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REVIEW

Phototherapy in Scleroderma

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ABSTRACT

Systemic and localized scleroderma are difficult to manage diseases with no accepted gold standard of therapy to date. Phototherapeutic modalities for scleroderma show promise. A PubMed search of information on phototherapy for scleroderma was conducted. The information was classified into effects on pathogenesis and clinical outcomes. Studies on photopheresis were excluded. There were no randomized, double-blind, placebo-controlled studies, and only three controlled studies. The vast majority of identified studies evaluated ultraviolet A1 (UVA1) phototherapy. More rigorous studies are needed to evaluate phototherapy in the treatment of scleroderma. Based on the limited studies available, 20–50 J/cm^2 of UVA1 therapy 3–4 times a week for 30 treatments is recommended.

Keywords: Morphea; Phototherapy; PUVA; Scleroderma; UVA; UVB

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INTRODUCTION: BACKGROUND ON MORPHEA/SCLERODERMA

Scleroderma is a chronic autoimmune disease associated with cutaneous, joint, and internal organ involvement. Cutaneous scleroderma is characterized by enhanced fibroblast activity leading to hypertrophic dermal collagen. There are localized and systemic forms of scleroderma. The localized forms include morphea and linear scleroderma. Localized scleroderma has a better prognosis and does not involve internal organs. There are currently no curative treatments for scleroderma. Current treatments include immunosuppressants; intralesional, topical, and oral steroids; topical vitamin D; and phototherapy. This review serves to provide insight into the use of phototherapy in the

management of scleroderma. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

PHOTOTHERAPY IN DERMATOLOGY

Phototherapy modalities utilize specific wavelengths of the electromagnetic spectrum to disrupt the dysfunctional and pathologic tissue that has developed in some patients with skin disease. Various phototherapy modalities possess anti-inflammatory effects [1]. The longer the wavelength of phototherapy, the deeper in the dermis it penetrates [2]. Current phototherapeutic modalities being used for dermatoses include broadband ultraviolet B (UVB 290–320 nm), narrowband UVB (311–313 nm), excimer laser (308 nm), ultraviolet A (UVA 320–400 nm), ultraviolet A1 (UVA1 340–400 nm), psoralen and UVA (PUVA), and extracorporeal photochemotherapy.

MECHANISM BEHIND PHOTOTHERAPEUTIC MODALITIES USED IN SCLERODERMA

A common theory behind the mechanism of phototherapy in scleroderma is that light is converted to chemical energy resulting in the increase of reactive oxygen species or singlet oxygen production, which can modulate the expression of cytokines [3, 4]. Ultraviolet radiation includes UVA and UVB therapy, with UVA1 studied the most. UVA1 can have an output categorized as low (10–30 J/cm^2), moderate (40–70 J/cm^2), or high (up to 130 J/cm^2).

UVA1 radiation increases collagenase [also known as the matrix metalloproteinase-1 (MMP-1)] gene, mRNA, and protein expression by fibroblasts [5–9]. In mice models, UVA1 radiation reduces fibroblast proliferation in a dose-dependent fashion [10, 11]. Additionally, UVA1 radiation administered three times a week showed decreased hydroxyproline and collagen levels in a dose-dependent fashion [11]. The quality of the collagen is altered after UVA1 therapy, as collagen appears less dense and smoother compared to before treatment [12]. Decorin (a proteoglycan component of connective tissue) mRNA levels are lower in lesional scleroderma versus non-lesional skin, and decorin levels are increased after UVA1 phototherapy [13]. Transforming growth factor beta (TGF-β) protein levels (TGF-β is profibrotic) are inversely correlated with decorin levels. On the other hand, another study showed that after UVA1 phototherapy, decorin was decreased in the upper to middle dermis, although decorin slightly increased in the papillary dermis [14]. In patients, UVA has been shown to reduce collagen I, collagen III, and TGF-β and increase interferon-γ [9]. UVB radiation increases alpha melanocyte-stimulating hormone (α-MSH) receptor synthesis in keratinocytes and melanocytes [15]. Human fibroblast dermal cultures treated with α-MSH demonstrated an increase in MMP-1 mRNA, indicating that α-MSH may be one of UVB's mediators of anti-fibrosis [16].

The source of the mediators that contribute to the reduction in sclerosis comes mostly from the dermis. Subsequently, certain parts of the dermis may be impacted more than others. An image analyzer showed a greater reduction in collagen fibers in the upper and middle dermis and less reduction in the lower dermis [12]. In 18 patients treated with UVA1, the MMP-1 level was higher in the papillary layers and lower in

the reticular layers [17]. The anti-fibrotic effects of phototherapy may not come exclusively from the dermis. Samples taken 18 h after the final UVA1 treatment in a set of patients showed an increase in interstitial collagenase in the upper layer of keratinocytes, melanocytes, and endothelial cells [5].

Evidence supports the regimen of multiple UVA1 therapy sessions a week. The anti-sclerotic effects of a single exposure of UVA1 effects are typically seen to last less than 1 week. In human skin, mRNAs of type I and III procollagen were decreased and MMP-3 was increased after 3 days of a single UVA1 dose [18]. MMP-1 and MMP-3 were upregulated for 3 to 5 days, while procollagen levels were suppressed for at least 7 days [18]. In this small study, anti-fibrotic responses became refractory to multiple UVA1 exposures over the course of 1 week, as repeated exposures weekly showed no reduction in type I procollagen levels [18].

UVA1 therapy can have an immunomodulatory effect on lesional skin. UVA1 can reduce inflammation in the dermis [12]. UVA1 causes apoptosis of T-cells [19]. Patients with morphea exposed to UVA1 with a dose of 30 J/cm^2 and a cumulative dose of 900 J/cm^2 were found to have an increase in CD34$^+$ dendritic cells [20]. Human beta defensin[s] (HBD), interleukin (IL)-6 and IL-8 are downregulated in patients with localized scleroderma treated with UVA1 phototherapy [6]. On the other hand, another study showed that UVA1 induces MMP-1 through a mechanism involving IL-1 and IL-6 [21].

UVA1 radiation may induce oxidative stress, as evidenced by an increase in UVA1-induced heme oxygenase-1 in fibroblasts [7]. Glutathione was lower in systemic sclerosis (SSc) fibroblasts than control samples, but glutathione was increased and became equivalent between normal and SSc fibroblasts after in vitro irradiation with UVA1 [8]. Thus, the SSc fibroblasts may be more susceptible to phototherapy-induced oxidative stress than normal fibroblasts [8]. Additionally, heme oxygenase-1 may reduce fibrotic conditions via TGF-β [22]. UVA1 may play a role in angiogenesis. In patients exposed to UVA1 phototherapy for 14 weeks, there was an increase in CD34$^+$ cells and an increase in vascular endothelial growth factor (VEGF) [23]. The neuroendocrine system may be involved, as UVA1 therapy decreases dermal expression of neuron-specific enolase, which correlated with softening of skin lesions in patients with SSc with acral lesions [24].

UVB phototherapy results in DNA damage, forming cyclobutane pyrimidine dimers between nucleotides [25]. There is evidence that broadband UVB can induce interstitial collagenase, stromelysin, and IL-6 [26]. There may be an interplay between these enzymes and cytokines [26]. Broadband UVB radiation can induce production of MMP-1 in fibroblasts [27]. When keratinocytes are exposed to UVB, there is an increase in IL-1α and IL-6, which induced MMP-1 [27]. Human keratinocytes cultured in a model system exposed to 300 J/cm^2 of broadband UVB produced IL-1α, IL-6, and tumor necrosis factor alpha (TNF-α) [28].

