protection against UVA radiation. Emollients had been applied once daily in the evening. Emollients were not applied shortly before or after UVA1 phototherapy.

Assessment

Clinical evaluation

All patients were assessed before, during, and after UVA1 phototherapy by palpation for tethering and thickening of the skin. Clinical severity of LS was assessed by a scoring system created by Rook *et al.*[17] Briefly, the method consists of scoring sclerosis of different topographic sites. The most severely affected site selected for assessment of clinical severity was examined in each patient by the same investigator (OS). The severity of sclerosis was scored from 0 (like normal skin) to 10 (extremely sclerotic, wooden hard).

Ultrasound analysis (13 MHz)

Ultrasound imaging was performed with a high-resolution B-mode ultrasound system (Sanoline Antares; Siemens Medical System, Erlangen, Germany) with a 13 MHz CVFX 13-5 linear probe by a second investigator (HK). The usable depth of signal penetration is about 60 mm. During ultrasound analysis, an

aqua flex ultrasound gel pad was placed on representative skin areas to eliminate the risk of cross-contamination and to provide better visualization of near field and superficial structures. All of the plaques were examined, and measurements were taken in the area where the echographic lesions appeared the most severe, usually in the center of the lesion. The most severely affected site was selected for evaluation and follow-up. The thickness of the dermis and hypodermis was measured and compared with adjacent normal skin. The following morphological criteria were determined as being present or absent: (I) in the dermis, homogenization and undulations; (II) in the hypodermis, reduction of the thickness, disorganization, and thickened hyperechoic bands; (III) in both, the presence or absence of a yo-yo image with a lateral limit resembling a "V "on its side (described in Results), and the presence or absence of vascular lesions.

Histopathological analysis

Skin biopsies were obtained from the center of markedly sclerotic areas and included subcutaneous tissue. The first pretreatment biopsy specimen was taken immediately before initiation of UVA1 phototherapy. The clinical diagnosis of morphea was confirmed microscopically, using standard histopathological criteria. Skin biopsies were taken from only four patients after phototherapy because we were unable to obtain written consent from the rest of the patients. Post-treatment biopsy specimens were taken from previously affected areas adjacent to the first biopsy sites. The specimens were fixed in 4% buffered formalin solution, routinely processed, and histological sections were prepared and stained with hematoxylin–eosin and Verhoeffl–van Gieson stains. Histopathological assessment was performed in a blinded fashion by a third investigator (AS).

Statistical analysis

Clinical score and skin thickness value data are given as mean ± standard deviation. A Student's *t*-test ($P < 0.05$, two-sided) was used to analyze differences in skin thickness before and after UVA1 phototherapy.

Results

UVA1 phototherapy was well tolerated and completed by all patients. All patients had mean 41.14 (30–45) treatments with doses of 30 J/cm^2 at each treatment session resulting in a mean cumulative UVA1 dose of 1180.29 (900–1350) J/cm^2. During and after phototherapy, no serious adverse effects were recorded. Two patients initially developed painless UVA1 erythema, and one of these patients also reported pruritus at the beginning of therapy. Moderate to significant generalized hyperpigmentation due to phototherapy was observed in all patients. In most patients, sclerosis greatly regressed after fewer than 18 sessions. At this time, a more intense tanning of most plaques was observed when compared with the surrounding unaffected skin. However, except in the lesions with overlying LSA, this inhomogeneous tanning almost completely leveled off within the remaining treatment sessions or thereafter. After completion of the treatment, only a slight discoloration of the skin remained in the lesion with overlying LSA.