PUVA is another modality that can be used for scleroderma. PUVA can lead to apoptosis of T-cells in the dermis [19]. In patients with SSc treated with PUVA, the majority of patients experienced an increase in circulating TNF-α levels, E-selectin, and vascular cell adhesion molecule (VCAM). In the majority of patients, there was a reduction in VEGF and TGF-β [29]. On the other hand, in patients with morphea treated with PUVA, there was a fall in serum VCAM molecules and an increase in TNF-α in most patients [30]. In a bleomycin-induced

scleroderma rat model, PUVA treatment reduced dermal thickness and hydroxyproline content and downregulated expression of type I and III collagen genes [10]. In one patient with SSc, treatment with oral PUVA therapy three times a week for 4 weeks resulted in loosening of collagen, reduction in edema, and decreased $CD34^+$ cells [31]. Bath PUVA treatment has effects on collagen cross-links in human skin samples of scleroderma, reducing hydroxylysylpyridinoline and lysylpyridinoline [32]. UVA1 treatment affected collagen fibrils mostly in the upper reticular dermis [33], whereas PUVA affected collagen fibrils in the upper and middle reticular layers [33]. Additionally, collagen fibrils decreased and new fibrils developed, suggesting UVA1 and PUVA phototherapies' impact on sclerotic lesions occurs via collagen degradation and new collagen synthesis [33].

Other modalities have also been studied. Photodynamic therapy (PDT) with 5-aminolevulinic acid (5-ALA) treatment of scleroderma fibroblasts increased MMP-1 and MMP-3, and there was a decrease in collagen type 1 mRNA as early as 6 h after treatment [34]. Keratinocytes exposed to PDT with 5-ALA had an increase in IL-1α and TNF-α [35]. In fibroblasts that were incubated with keratinocytes pre-exposed to PDT with 5-ALA, there was an increase in MMP-1 and MMP-3; Karrer et al. [35] subsequently suggested paracrine signaling between the phototherapy exposed keratinocytes and the fibroblasts. Furthermore, an IL-1 antagonist reversed the induction of MMP-1 and MMP-3 in fibroblasts [35]. Blue light up to 453 nm is toxic to cultured T cells, causing apoptosis, but was nontoxic for other skin cell types [36].

THE USE OF PHOTOTHERAPY IN DERMATOLOGY

Phototherapy is commonly used for many dermatoses, but there is less usage for scleroderma. Of 653 patients using phototherapy in a Brazilian clinic, 11 were there for scleroderma treatment [37]. In a multi-center response from 155 British pediatric physicians, PUVA was the most popular phototherapy modality (38%), followed by narrowband UVB (23%) and UVA1 (16%) for morphea [38]. These same clinicians were also asked what would be the best treatment option overall in their opinion for active morphea: 17% responded phototherapy and about 2/3 of these responses were for UVA1, which was only accessible to 27% of respondents [38]. Phototherapy for adult skin disorders is almost exclusively provided by dermatologists [39]. In a survey of physicians treating juvenile localized scleroderma in the UK, 19 of 28 pediatric dermatologists used UV therapy, whereas 0 of 10 pediatric rheumatologists used UV therapy [40]. A self-reported survey of dermatologists and rheumatologists revealed that 20% of dermatologists ($n = 40$) and 10.6% of pediatric dermatologist ($n = 47$) used phototherapy [41].

CLINICAL EVIDENCE OF PHOTOTHERAPY'S EFFICACY

Search Method

A PubMed search was performed with the Boolean search terms 'scleroderma' OR 'morphea' OR 'crest' AND 'phototherapy.' The search years yielded were from 1978 to 2016.

Clinical articles in a non-English language were excluded.

UVA1

UV therapy for patients with localized scleroderma was introduced as PUVA in 1994 [42]. In 1995, Kerscher et al. [43] reported that low-dose UVA1 phototherapy could be used in linear scleroderma. It is unclear whether there is an association between initial skin disease duration and response to UVA1 therapy. A study of ten patients with sclerodermic lesions determined that there was no correlation between disease duration and clinical response with UVA1 [44].

Table 1 lists the clinical reports of UVA1's efficacy in scleroderma or morphea. It is important to note that covered sclerotic lesions show less improvement after UVA1 therapy [45]. Ultrasound is an objective measure used to assess skin thickness in several UVA studies. Fourteen patients with localized scleroderma treated with UVA1 were evaluated with a 13-MHz ultrasound, and dermal thickness was increased before therapy and decreased from 3.11 ± 1.54 to 2.26 ± 0.86 [46]. Other studies have also supported a correlation of a decrease in dermal thickness when treating with UVA1 therapy [47].

Skin darkness or darkening likely has no effect on UVA1's efficacy. Forty-seven patients with morphea and 35 with SSc treated with UVA1 phototherapy were analyzed to see whether Fitzpatrick skin type makes an impact on the outcome, with the result being that medium- to high-dose UVA1 had similar efficacy in skin types I–V [48]. There was also no correlation noted for Fitzpatrick skin type and cumulative dose or clinical improvement.

The current evidence suggests that UVA1 effects are dose-related. In an observational report for patients with SSc who completed at least ten treatments, 20% of those treated with low-dose (20–40 J/cm^2) UVA1 ($n = 5$), 83.3% of those treated with medium-dose (>40–80 J/cm^2) UVA1 ($n = 6$), and 100% of those treated with high-dose (>80–120 J/cm^2) UVA1 ($n = 5$) reported improvement [49]. A 14-patient study showed a 70-J/cm^2 dose was more effective in treating localized scleroderma lesions than a 20 J/cm^2 dose [45]. In six patients with localized scleroderma treated two to three times a week, three patients experienced complete remission [50]. Two of the three received high-dose 100 J UVA1 therapy, of which one of them received 67 treatments and relapsed after 6 months, compared to one patient which received low-dose UVA1 twice weekly for 6 weeks for a total of 39 irradiations and did not relapse after 84-month follow up [50]. A broadband UVA trial examined 63 patients with morphea and 15 patients treated with UVA1 5, 10, or 20 J/cm^2 with cumulative doses of 100, 200, and 400 J/cm^2, respectively [51]. Clinical improvement was observed in all patients, but there was no comparable difference between the UVA doses.

Long-term outcome of UVA1 therapy is unclear. In a cohort study of 37 patients with morphea with positive clinical benefits from UVA1 treatment 44.5% recurred at 2 years, and 48.4% recurred at 3 years [52]. There was no difference between medium- (60–90 J/cm^2) and high-dose (>90 J/cm^2) UVA1 phototherapy with respect to recurrence. There was a 1.15-times higher chance of disease recurrence for an increment of 1 year in duration of morphea prior to UVA1 treatment [52].

Broadband UVA

Twelve patients with morphea were treated with low-dose (20 J/cm^2) broadband UVA 3 times a week for a total of 20 sessions [12].

Table 1 Studies of UVA1, UVB, and PUVA treatment in patients with scleroderma or morphea