Patient satisfaction with the clinical outcome was generally very high, with the majority of patients reporting that treatment had induced a substantial softening of their skin lesions. All patients responded to treatment, according to clinical score results. Sclerotic plaques resolved leaving smooth and soft yellowish tanned skin with normal consistency and folding capability. According to clinical criteria, 50% of the lesions disappeared, and more than 50% showed marked improvement during UVA1 irradiation in 29 of the 35 patients. Six patients showed fair to poor responses (20–44.45%). One of these patients had deep (subcutaneous) lesions of LS. The remaining patients had circumscribed plaques with sclerotic stage. These lesions were also late, fibrotic, and white. In all patients, palpation revealed a softening of the sclerotic lesions resulting in a decreased score from 7.91 ± 1.17 at the beginning to 2.85 ± 1.88 by the end of phototherapy ($P = 0.000$) (Table 1, Fig. 1a,b). Fourteen patients were confirmed by 13 MHz ultrasound evaluation. Dermal thickness was increased before therapy and decreased from 3.11 ± 1.54 to 2.26 ± 0.86. This difference was highly significant ($P = 0.002$) (Table 1, Fig. 1c,d).

As shown in Figure 1d, there was a marked reduction in the highly reflective echo-rich bands within the epidermis and subcutis. Similar results were obtained by histopathological evaluation of biopsy specimens in four patients. In the pretreatment biopsy specimens, the collagen bundles in the reticular dermis were thickened, closely packed, and homogeneous in appearance. Skin adnexal structures became atrophic (Fig. 2a). Post-treatment biopsy specimens showed that the thickness of collagen bundles was significantly less than that seen in the pretreatment specimens. The single collagen bundles revealed regular thickness and were separated by regular spaces. Skin annealing structures were less atrophic. There were no or few collagen bundles infiltrating between adipocytes. After completion of therapy, the structure of the dermis returned to almost normal human dermis (Fig. 2b).

In one patient with LS, joint mobility and function of the upper extremity was restored to normal levels (Fig. 3a,b) and in another patient with circumscribed

Table 1 Characteristics of patients with localized scleroderma treated with medium-dose ultraviolet A1 phototherapy

	Only clinical evaluated patients *n* = 21	Both clinical evaluated patients *n* = 14	All patients *n* = 35
Sex			
Male	4	4	8
Female	17	10	27
Age, year			
Mean	40.45	43.50	41.67
SD	17.00	20.82	18.39
Range	3.5–70	10–75	3.5–75
Duration of disease, year			
Mean	7.33	3.01	5.60
SD	12.44	4.38	10.15
Range	0.25–55	0.25–16	0.25
Stage of disease			
Inflammatory	9	5	14
Sclerotic	12	9	21
Clinical score before tx			
Mean	7.90	7.92	7.91
SD	1.09	1.32	1.17
Range	6–10	4–9	4–10
Clinical score after tx			
Mean	2.42	3.50	2.86
SD	1.85	1.78	1.88
Range	0–8	0–6	0–8
P value	0.000	0.000	0.000
USG score before tx			
Mean		3.11	3.11
SD		1.54	1.54
Range		0.9–5.4	0.9–5.4
USG score after tx			
Mean		2.26	2.26
SD		0.82	0.82
Range		0.7–4	0.7–4
P value		<0.002	<0.002
Follow-up (month)			
Mean	29	3.11	18.76
SD	14.50	1.54	17.10
Range	3–48	3–24	3–48

USG, ultrasonography.

plaques (sclerotic stage), the limb ulcer was healed after UVA1 phototherapy that was inadequately exposed by UVA. Lesions in the abdominal crease, axillary region, or submammary area remained tauter than the other lesions. This suggests that a local, rather than systemic, effect of UVA1 induces the therapeutic effect.

The mean follow-up period after cessation of therapy was 21.63 (3–48) months. In five patients, a partial relapse was observed. Two of the five patients reported reappearance of new lesions after 12 months following cessation of therapy. The other three patients recurred at 6, 22, and 24 months, respectively, after stopping the therapy. Two of these patients had ECDS. Three patients had linear morphea, generalized morphea with inflammatory stage, and circumscribed plaque with inflammatory stage. Four of the five patients had 36 treatments, resulting in a cumulative UVA1 dose of 1080 J/cm^2. No further clinical improvement of skin symptoms was observed in any patient after UVA1 phototherapy was stopped.