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Randomized, controlled, single-blinded controlled study	9	Systemic sclerosis (acrosclerosis)	UVA1	40 J/cm^2 3 times a week	1680	14 weeks	42	Modified Rodnan skin scoring: no improvement seen in control vs. placebo	No	Durand et al. [69]
Randomized, controlled trial	64	Localized scleroderma	UVA1/UVB	Twenty-seven patients received 20 J/cm^2 UVA1; 18 patients received 50 J/cm^2 UVA1; 19 patients received narrowband UVB. All phototherapy was performed 5 times a week	Low dose 800, medium dose 2000	8 weeks	40	Reduction in clinical scores in all groups. No statistical difference between the UVA groups. There was a statistically significant difference between UVB and medium dose UVA1	No	Kreuter et al. [70]
Controlled study	8	Localized scleroderma	UVA1	48 J/cm^2 4 times a week	960	5 weeks	20	At 12 weeks no significant difference between skin elasticity in treated versus control skin. Fast Fourier transform did not show a significant change after 12 weeks. Skin softening was clinically noted after 7 weeks	No	de Rie et al. [71]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Prospective uncontrolled study	18	Systemic sclerosis (acrosclerosis)	UVA1	30 J/cm^2 4 times a week for 8 weeks, then 3 times a week for 6 weeks	1500	14 weeks	50	Improvement in clinical score and dermal thickness in 16 patients with softening of the skin and increased finger mobility. Follow-up in 6 months showed stable clinical outcome in most patients	Eight patients were on other systemic medications	Kreuter et al. [17]
Prospective uncontrolled study	14	Localized scleroderma	UVA1	20 and 70 J/cm^2 were given 4 times a week for 5 weeks, then 2 times a week for 5 weeks	Low dose 600, medium dose 2100	10 weeks	30	Skin thickness decreased in patients in both groups, but more so in the higher dosage group at a 12-month follow-up	No	Sator et al. [45]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Prospective uncontrolled study	35	Localized scleroderma	UVA1	30 J/cm^2 3–5 times a week	900–1350 (mean 1180.29)	10–15 weeks	30–45 (mean 41.14)	The mean follow-up period was 21.63 months. In five patients, a partial relapse was observed. Two of the five patients reported reappearance of new lesions after 12 months. Softening of plaques and improvement in 29 of 35 patients (82.85%). Dermal thickness decreased after therapy in 14 of 35 patients	No	Su et al. [46]
Prospective uncontrolled study	20	Localized scleroderma	UVA1	20 J/cm^2 4 times a week for 6 weeks and once a week for another 6 weeks	600	12 weeks	30	More than 80% of the lesions disappeared in 18 patients. Decreased dermal thickness	No	Kerscher et al. [47]
Prospective uncontrolled study	10	Localized scleroderma	UVA1	20 J/cm^2 4 times a week	480	6 weeks	24	Lesions started to regress after 15 treatments. More than 80% of lesions regressed after 24 treatments	No	Kerscher et al. [43]
Prospective uncontrolled study	34	Localized scleroderma	UVA1	6 patients were treated with medium dose and 28 were treated with high dose. Both groups treated 3 times a week	5234 ± 3611	Unavailable	Unavailable	Patients reported an improvement of at least 25%	Unknown	Jacobe et al. [48]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Prospective uncontrolled study	17	Localized scleroderma	UVA1	Ten patients with high dose 130 J/cm^2. Seven patients with low-dose 20 J/cm^2. Patients treated 4 times a week during 5 weeks, then twice a week for 5 weeks	Low dose 600, high dose 3900	10 weeks	30	Softening of skin lesions in all high dose patients, and complete clearance in four of ten patients. Three months after treatment, nine of ten patients have clinical stability. Two of seven patients in the low-dose group reported improvement or had clinical signs of improvement. Skin thickness by ultrasound was reduced in all patients	No	Stege et al. [72]
Prospective uncontrolled study	13	Localized scleroderma	UVA1	Unavailable	750–1250	3–5 weeks	20.8 ± 4.0	Modified Rodnan score improvement. Reduction of skin thickness in 11 patients. Skin elasticity increased in ten patients	No	Andres et al. [73]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Prospective uncontrolled study	7	Morphea	UVA1	30 J/cm^2 3 times a week	900	10 weeks	30	Clinical improvement in induration of all patients. One patient reported improved elbow joint mobility. After a 6–9-month follow-up, there was clinical stability	No	Camacho et al. [20]
Prospective uncontrolled study	3	Morphea	UVA1	20 J/cm^2 4 times a week for 6 weeks, then once a week for 6 weeks	600	12 weeks	30	Resolution of sclerotic plaques in all patients. No signs of recurrence after 2 year follow-up	No	Gruss et al. [74]
Prospective uncontrolled study	19	Childhood morphea	UVA1	20 J/cm^2 4 times a week	800	10 weeks	40	Mean clinical score (skin inspection and palpation every week) improved–relative reduction of 67.1%. The treatment outcome remained stable for at least 1 year in all patients	Topical calcipotriol 0.005% twice a day	Kreuter et al. [64]
Prospective uncontrolled study	47	Morphea	UVA1	Six were treated with medium dose (50–60 J) and 41 were treated with high dose (120 J) UVA1; 3 times a week	5329 ± 4398	Unavailable	Unavailable	Patients reported an improvement of at least 25%	May/may not	Jacobe et al. [48]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Prospective uncontrolled study	30	Morphea	UVA1	3 times a week, 21 cases of morphea were treated with UVA 20 J/cm^2 for 20 sessions. Nine cases of morphea received 10 J/cm^2	High dose 400, low dose 200	6 + weeks	20	No difference in improvement between the 10 and 20 J/cm^2 group. Overall, 18 patients reported softening of the skin lesions. Twelve patients reported moderate improvement, four patients reported good improvement, and two patients reported very good improvement	No	El-Mofty et al. [9]
Prospective uncontrolled study	49/M	Morphea	UVA1	70 J/cm^2 5 times a week	1400	4 weeks	Unavailable	Durometer scores improved significantly during first 3 weeks, and borderline significantly the last week. Improvements were maintained at 4-month follow-up	No	Kroft et al. [44]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Prospective uncontrolled study	4	Systemic sclerosis	UVA1	60 J/cm^2 5 times a week	510–1740	Unavailable	9–29	Skin elasticity before treatment was improved as assessed by cutometer. The mean thermography and joint passive range of motion both increased after treatment	Unknown	Morita et al. [75]
Prospective uncontrolled study	83	Morphea (63), systemic sclerosis (15)	UVA	5, 10, and 20 J/cm^2	100, 200, 400	6 + weeks	20	Clinical improvement. No difference between the groups	No	El-Mofty et al. [51]
Prospective uncontrolled study	12	Morphea	UVA	20 J/cm^2 3 times a week	400	6 + weeks	20	90% cure of early lesions, 50% cure of "late" lesions	No	El-Mofty et al. [12]
Prospective uncontrolled study	11	Scleroderma	Oral + topical PUVA, Narrowband UVB	Unavailable	Unavailable	Unavailable	Mean 10	Most lesions had a decreased dermal thickness on ultrasound at 12 weeks	Unknown	Buense et al. [56]
Prospective uncontrolled study	12	Systemic sclerosis	PUVA, bath or oral	Unavailable	Median cumulative exposure 68.25	Unavailable	Median 24	Improvement in 11 patients	No	Usmani et al. [29]
Prospective uncontrolled study	4	Localized scleroderma	PUVA cream	4 times a week. Maximum single dose of 3.5 J/cm^2	89.5 (range 67.5–121)	Unavailable	30	Decrease in dermal thickening	No	Grundmann-Kollmann et al. [76]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Prospective uncontrolled study	4	Systemic sclerosis	PUVA oral	3 times a week for 10 weeks	Mean of 70.5 (range 50.5–92.0)	10 weeks	30	Improvement of skin, joint mobility, grip strength, and skin thickness in three of four patients	No	Hofer and Soyer [77]
Prospective uncontrolled study	17	Localized scleroderma	PUVA bath	0.2–0.5 J/cm^2 up to 1.2–3.5 J/cm^2 per treatment. First 20 treatments 4 times a week, twice a week for the following ten treatments, and once a week for the last four treatments	Mean UVA dose of 41.5 (range 15.7–64.3)	15 weeks	25–35	Clinical and ultrasound improvement noted in 13 patients. In most patients, softening of sclerotic lesions was noted at the 15th treatment. Patients were followed up regularly for more than a year; there were two cases of recurrence	No	Kerscher et al. [54]
Prospective uncontrolled study	5	Localized scleroderma	3% ALA + PDT (10 J/cm^2)	Once or twice weekly	Unavailable	3–6 months	25–43	A reduction of skin hardness and pruritus in lesions. In two patients, joint mobility was improved. One control plaque was untreated, and showed no signs of regression	No	Karrer et al. [78]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Retrospective study	8	Localized and systemic scleroderma	UVA1	15 J/cm^2 3 times a week. Then increased up to maximum dose of 30 J/cm^2 for seven patients and 40 J/cm^2 for three patients	Range 529–1029.4	Unavailable	Range 26–32	Modified Rodnan skin score percentage improvement was 57%. One in remission for 12 months, four were in remission for 24 months	One patient on mycophenolate mofetil, one patient on pulsed cyclophosphamide, methotrexate, and ciclosporin. One patient on azathioprine	Rose et al. [79]
Retrospective study	17	Localized scleroderma	UVA1	5 times weekly	750–1400	3–6 weeks	19.3 ± 3.8	Fourteen patients reported clinical improvement	No	Andres et al. [73]
Retrospective study	3	Systemic scleroderma	UVA1	Mean dose of 29.5 J/cm^2	Mean cumulative dose 1160 (range 660–1695)	Unavailable	Mean 26	Patients showed an improvement in the modified Rodnan scoring system. One patient had complete remission	Unknown	Pereira et al. [80]
Retrospective study	18	Morphea	UVA1	Mean dose of 31 J/cm^2	Mean cumulative dose of 1662 (range 310–4270)	Unavailable	Mean 33	77.8% had marked improvement, 11.1% had moderate improvement, 5.6% had slight improvement, and 5.6% had no improvement	Unknown	Pereira et al. [80]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case series	8	Systemic sclerosis	UVA1	30 J/cm^2 4 times a week for 8 weeks, then 3 times a week for 6 weeks	1500	14 weeks	50	Modified Rodnan skin score improved after treatment. Seven patients experienced improvement in sclerosis in 6 months. Resulting in marked softening of skin and clinically significant improvement including finger mobility	Unknown	Von Kobyletzki et al. [81]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case series	37	Morphea	UVA1	Treatments varied 2–5 times a week; 13 patients received 20 J/cm^2 of UVA1. Eleven patients received 50–60 J/cm^2 UVA1. Ten patients received medium-dose increased to high-dose 50–120 J/cm^2. One patient received low-dose, followed by medium-dose UVA1 (60 treatments), and two patients received low-dose increased to high-dose UVA1 (mean 23.5 treatments, mean cumulative dose 2090 J/cm^2)	20 J/cm^2 group mean 683.9, 50–60 J/cm^2 group mean 1468.5, 50–120 J/cm^2 group 2560	Ranged	20 J/cm^2 group 11–78 (mean 35), 50–60 J/cm^2 group 13–36 (mean 27.8), 50–120 J/cm^2 group 9–41 (mean 20.7)	26–100% improvement was found in 46.2% of patients treated with low-dose UVA1 phototherapy compared with 72.7% and 70% treated with medium and medium to high-dose UVA1, respectively	Unknown	Tuchinda et al. [85]
Case series	6	Morphea/SS/CREST	UVA1	Unavailable	Unavailable	Unavailable	30–60	Dermal thickness had decreased in five patients	No	Oikarinen and Knuutinen [82]
Case series	54	Scleroderma	UVA1	59.81 ± 27.40 J/cm^2	1203.15 ± 1133.95	Unavailable	21.10 ± 13.1	Clinical improvement was noted by physician in 79.6% of patients	Unknown	Rombold et al. [83]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case series	8	Localized scleroderma	UVA1	50 J/cm^2 5 times a week	2000	8 weeks	40	The modified skin score improved in all patients	Unknown	Kreuter et al. [84]