Discussion

Different types of phototherapy, such as psoralen and UVA,[10] broadband UVA (320–400),[11] narrowband (NB) UVB (311 nm),[12] and UVA1 (340–400 nm)[4,13,14] have been suggested for LS treatment. The data available in the literature indicate that the best results have been achieved with UVA1 phototherapy, whereas UVA phototherapy appears to be less effective, with greater side-effects. Different dosages have been used for UVA1 treatment of LS: low (20 J/cm^2), moderate/medium (40–70J/cm^2), and high (90–130 J/cm^2). Another classification is based on the administered cumulative dose. HD is defined as a cumulative dose of 975–1840 J/cm^2, MD as a cumulative dose of 300–975 J/cm^2 and finally, LD as a cumulative dose of 300 J/cm^2 or lower.[15,18] The optimal dose regarding therapeutic efficacy vs. possible side effects is still being evaluated.

Stege *et al.*[13] compared HD (130 J/cm^2) with LD (20 J/cm^2) UVA1 and observed a very good response with HD UVA1 but no response with LD UVA1 in plaque or linear type LS. In contrast, Kerscher *et al.*[14] reported excellent results with LD UVA1 phototherapy. Similar, other studies obtained good or excellent results with LD phototherapy. Camacho *et al.*[19] found MD UVA1 therapy was effective in the treatment of LS and that effectiveness was associated with an increase in the number of CD34+ dendritic cells in the dermis. Kreuter *et al.*[12] reported dermal thickness was significantly decreased by MD UVA1 but not by LD UVA1 or narrowband UVB. Similarly, empirical data collected in four medical centers in the United States showed that MD and MD-HD UVA1 were superior to the LD regimen for the treatment of morphea.[20] Sator *et al.*[8] compared MD with LD and intrapatient and observed better long-term results with MD than LD UVA1 in LS, as shown by ultrasound assessment. In agreement with the literature, our results demonstrate that MD UVA1 phototherapy is effective in the treatment of long-standing and different types of LS. The effectiveness of this treatment showed as a significant reduction in skin thickness by ultrasound examination of nine of 14 patients.

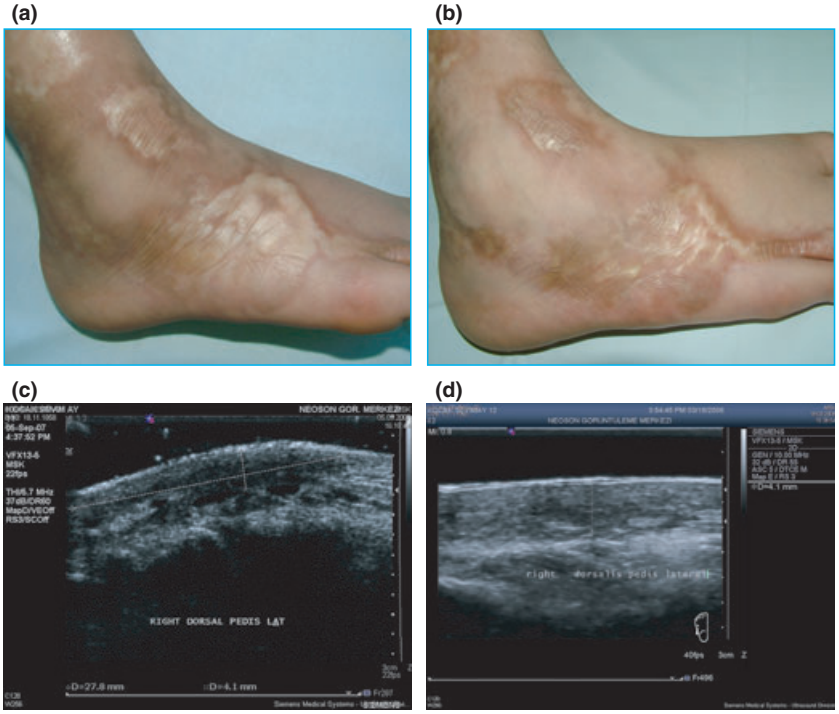

Figure 1 Late-stage morphea plaques before (a,c) and after (b,d) medium-dose ultraviolet (UV) A1 phototherapy. (a) Sclerotic morphea plaques deforming the right foot of the patient. (b) A marked decrease in sclerosis after UVA1 therapy on the right foot of the patient. (c) Increased echogenicity, disorganization and thickened trabecular structures within dermis and subcutis. (d) A marked reduction in highly reflective echorich bands within dermis and subcutis