Case series	14	Localized scleroderma	UVA1	20 J/cm^2 5 times a week	800	8 weeks	40	The modified skin score improved in all patients	Unknown	Kreuter et al. [6]
Case series	12	Systemic sclerosis/ CREST	UVA1	Treatments varied 2–5 times a week	Unavailable	Unavailable	Unavailable	41.7% of patients experienced 51–100% improvement	Unknown	Tuchinda et al. [85]
Case series	2	Localized scleroderma	PUVA	0.2 J/cm^2 up to a maximum dose of 20 J/cm^2, 4 times a week over 5 weeks, then 2 times per week for an additional 5 weeks	Unavailable	10 weeks	30	Skin lesions cleared, ultrasound revealed normal ratio of treated skin thickness to uninvolved skin	No	Kerscher et al. [42]
Case series	4	Localized scleroderma	PUVA	The initial daily UVA doses were 1–1.5 J/cm^2	Range 242–405.5	12 weeks of PUVA daily, then maintenance PUVA treatment given twice or once per week for 3 months	57–72	The modified skin score improved after therapy	Acitretin	Ozdemir et al. [86]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case series	13	Localized morphea	PUVA	Two patients treated with bath PUVA and all other patients with oral PUVA. Treatment was given twice weekly.	Mean 135 (range 42–244)	7–15 weeks	14–30	Mean reduction of 62.9% in modified Rodnan score	Five patients had concurrent therapies	Usmani et al. [30]
Case series	23	Localized morphea	PUVA	Patients were treated with a weekly regimen of bath immersion in 0.2 mg/l water solution of 8-methoxypsoralen, followed by irradiation with UVA 3 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	Mean 115	Unavailable	Mean 71	Eleven patients (39%) showed complete remission. Partial response in 14 patients (50%). In the complete remission group; no recurrence was observed in seven patients after a mean follow-up period of 7 months (range 1–18 months)	No	Pavlotsky et al. [87]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case series	4	Linear and generalized morphea	PUVA oral	3 times a week. UVA dose ranged from 42.5–94 J/cm^2. After improvement (loss of induration), then maintenance treatment weekly and biweekly was given	Unavailable	Unavailable	44–88	Number of treatments to show clearance ranged from 44–88. UVA dose to clear lesions ranged from 358–838.5 J/cm^2	No	Morison et al. [88]
Case series	7	Six with localized scleroderma, one with systemic scleroderma	PUVA topical	4 times a week. Highest UVA dose per treatment mean was 3.5 J/cm^2	Mean 53.5	Unavailable	Mean 25 (range 14–39)	Marked improvement in softening of sclerotic plaques in all patients	Unknown	Pasic et al. [89]
Case series	10	Scleroderma	Water-filtered infrared A plus visible light treatment	Total irradiance was 180–200 mW/cm^2. Treatment was done 2–5 times a week.	Unavailable	Unavailable	16–48	Seven patients reported improvement, follow-up was 1–7.5 years after treatment	Unknown	Von Felbert et al. [90]
Case report	16/F	Nodular morphea	PUVA topical	Unavailable	2.32	Unavailable	Unavailable	Slight improvement of regression of nodules. The patient was lost to follow-up	Penicillin G for 10 days	Kauer et al. [91]
Case report	12/F	Localized scleroderma	PUVA topical	0.2–4.0 J/cm^2 to total dose of 62.8 J/cm^2. Initiated for 10 days, then subsequently once a week for 4 months	Unavailable	4 months	Unavailable	Rodnan score + range of motion of affected joint improvement	Oral prednisolone	Uchiyama et al. [92]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case report	43/F	Systemic sclerosis	PUVA topical	UVA dose started at 0.6 J/cm^2 then gradually increased to 2.4 J/cm^2. Treatments were given once a week	167.3	Unavailable	107	Significant softening of the affected areas, and normalization of skin temperature	No	Morita et al. [93]
Case report	58/M	Systemic sclerosis	PUVA topical	0.10 J/cm^2 3 times a week, increasing to a maximum single dose of 8 J/cm^2	272.3	29 weeks	Unavailable	Decreased necrosis in fingers, reduced symptoms of swelling, erosions, crusting, and induration in fingers. Follow-up at 5 months showed slight swelling of both hands without new fingertip lesions	Sildenafil 150 mg daily	Mohanna et al. [94]
Case report	65/F	Generalized morphea	PUVA	0.4 J/cm^2 3 times a week	Unavailable	8 weeks	24	Hand closure and skin sclerosis index. Score went from three to one. Disease free after 2-year follow-up with weekly maintenance therapy	No	Kanekura et al. [95]
Case report	61/M	Progressive systemic sclerosis	PUVA	0.25 J/cm^2 4 times a week. Total dose of 5 J/cm^2.	Unavailable	5 weeks	20	Hand closure and skin sclerosis index improved from 4 to 1	No	Kanekura et al. [95]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case report	42/M	Progressive systemic sclerosis	PUVA	PUVA 0.4 J/cm^2 6 times a week. Total dose of 7.2 J/cm^2.	Unavailable	3 weeks	18	Hand closure and skin sclerosis index improved from 3 to 0	No	Kanekura et al. [95]
Case report	32/F	Progressive systemic sclerosis	PUVA	PUVA 0.25 J/cm^2 twice a week. Total dose of 3.5 J/cm^2.	Unavailable	7 weeks	14	Skin sclerosis index improved from 3 to 1	No	Kanekura et al. [95]
Case report	80/M	Localized scleroderma	PUVA	Initial 3 times weekly UVA dose of 4 J/cm^2, which was gradually increased, weekly, to a maximal single dose of 18 J/cm^2	Unavailable	11 months	127	After 9 months, the skin plaques were softening. Treatment was then continued twice every week for another 2 months. After 127 treatments, there was clearance of the lesion. Clinical stability remained after 8 months	No	Garcia-Bustinduy et al. [96]
Case report	7/F	Pansclerotic morphea	PUVA	0.6 mg/kg for 4 times a week. Dose started at 0.5 J/cm^2 and was gradually increased to 2.0 J/cm^2 over 2 months	Unavailable	10 weeks	Unavailable	After 10 weeks her condition worsened with spread of disease, ulceration and contraction deformities	Penicillamine 20 mg/kg/day	Todd et al. [97]
Case report	56/F	Systemic sclerosis	PUVA	3 times a week. Then once a week for maintenance therapy once improvement seen	483	19 months	Unavailable	100% improvement (patient self-evaluation)	No	Baum et al. [98]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case report	66/M	Systemic sclerosis	PUVA	3 times a week then once a week for maintenance therapy once improvement seen	20	1.5 months	Unavailable	>70% response rate (patient self-evaluation)	No	Baum et al. [98]
Case report	27/M	Generalized morphea	PUVA	3 times a week, then once a week for maintenance therapy once improvement seen	288	10 months	Unavailable	>70% response rate (patient self-evaluation)	No	Baum et al. [98]
Case report	40/M	Diffuse morphea	PUVA	Twice weekly at 5 J/session	115	23 months	N/A	Increased mobility, reduced progression of plaques and sclerosis	Cyclosporine for 2 years. Then transitioned to mycophenolate mofetil for 1 year and phototherapy discontinued	Rose and Goodfield [99]
Case series	2/F	En coup de sabre	PUVA topical	Initial dose was 0.3 J/cm^2. 3 times a week. And UVA dose was increased after 3 days with 0.2 J/cm^2	71	Unavailable	40	Softening of lesions after 90 days	Topical calcipotriol twice a day	Gambichler et al. [100]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case report	64/F	Disseminated scleroderma	PUVA	Initial dose of 0.76 J/cm^2, maximum tolerated dose 10 J/cm^2. The first 28 treatments were conducted 4 times a week. Then twice a week during the following ten treatments	Unavailable	Unavailable	Unavailable	The skin sclerosis index was a four before therapy, and a one or two after therapy. Improvement was also noted from infrared thermography before and after treatment. No recurrence approximately 2 years later	No	Aragane et al. [101]
Case report	27/F	Localized scleroderma	PUVA	0.4 J/cm^2 up to a total dose of 5 J/cm^2	Unavailable	Unavailable	Unavailable	Clinical improvement observed with reduced hardness. No recurrence after 20-month follow-up	No	Yamaguchi et al. [102]
Case report	12/M	Pansclerotic morphea	PUVA	Unavailable	Unavailable	Unavailable	Unavailable	Improvement in skin and ulceration that lasted 1.5 years	Unknown	Wollina et al. [103]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case report	40/F	Post-radiation morphea	PUVA	Twice weekly for 22 treatments (107.8 J/cm^2). Patient subsequently had 47 treatments of UVA1. This was started at medium dose (35 treatments at 50 J/cm^2) and progressed to high dose (12 treatments at 80 J/cm^2	2633.6	Unavailable	69	Patient reported better improvement with high-dose UVA1 then medium-dose UVA1	No	Lim et al. [104]
Case report	8/F	Pansclerotic morphea	PUVA	UVA dose 0.5 J/cm^2, which was gradually increased to 1.8 J/cm^2 during the next 2 months using four irradiations weekly. She was maintained on two treatments per week for 6 months	Unavailable	Unavailable	68	Softening of skin was observed within 1st month. Improved healing of ulcers and joint mobility. No evidence of relapse after a 14 month follow-up	No	Scharffetter-Kochanek et al. [105]
Case report	72/F	Traumatic scleroderma	UVA1	70 J/cm^2 5 times a week	1400	4 weeks	Unavailable	Durometer scores improved significantly during first 3 weeks and borderline significantly the last week. Remission after >31 months	No	Kroft et al. [44]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case report	8/F	Pansclerotic morphea	UVA1	5 J/cm^2 3 times a week. Then the doses were increased gradually to a maximum of 20 J/cm^2	480	Unavailable	Unavailable	Improvement was seen at 10–12 sessions. Softening of sclerotic lesions. Hypopigmented areas began to have pigmentation	No	Yildirim et al. [106]
Case report	45/F	Systemic sclerosis	UVA1	50 J/cm^2 2–3 times a week	2222	Unavailable	40	Microstomia had improved; all of her sclerotic lesions were softer. She could articulate words normally and had reduced furrowing around the mouth	Unknown	Tewari et al. [107]
Case report	19/F	Scleroderma	UVA1	20 J/cm^2 5 times a week	Unavailable	Unavailable	Unavailable	Softening of fibrotic skin, improved mobility of joints	Methylprednisolone, methotrexate, pentoxiflyin, asprin, and piascledine	Forsea, et al. [108]
Case report	71/M	Pansclerotic morphea	UVA1	30 J/cm^2 3 times a week	1350	15 weeks	45	Softening, increased elasticity	No	Herzinger et al. [109]
Case report	16/M	Pansclerotic morphea	UVA1	20 J/cm^2 4 times a week	640	8 weeks	32	Within 3 weeks there was softening of the skin on the trunk and head. There was an increase in joint mobility. Therapeutic effects lasted for 6 months	No	Gruss et al. [110]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case report	42/F	Progressive systemic sclerosis	UVA	20 J/cm^2 3 times a week	Unavailable	Unavailable	Unavailable	Softening of facial sclerosis softening and decreased pruritus at 3 week. At 2 months, lesions on her abdomen and upper legs softened	Unknown	Steger and Matthews [111]
Case report	11/M	Localized scleroderma	UVA	20 J/cm^2 4 times a week for 6 weeks, then once weekly for 6 weeks	Unavailable	12 weeks	Unavailable	Lesion cleared with softening, tanning, and thinning of the skin. At 3-month follow-up the lesion is still in remission	No	Steger and Matthews [111]
Case report	32/F	En coup de sabre	Narrowband UVB	3 times a week	Unavailable	24 weeks	N/A	Prevented progression of disease. Patient remained stable for a year off of UVB, but then disease recurred and had to resume UVB and oral colchicine	No	Brownell et al. [112]
Case report	22/F	Secondary cicatricial alopecia/ scleroderma	Non-ablative fractional laser	Fluence of 6–8 mJ and a density of 300 spots/cm^2/pass. For ablative fractional laser, a fluence of 30–50 mJ was delivered to the affected area 150 spots/cm^2	Unavailable	Non-ablative/ ablative laser with a 4 week interval between treatments	15	Eight treatments before clinical improvement observed. 26–50% clinical improvement assessment	Topical calcipotriol cream 0.005%	Cho et al. [113]