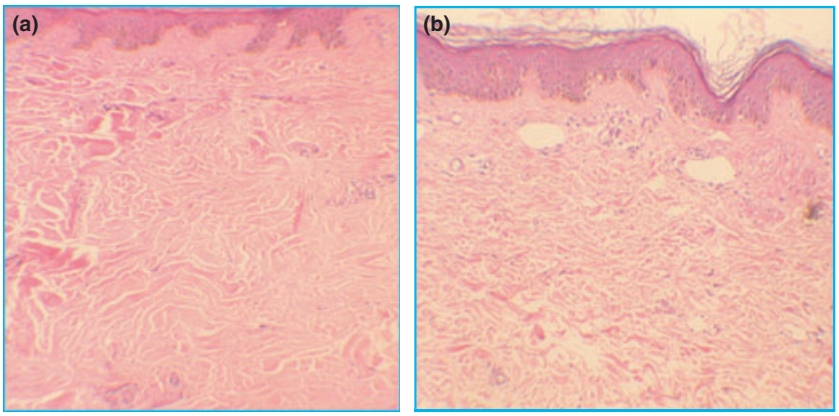

Figure 2 Histopathology of a sclerotic lesion before (a) and after (b) medium-dose ultraviolet A1 phototherapy. (a) Thickened collagen bundles and replacement of the subcutaneous fat (hematoxylin–eosin × 40). (b) Post-treatment biopsy specimen of the same plaque, showing loosely arranged collagen fibers and a dermal structure close to normal skin (hematoxylin–eosin × 40)

The precise action of UVA1 therapy is unknown. Photoimmunologic studies indicate that keratinocytes,[20] epidermal Langerhans cells,[21] T-helper cells,[22] fibroblasts,[23] and mast cells[24] may be target cells in UVA radiation-induced immunomodulation. It is now accepted that dermal fibroblasts are key in the pathogenesis of skin sclerosis through synthesis of increased amounts of collagen I and III.[13] UVA1 exhibits its effects in all these directions by upregulation of specific messenger RNAs of matrix metalloproteinases and inhibition of collagen synthesis, by depletion of skin-infiltrating T cells and proinflammatory cytokines (interleukins 1 and 6), by induction of a shift of the balance between proto-oncogenes and tumor suppressor genes toward the induc-

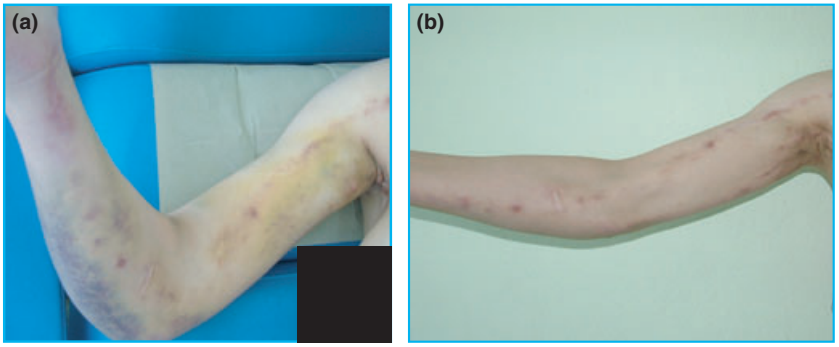

Figure 3 Before (a) and after (b) medium-dose ultraviolet A1 treatment in linear morphea. (a) Impairment in joint mobility and function of the right upper extremity of the patient. (b) Restoration to normal levels of joint mobility and function of the right upper extremity of the patient

tion of apoptosis, and by modulation of endothelial regulation and transformation.[23,25–27] *In vitro* studies have shown that UVA1 radiation induced a dose-dependent upregulation of steady-state levels of collagenase I-specific messenger RNA.[25–29]

We have chosen UVA1 phototherapy in our patients with LS. UVA1, long wavelengths, penetrate the dermis more deeply than UVB and PUVA. Therefore, UVA1 might be able to initiate more collagenase (matrix metalloproteinase-1) activity.[12] The disadvantages of UVA1 are as follows. First, UVA1 is available only in special centers focused on photodermatology. Second, UVA1 is more expensive.