Table 1 continued

Study (clinical trial, case report, etc.)	Patients[a]	Disease	Treatment modality	Treatment duration	Cumulative dose (J/cm^2)	Duration of phototherapy	Total treatments	Improvement outcome (clinical, radiologic)	Was the patient(s) reported to be on another treatment concurrently?	Author
Case report	34/M	Secondary cicatricial alopecia/ scleroderma	Non-ablative fractional laser	Fluence of 6–8 mJ and a density of 300 spots/cm^2/pass. For ablative fractional laser, a fluence of 30–50 mJ was delivered to the affected area 150 spots/cm^2	Unavailable	Non-ablative/ ablative laser with a 4 week interval between treatments	20	Five treatments before clinical improvement observed. 26–50% clinical improvement	Topical calcipotriol cream 0.005%	Cho et al [113]
Case report	41/F	Morphea	585-nm long pulsed (1.5 ms) dye laser	Four treatments, 2 weeks between treatments. 5 J/cm^2 fluence	Unavailable	8 weeks	4	Softening of the plaque noted after each treatment. 6 months after 1st treatment, there was clinical stability	No	Eisen and Alster [114]

ALA aminolevulinic acid, *F* female, *M* male, *PDT* photodynamic therapy, *PUVA* psoralen and ultraviolet, *UVA* ultraviolet A, *UVA1* ultraviolet A1, *UVB* ultraviolet B

[a] Total number, if case report age/gender

Improved softness of skin lesions assessed by palpation was reported as early as three treatments and as late as ten treatments. Longer standing lesions did not respond as well as therapy. As a control, some lesions in the same patients were covered to prevent UVA1 exposure during treatment, and less softening was reported in these covered lesions. After a 1-year follow-up, only two patients reported a reappearance of lesions. Lesions on skin creases or over joints did not respond as well to therapy [12].

PUVA

A 15-year-old male with scleroderma with indurated patches on the trunk and joint restrictions was recalcitrant to hydroxychloroquine, prednisolone, and methotrexate [53]. PUVA at a dose of 0.6 mg/kg twice weekly was subsequently added for 20 sessions over 10 weeks at a cumulative dose of 25.4 J/cm^2. Methotrexate was subsequently administered for 7 months. After this period, he was able to make a full fist and increase to a normal range of motion in the ankles; his skin was less indurated and has maintained clinical stability for 2 years [53]. Table 1 lists additional PUVA treatment studies in scleroderma/morphea. PUVA's effects may be due to local effects rather than systemic effects, as Kerscher et al. [54] noted that residual sclerotic lesions remained in patients in areas hidden from UVA exposure such as parts of the elbow in patients undergoing PUVA.

UVB

A 43-year-old female with radiation-induced morphea was given acitretin daily and UVB three times a week [55]. Two months afterwards there was less induration of her plaque, decreased tenderness, and improved range of motion of the left arm [55]. Eleven patients that underwent phototherapy treatment (seven treated with PUVA and four treated with narrowband UVB) for an average of ten sessions experienced a 48% improvement of their localized scleroderma as indicated by a clinical pinching test [56]. Additionally, the ultrasound examination showed a dermal thickness reduction ranging from 20% to 100% [56]. There was no correlation between the type of phototherapy and clinical response rate [56]. Additional studies on UVB therapies are included in Table 1.

Targeted Phototherapy

Targeted phototherapy is a modality that spares non-lesional skin and is able to deliver a higher fluence. A patient with limited scleroderma and elbow mobility restrictions was treated 2–3 times a week for 13 weeks with 940-nm low-level light therapy with millisecond pulsing and continuous wave modes. Using a sequential pulsing dose on one elbow and continuous wave mode on the other, better results were seen with the pulsing mode showing improvement in skin thickness [57].

Five patients with a total of 11 plaques were treated with a 308-nm monochromatic excimer laser for 4 weeks at a power density of 48 mW/cm^2 with a maximum irradiation area of 512 cm^2 [58]. The mean number of treatments was seven, and the dose per session was 1.5 J/cm^2. The mean total dose was 10 J/cm^2. After 4 weeks, 3 out of 5 patients experienced marked improvement with residual hyperpigmentation [58].

A 27-year-old Hispanic female had a contracture of her knee with sclerotic bands

on her left lower leg, ankle, and foot that were recalcitrant to methotrexate, UVA1, topical calcipotriene, intralesional triamcinolone acetonide, and physical therapy [59]. The patient was treated with a single treatment of 10.6 μm carbon dioxide laser with a 50 J/cm^2 pulse energy, while remaining on methotrexate and topical agents [59]. After 1 week, she experienced an increase in range of motion. After 4 months of follow-up, there was softening of her contracture, and she regained full plantar flexion of her left foot. After a 1-year follow-up, she maintained a full range of motion [59].

Four patients with microstomia and SSc were treated with intense pulsed light. 530–570 mm, 11–14 J/cm^2; 10–14 pulse durations was used for the patients every 4 weeks [60]. Patients were followed for 4 months. Three patients experienced an increased interincisal distance of ~1 mm per treatment [60]. One patient did not have improved interincisal distance, but did note activities of daily living became easier. One patient did report recurrence of the stiffness after 3 weeks [60]. Table 1 lists additional reports of targeted phototherapy.

Photodynamic Therapy

In six patients, 20% 5-ALA was applied under occlusion to areas of morphea for 5 h. A band width of 570–670 nm, peak 635-nm light was given. A dose of 25 J/cm^2 was given for a total of six weekly treatments. In four of the patients there was clinical improvement as determined by skin scoring, although only one of these patients showed histologic evidence of improvement. The side effects patients reported included burning sensation, dryness, erythema, pigmentation, and pruritus [61]. Table 1 lists an additional study.

DISCUSSION

There are mostly care reports of UVA1, UVB, PUVA (bath and topical), and targeted phototherapies in cases of scleroderma. UVA1 appears to be the most efficacious, but it is also the most studied. There are not many studies on high-dose UVA1, and this needs to be investigated further to assess the optimal dose of UVA to use in scleroderma. Additionally, longer term studies are needed to study the long-term outcome and safety of these treatments. A similar literature review study delineated UVA and PUVA's efficacy and safety in the context of SSc, localized scleroderma, extragenital lichen sclerosus et atrophicus, sclerodermoid graft-versus-host disease, lupus erythematosus, and other rare sclerotic diseases [62]. This review also asserts that there need to be more rigorous studies to help establish a guide for UVA's indications as well as its efficacy compared to other conventional medical therapies [62].

Based on the studies available, a reasonable regimen is UVA1 therapy 20–50 J/cm^2 3–4 times a week for a total of 30 treatments. There were no double-blind, placebo-controlled trials available, and only three controlled trials. Adverse effects thus far do not correlate with the intensity of therapy. The side effects noted in scleroderma phototherapy include fatigue, a burning sensation, hyperpigmentation, pruritus, erythema, edema, headaches, gastrointestinal upset, and joint and muscle pain. Additionally, one patient undergoing UVA1 phototherapy for disseminated morphea developed bullous pemphigoid after 29 treatments [63]. The long-term effects of UVA1 on patients have not reported skin cancer [64]. Phototherapy should be safe in pregnancy [65] although folate may need to be supplemented as reports show that UVB and solar UV radiation

may cause photodegradation [66, 67]. Multiple treatments, as well as limited availability of in-office phototherapy, are barriers to treatment. In a review by Bielsa Marsol [68], it was pointed out that most of the studies for UVA1 therapy were performed in countries where patients are predominantly Fitzpatrick types I–III, although, as noted earlier, the Fitzpatrick skin type thus far has not been shown to have an impact on therapy. Phototherapy may not be as useful for sclerotic diseases that affect structures deeper than the dermis.

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REFERENCES

1. Morgan MC, Rashid RM. The effect of phototherapy on neutrophils. Int Immunopharmacol. 2009;9(4):383–8.
2. Kerr HA, Lim HW. Photobiology and phototherapeutics. Adv Dermatol. 2003;19:11–36.
3. Wlaschek M, Briviba K, Stricklin GP, Sies H, Scharffetter-Kochanek K. Singlet oxygen may mediate the ultraviolet A-induced synthesis of interstitial collagenase. J Invest Dermatol. 1995;104(2):194–8.
4. Amat A, Rigau J, Waynant RW, Ilev IK, Tomas J, Anders JJ. Modification of the intrinsic fluorescence and the biochemical behavior of ATP after irradiation with visible and near-infrared laser light. J Photochem Photobiol B. 2005;81(1):26–32.
5. Gruss C, Reed JA, Altmeyer P, McNutt NS, Kerscher M. Induction of interstitial collagenase (MMP-1) by UVA-1 phototherapy in morphea fibroblasts. Lancet. 1997;350(9087):1295–6.
6. Kreuter A, Hyun J, Skrygan M, Sommer A, Bastian A, Altmeyer P, Gambichler T. Ultraviolet Al-induced downregulation of human beta-defensins and interleukin-6 and interleukin-8 correlates with clinical improvement in localized scleroderma. Br J Dermatol. 2006;155(3):600–7.
7. Nisar MF, Parsons KS, Bian CX, Zhong JL. UVA irradiation induced heme oxygenase-1: a novel phototherapy for morphea. Photochem Photobiol. 2015;91(1):210–20.
8. Yin L, Yamauchi R, Tsuji T, Krutmann J, Morita A. The expression of matrix metalloproteinase-1 mRNA induced by ultraviolet A1 (340–400 nm) is phototherapy relevant to the glutathione (GSH) content in skin fibroblasts of systemic sclerosis. J Dermatol. 2003;30(3):173–80.
9. El-Mofty M, Mostafa W, Esmat S, Youssef R, Bousseila M, Nagi N, Shaker O, Abouzeid A. Suggested mechanisms of action of UVA phototherapy in morphea: a molecular study. Photodermatol Photoimmunol Photomed. 2004;20(2):93–100.
10. Hayashi S, Ikeda M, Kitamura Y, Hamasaki Y, Hatamochi A. UVA irradiation following treatment with topical 8-methoxypsoralen improves

bleomycin-induced scleroderma in a mouse model, by reducing the collagen content and collagen gene expression levels in the skin. J Dermatol Sci. 2012;67(1):20–5.