In recent years, NB UVB has been widely used to treat psoriasis, vitiligo, and atopic dermatitis. The NB UVB is also available in most dermatology centers and less expensive than UVA1. NB UVB has been demonstrated to penetrate into the dermis, but it does not reach deeper as much as UVA1 does. To our knowledge, only one study is available in the literature investigating the overall efficacy of NB UVB in patients with LS.[12] This study has demonstrated that NB UVB was effective as well as LD UVA1, but the size was too small to reach significance. As we mentioned previously, the same study showed that dermal thickness decreased significantly by MD UVA1 but not by LD UVA1 or NB UVB.[12] If UVA1 is not available, NB UVB might be considered as a treatment option in patients with LS.

Our clinical observation indicated that MD UVA1 therapy provided clinical improvement of lesions on the skin of patients with LS. Although the dose used per session in this study and that by Camacho *et al.*[19] was the same (i.e., 30 J/cm^2), the cumulative doses were different, at 1180 and 900 J/cm^2, respectively. MD UVA1 (50, 70 J/cm^2) used per session in the last two studies was higher than the dose in the present study. In these former studies, cumulative doses of UVA1 as high as 2000, 2100 J/cm^2 were attained. The results of both studies showed that MD UVA1 was more effective than LD UVA1 phototherapy.[8,12] It seems that both dose per session and the cumulative dose are important in providing an excellent response. Our results showed no relationship between the duration of disease or skin phototypes and clinical or ultrasonographic score improvement.

Concordant with the literature, we observed significant clinical improvement in two patients with morphea with overlying LSA after UVA1 phototherapy. In most studies, LD UVA1 regimens achieved good results in the treatment of morphea with overlying LSA or only LSA.[7,20]

Our patients were followed up for a mean 21-month (3–48) period to provide data on the long-term outcome of UVA1 phototherapy for LS. We observed a clinical relapse in five of 35 patients over an average of 14 months (6–24) after cessation of therapy. According to our results, follow-up of patients should be extended for at least two years. Maintenance therapy could be required to prevent disease relapse. However, 30 patients had a period of remission of at least 21 months, despite the often long, duration of disease (mean 6.25 years).

Previous studies have used a 20-MHz probe for the diagnosis and evaluation of UVA1 phototherapy in LS.[30,31] One study reported that 13 MHz ultrasound may be a valuable tool for the diagnosis of LS. The 20 MHz probe is a mechanical probe with a penetration depth of 7 mm, in contrast to a 60 mm penetration depth for the 13 MHz probe. This study showed that 13 MHz ultrasound disclosed a typical yo-yo image in LS with a high specificity and sensitivity for criteria analyzed in the dermis and hypodermis.[32] In Istanbul, only 13 MHz ultrasound probes are available, so we used this ultrasound probe. We found that a 13 MHz ultrasound probe can be used effectively for evaluating skin thickness.

The main acute reverse reactions are erythema, polymorphic light eruption, itching, xerosis cutis, tanning,

and recrudescence of herpes simplex infections.[33] One patient had an erythema, and the other patient had both erythema and pruritus. All the patients were tanned. The major long-term risk is photoaging and skin cancer.[32] In the present study, with a mean follow-up of 21 months, no skin cancer or actinic damage was observed. Even though no side effects of UVA1 irradiation have been observed so far, the potential for long-term risks is likely to be greater with increasing doses.[17] Long-term side effects are predicted to occur frequently, as compared with HD UVA1 therapy.[4] We suggest that the dose of UVA1 as an optimized benefit risk/ratio is the preferred treatment for LS.

The limitations of this study are as follows. The first limitation is lack of ultrasound examination in 21 of 35 patients. The second limitation is the modification of treatment sessions because of a patient's age, severity, and type of scleroderma and transportation problems of patients. The third limitation is the small sample size. The fourth is the lack of a placebo group.

The present study is, to our knowledge, the first study in Turkey showing an effect of UVA1 phototherapy in LS. This is also the first investigation in which a 13 MHz ultrasound probe was used for the evaluation of the UVA1 phototherapy results.

In conclusion, our study confirms that MD UVA1 phototherapy is a highly effective, safe, and well-tolerated therapeutic modality for treatment of all types of LS, including LS with overlying LSA. UVA1 phototherapy, if available, should be considered as a first-line therapy in the management of LS. Ultrasound imaging is a valuable method for the evaluation of UVA1 phototherapy results, and a 13 MHz ultrasound probe may be used for this method.

References

1 Laxer RM, Zulian F. Localized scleroderma. *Curr Opin Rheumatol* 2006; **18**: 606–613.

2 Zulian F. New developments in localized scleroderma. *Curr Opin Rheumatol* 2008; **20**: 601–607.

3 Rosenwasser TA, Eisen AZ. Scleroderma. In: Fitzpatrick TB, Eisen AZ, Wolff K, *et al.*, eds. *Dermatology in General Medicine*, 4th edn. New York: McGraw-Hill Book Company, 1993: 2156–2167.

4 de Rie MA, Enomoto DHN, de Vries HJC, Bos JD. Evaluation of medium-dose UVA1 phototherapy in localized scleroderma with the cutometer and fast Fourier transform method. *Dermatology* 2003; **207**: 298–301.

5 Lever WF, Schaumburg-Lever G. *Histopathology of the Skin*, 8th edn. Philadelphia: JB. Lippincott, 1997: 274–285.

6 Uitto J, Santa Cruz DJ, Baver EA, Eisen AZ. Morphea and lichen sclerosis et atrophicus. Clinical and histopathological studies in patients with combined features. *J Am Acad Dermatol* 1980; **3**: 271–279.

7 Rowell NR, Goodfield MJD. The connective diseases. In: Champion RH, Burton JL, Ebling FJG, eds. *Textbook of Dermatology*. Oxford: Blackwell Scientific Publications; 1992: 2163–2194.

8 Sator PG, Radakovic S, Schulmeister K, *et al.* Medium-dose is more effective than low dose ultraviolet A1 phototherapy for localized scleroderma as shown by 20 MHz ultrasound assessment. *J Am Acad Dermatol* 2009; **60**: 786–791.

9 Hatomochi A, Ono M, Arakawa M, *et al.* Analysis of collagen gene expression by cultured fibroblasts in morphea. *Br J Dermatol* 1992; **126**: 216–221.

10 Scharffetter Kochanek K, Goldermann R, Lehmann P, *et al.* PUVA therapy in disabling pansclerotic morphea of children. *Br J Dermatol* 1995; **132**: 830–831.

11 El-Mofty M, Zaher H, Basseila M. Low dose broad-band UVA in morphea using a new method for evaluation. *Photodermatol Photoimmunol Photomed* 2000; **16**: 43–49.

12 Kreuter A, Hyun J, Stücker M, *et al.* A randomized controlled study of low-dose UVA1, medium-dose UVA1, and narrowband UVB phototherapy in the treatment of localized scleroderma. *J Am Acad Dermatol* 2006; **54**: 440–447.

13 Stege H, Berneburg M, Humke S, *et al.* High-dose UVA1 radiation therapy for localized scleroderma. *J Am Acad Dermatol* 1997; **36**: 938–944.

14 Kerscher M, Volkanandt M, Gruss C, *et al.* Low-dose UVA1 phototherapy for treatment of localized scleroderma. *J Am Acad Dermatol* 1998; **38**: 21–26.

15 Kroft EBM, Berkhof NJG, van de Kerkhof PCM, *et al.* Ultraviolet A phototherapy for sclerotic skin disease: a systematic review. *J Am Acad Dermatol* 2008; **59**: 1017–1030.