11. Ju M, Chen K, Chang B, Gu H. UVA1 irradiation inhibits fibroblast proliferation and alleviates pathological changes of scleroderma in a mouse model. J Biomed Res. 2012;26(2):135–42.

12. El-Mofty M, Zaher H, Bosseila M, Yousef R, Saad B. Low-dose broad-band UVA in morphea using a new method for evaluation. Photodermatol Photoimmunol Photomed. 2000;16(2):43–9.

13. Gambichler T, Skrygan M, Tomi NS, Altmeyer P, Kreuter A. Differential expression of decorin in localized scleroderma following ultraviolet-A1 irradiation. J Am Acad Dermatol. 2007;56(6):956–9.

14. Sawada H, Isogai Z, Morita A. Altered decorin expression of systemic sclerosis by UVA1 (340–400 nm) phototherapy: immunohistochemical analysis of 3 cases. BMC Dermatol. 2003;3:2.

15. Chakraborty AK, Funasaka Y, Slominski A, Bolognia J, Sodi S, Ichihashi M, Pawelek JM. UV light and MSH receptors. Ann N Y Acad Sci. 1999;885:100–16.

16. Kiss M, Wlaschek M, Brenneisen P, Michel G, Hommel C, Lange TS, Peus D, Kemeny L, Dobozy A, Scharffetter-Kochanek K. Alpha-melanocyte stimulating hormone induces collagenase/matrix metalloproteinase-1 in human dermal fibroblasts. Biol Chem Hoppe Seyler. 1995;376(7):425–30.

17. Kreuter A, Breuckmann F, Uhle A, Brockmeyer N, Von Kobyletzki G, Freitag M, Stuecker M, Hoffmann K, Gambichler T, Altmeyer P. Low-dose UVA1 phototherapy in systemic sclerosis: effects on acrosclerosis. J Am Acad Dermatol. 2004;50(5):740–7.

18. Wang F, Garza LA, Cho S, Kafi R, Hammerberg C, Quan T, Hamilton T, Mayes M, Ratanatharathorn V, Voorhees JJ, et al. Effect of increased pigmentation on the antifibrotic response of human skin to UV-A1 phototherapy. Arch Dermatol. 2008;144(7):851–8.

19. De Rie MA, Bos JD. Photochemotherapy for systemic and localized scleroderma. J Am Acad Dermatol. 2000;43(4):725–6.

20. Camacho NR, Sanchez JE, Martin RF, Gonzalez JR, Sanchez JL. Medium-dose UVA1 phototherapy in localized scleroderma and its effect in CD34-positive dendritic cells. J Am Acad Dermatol. 2001;45(5):697–9.

21. Vielhaber G, Grether-Beck S, Koch O, Johncock W, Krutmann J. Sunscreens with an absorption maximum of > or = 360 nm provide optimal protection against UVA1-induced expression of matrix metalloproteinase-1, interleukin-1, and interleukin-6 in human dermal fibroblasts. Photochem Photobiol Sci. 2006;5(3):275–82.

22. Nakamura T, Matsushima M, Hayashi Y, Shibasaki M, Imaizumi K, Hashimoto N, Shimokata K, Hasegawa Y, Kawabe T. Attenuation of transforming growth factor-β-stimulated collagen production in fibroblasts by quercetin-induced heme oxygenase-1. Am J Respir Cell Mol Biol. 2011;44(5):614–20.

23. Breuckmann F, Stuecker M, Altmeyer P, Kreuter A. Modulation of endothelial dysfunction and apoptosis: UVA1-mediated skin improvement in systemic sclerosis. Arch Dermatol Res. 2004;296(5):235–9.

24. Breuckmann F, Appelhans C, Bastian A, Stuecker M, Altmeyer P, Kreuter A. UVA1-induced decrease in dermal neuron-specific enolase (NSE) in acrosclerosis. Arch Dermatol Res. 2004;296(4):182–4.

25. Bulat V, Situm M, Dediol I, Ljubicic I, Bradic L. The mechanisms of action of phototherapy in the treatment of the most common dermatoses. Coll Antropol. 2011;35(Suppl 2):147–51.

26. Brenneisen P, Wlaschek M, Wenk J, Blaudschun R, Hinrichs R, Dissemond J, Krieg T, Scharffetter-Kochanek K. Ultraviolet-B induction of interstitial collagenase and stromelyin-1 occurs in human dermal fibroblasts via an autocrine interleukin-6-dependent loop. FEBS Lett. 1999;449(1):36–40.

27. Fagot D, Asselineau D, Bernerd F. Direct role of human dermal fibroblasts and indirect participation of epidermal keratinocytes in MMP-1 production after UV-B irradiation. Arch Dermatol Res. 2002;293(11):576–83.

28. Kondo S, Kooshesh F, Sauder DN. Penetration of keratinocyte-derived cytokines into basement membrane. J Cell Physiol. 1997;171(2):190–5.

29. Usmani N, Murphy A, Veale D, Goulden V, Goodfield M. Photochemotherapy for systemic sclerosis: effect on clinical and molecular markers. Clin Exp Dermatol. 2010;35(6):608–13.

30. Usmani N, Murphy A, Veale D, Goulden V, Goodfield M. Photochemotherapy for localized morphoea: effect on clinical and molecular markers. Clin Exp Dermatol. 2008;33(6):698–704.

31. Inoue T, Yamaoka T, Murota H, Yokomi A, Tanemura A, Igawa K, Tani M, Katayama I. Effective oral psoralen plus ultraviolet A therapy for digital ulcers with revascularization in systemic sclerosis. Acta Derm Venereol. 2014;94(2):250–1.

32. Brinckmann J, Neess CM, Gaber Y, Sobhi H, Notbohm H, Hunzelmann N, Fietzek PP, Muller PK, Risteli J, Gebker R, et al. Different pattern of collagen cross-links in two sclerotic skin diseases: lipodermatosclerosis and circumscribed scleroderma. J Invest Dermatol. 2001;117(2):269–73.

33. Sakakibara N, Sugano S, Morita A. Ultrastructural changes induced in cutaneous collagen by ultraviolet-A1 and psoralen plus ultraviolet A therapy in systemic sclerosis. J Dermatol. 2008;35(2):63–9.

34. Karrer S, Bosserhoff AK, Weiderer P, Landthaler M, Szeimies RM. Influence of 5-aminolevulinic acid and red light on collagen metabolism of human dermal fibroblasts. J Invest Dermatol. 2003;120(2):325–31.

35. Karrer S, Bosserhoff AK, Weiderer P, Landthaler M, Szeimies RM. Keratinocyte-derived cytokines after photodynamic therapy and their paracrine induction of matrix metalloproteinases in fibroblasts. Br J Dermatol. 2004;151(4):776–83.

36. Liebmann J, Born M, Kolb-Bachofen V. Blue-light irradiation regulates proliferation and differentiation in human skin cells. J Invest Dermatol. 2010;130(1):259–69.

37. Casara C, Eidt L, Cunha V. Prevalence study of dermatoses referred to the phototherapy unit at the Dermatology Service of the Clinics Hospital of Porto Alegre, RS, Brazil. An Bras Dermatol. 2013;88(2):211–5.

38. Warburton KL, McPhee MJ, Savage LJ, Honan AE, Montgomery R, Ghazavi M, Torley D, Shams K, Ingram JR. Management of morphoea: results of a national survey of UK clinicians. Br J Dermatol. 2014;171(5):1243–5.

39. Johnson W, Jacobe H. Morphea in adults and children cohort II: patients with morphea experience delay in diagnosis and large variation in treatment. J Am Acad Dermatol. 2012;67(5):881–9.

40. Hawley DP, Pain CE, Baildam EM, Murphy R, Taylor AE, Foster HE. United Kingdom survey of current management of juvenile localized scleroderma. Rheumatology (Oxford). 2014;53(10):1849–54.

41. Strickland N, Patel G, Strickland A, Jacobe H. Attitudes and trends in the treatment of morphea: a national survey. J Am Acad Dermatol. 2015;72(4):727–8.