16 Steger JW, Matthews JH. UVA therapy for scleroderma. *J Am Acad Dermatol* 1999; **40**: 787–788.

17 Rook AH, Freundlich B, Jegasothy BV, *et al.* Treatment of systemic sclerosis with extracorporeal photo chemotherapy. *Arch Dermatol* 1992; **28**: 337–346.

18 Gross CJ, von Kobyletzki G, Behrens-Williams SC, *et al.* Effects of low dose ultraviolet A-1 phototherapy on morphea. *Photodermatol Photoimmunol Photomed* 2001; **17**: 148–155.

19 Camacho NR, Sanchez JE, Martin RF, *et al.* Medium-dose UVA1 phototherapy in localized scleroderma and its effect in CD34-positive dendritic cells. *J Am Acad Dermatol* 2001; **45**: 697–699.

20 Tuchinda C, Kerr HA, Taylor CR, *et al.* UVA1 phototherapy for cutaneous diseases: an experience of 92 cases in the United States. *Photodermatol Photoimmunol Photomed* 2006; **22**: 247–253.

21 Grewe M, Gyufko K, Krutmann J. Interleukin-10 production by cultured human keratinocytes: regulation

by ultraviolet B and ultraviolet A1 radiation. *J Invest Dermatol* 1995; **104**: 3–6.
22 Baadsgacid O, Lisby S, Lange Kantzin G, *et al.* Rapid recovery of Langerhans cell alloreactivity, without induction of autoreactivity, after in vivo ultraviolet A1, but not ultraviolet B exposure of human cells. *J Immunol* 1989; **142**: 4213–4218.
23 Krutmann J. Ultraviolet A1 radiation-induced immunomodulation: high-dose UVA1 therapy of atopic dermatitis. In: Krutmann J, Elmets CA, eds. *Photoimmunology*. Oxford: Blackwell Science Ltd. 1995: 246–256.
24 Gruss C, Reed JA, Altmeyer P, *et al.* Induction of interstitial collagenase (MMP-1) by UVA1 phototherapy in morphea fibroblasts. *Lancet* 1997; **350**: 1295–1296.
25 Grabbe J, Welker P, Humke S, *et al.* High-dose UVA1, but not UVA/UVB therapy decreases IgE binding cells in lesional skin of patients with atopic eczema. *J Invest Dermatol* 1996; **107**: 419–422.
26 Scharffetter K, Wlaschek M, Hogg A, *et al.* UVA irradiation induces collagenase in human dermal fibroblasts in vitro and in vivo. *Arch Dermatol Res* 1991; **283**: 506–511.
27 Wlaschek M, Heinen G, Postwig A, *et al.* UVA-induced autocrine stimulation of fibroblast-derived-collagenase/MMP.1 by interrelated loops of interleukin-1 and interleukin-6. *Photochem Photobiol* 1994; **59**: 550–556.
28 Breuchkmann F, Stuocker M, Altmeyer P, Kreuter A. Modulation of endothelial dysfunction and apoptosis: UVA1-mediated skin improvement in systemic sclerosis. *Arch Dermatol Res* 2004; **296**: 235–239.
29 Petersen MJ, Wason C, Craig S. Ultraviolet A irradiation stimulates collagenase production in cultured human fibroblast. *J Invest Dermatol* 1992; **99**: 440–444.
30 Hoffmann K, Gerbaulet U, El-Gammal S, Altmeyer P. 20 MHz B-mode ultrasound in monitoring the course of localized scleroderma (morphea). *Acta Derm Venereol Suppl (Stockh)* 1991; **164**(Suppl.): 3–16.
31 Kreuter A, von Kobyletzki G, Happe M, *et al.* Ultraviolet-A1 (UVA1) phototherapy in lichen sclerosis et atrophicus. *Hautarzt* 2001; **52**: 878–881.
32 Tosnes A, Anglade MC, Revaz J, Radier C. Thirteen-megahertz ultrasound probe: its role in diagnosing localized scleroderma. *Br J Dermatol* 2003; **148**: 724–729.
33 Dawe RS. Ultraviolet A1 phototherapy. *Br J Dermatol* 2003; **148**: 626–637.