42. Kerscher M, Volkenandt M, Meurer M, Lehmann P, Plewig G, Röcken M. Treatment of localised scleroderma with PUVA bath photochemotherapy. Lancet. 1994;343(8907):1233.

43. Kerscher M, Dirschka T, Volkenandt M. Treatment of localised scleroderma by UVA1 phototherapy. Lancet. 1995;346(8983):1166.

44. Kroft EB, van de Kerkhof PC, Gerritsen MJ, de Jong EM. Period of remission after treatment with UVA-1 in sclerodermic skin diseases. J Eur Acad Dermatol Venereol. 2008;22(7):839–44.

45. Sator PG, Radakovic S, Schulmeister K, Honigsmann H, Tanew A. Medium-dose is more effective than low-dose ultraviolet Al phototherapy for localized scleroderma as shown by 20-MHz ultrasound assessment. J Am Acad Dermatol. 2009;60(5):786–91.

46. Su O, Onsun N, Onay HK, Erdemoglu Y, Ozkaya DB, Cebeci F, Somay A. Effectiveness of medium-dose ultraviolet Al phototherapy in localized scleroderma. Int J Dermatol. 2011;50(8):1006–13.

47. Kerscher M, Volkenandt M, Gruss C, Reuther T, von Kobyletzki G, Freitag M, Dirschka T, Altmeyer P. Low-dose UVA phototherapy for treatment of localized scleroderma. J Am Acad Dermatol. 1998;38(1):21–6.

48. Jacobe HT, Cayce R, Nguyen J. UVA1 phototherapy is effective in darker skin: a review of 101 patients of Fitzpatrick skin types I–V. Br J Dermatol. 2008;159(3):691–6.

49. Connolly KL, Griffith JL, McEvoy M, Lim HW. Ultraviolet A1 phototherapy beyond morphea: experience in 83 patients. Photodermatol Photoimmunol Photomed. 2015;31(6):289–95.

50. Suh KS, Kang JS, Baek JW, Kim TK, Lee JW, Jeon YS, Jang MS, Kim ST. Efficacy of ultraviolet A1 phototherapy in recalcitrant skin diseases. Ann Dermatol. 2010;22(1):1–8.

51. El-Mofty M, Mostafa W, El-Darouty M, Bosseila M, Nada H, Yousef R, Esmat S, El-Lawindy M, Assaf M, El-Enani G. Different low doses of broad-band UVA in the treatment of morphea and systemic sclerosis. Photodermatol Photoimmunol Photomed. 2004;20(3):148–56.

52. Vasquez R, Jabbar A, Khan F, Buethe D, Ahn C, Jacobe H. Recurrence of morphea after successful ultraviolet A1 phototherapy: a cohort study. J Am Acad Dermatol. 2014;70(3):481–8.

53. Ridge CA, Moktar A, Barry J, Murphy GM. Photochemotherapy and methotrexate used to treat generalized cutaneous scleroderma. J Eur Acad Dermatol Venereol. 2007;21(5):692–3.

54. Kerscher M, Meurer M, Sander C, Volkenandt M, Lehmann P, Plewig G, Rocken M. PUVA bath photochemotherapy for localized scleroderma. Evaluation of 17 consecutive patients. Arch Dermatol. 1996;132(11):1280–2.

55. Newland K, Marshman G. Success treatment of post-irradiation morphoea with acitretin and narrowband UVB. Australas J Dermatol. 2012;53(2):136–8.

56. Buense R, Duarte IA, Bouer M. Localized scleroderma: assessment of the therapeutic response to phototherapy. An Bras Dermatol. 2012;87(1):63–9.

57. Barolet D. Pulsed versus continuous wave low-level light therapy on osteoarticular signs and symptoms in limited scleroderma (CREST syndrome): a case report. J Biomed Opt. 2014;19(11):118001.

58. Nistico SP, Saraceno R, Schipani C, Costanzo A, Chimenti S. Different applications of monochromatic excimer light in skin diseases. Photomed Laser Surg. 2009;27(4):647–54.

59. Kineston D, Kwan JM, Uebelhoer NS, Shumaker PR. Use of a fractional ablative 10.6-μm carbon dioxide laser in the treatment of a morphea-related contracture. Arch Dermatol. 2011;147(10):1148–50.

60. Comstedt LR, Svensson A, Troilius A. Improvement of microstomia in scleroderma after intense pulsed light: a case series of four patients. J Cosmet Laser Ther. 2012;14(2):102–6.

61. Batchelor R, Lamb S, Goulden V, Stables G, Goodfield M, Merchant W. Photodynamic therapy for the treatment of morphoea. Clin Exp Dermatol. 2008;33(5):661–3.

62. Breuckmann F, Gambichler T, Altmeyer P, Kreuter A. UVA/UVA1 phototherapy and PUVA photochemotherapy in connective tissue diseases and related disorders: a research based review. BMC Dermatol. 2004;4(1):11.

63. Sacher C, Konig C, Scharffetter-Kochanek K, Krieg T, Hunzelmann N. Bullous pemphigoid in a patient treated with UVA-1 phototherapy for disseminated morphea. Dermatology. 2001;202(1):54–7.

64. Kreuter A, Gambichler T, Avermaete A, Jansen T, Hoffmann M, Hoffmann K, Altmeyer P, von Kobyletzki G, Bacharach-Buhles M. Combined treatment with calcipotriol ointment and low-dose ultraviolet A1 phototherapy in childhood morphea. Pediatr Dermatol. 2001;18(3):241–5.

65. Lam J, Polifka JE, Dohil MA. Safety of dermatologic drugs used in pregnant patients with psoriasis and other inflammatory skin diseases. J Am Acad Dermatol. 2008;59(2):295–315.

66. Park KK, Murase JE. Narrowband UV-B phototherapy during pregnancy and folic acid depletion. Arch Dermatol. 2012;148(1):132–3.

67. Borradale D, Isenring E, Hacker E, Kimlin MG. Exposure to solar ultraviolet radiation is associated with a decreased folate status in women of childbearing age. J Photochem Photobiol B. 2014;131:90–5.

68. Bielsa Marsol I. Update on the classification and treatment of localized scleroderma. Actas Dermosifiliogr. 2013;104(8):654–66.

69. Durand F, Staumont D, Bonnevalle A, Hachulla E, Hatron PY, Thomas P. Ultraviolet Al phototherapy for treatment of acrosclerosis in systemic sclerosis: controlled study with half-side comparison analysis. Photodermatol Photoimmunol Photomed. 2007;23(6):215–21.

70. Kreuter A, Hyun J, Stucker M, Sommer A, Altmeyer P, Gambichler T. 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(3):440–7.

71. de Rie MA, Enomoto DN, de Vries HJ, Bos JD. Evaluation of medium-dose UVA1 phototherapy in localized scleroderma with the cutometer and fast Fourier transform method. Dermatology. 2003;207(3):298–301.

72. Stege H, Berneburg M, Humke S, Klammer M, Grewe M, Grether-Beck S, Boedeker R, Diepgen T, Dierks K, Goerz G, et al. High-dose UVA1 radiation therapy for localized scleroderma. J Am Acad Dermatol. 1997;36(6 Pt 1):938–44.

73. Andres C, Kollmar A, Mempel M, Hein R, Ring J, Eberlein B. Successful ultraviolet A1 phototherapy in the treatment of localized scleroderma: a retrospective and prospective study. Br J Dermatol. 2010;162(2):445–7.

74. Gruss CJ, Von Kobyletzki G, Behrens-Williams SC, Lininger J, Reuther T, Kerscher M, Altmeyer P. Effects of low dose ultraviolet A-1 phototherapy on morphea. Photodermatol Photoimmunol Photomed. 2001;17(4):149–55.

75. Morita A, Kobayashi K, Isomura I, Tsuji T, Krutmann J. Ultraviolet A1 (340–400 nm)

phototherapy for scleroderma in systemic sclerosis. J Am Acad Dermatol. 2000;43(4):670–4.

76. Grundmann-Kollmann M, Ochsendorf F, Zollner TM, Spieth K, Sachsenberg-Studer E, Kaufmann R, Podda M. PUVA-cream photochemotherapy for the treatment of localized scleroderma. J Am Acad Dermatol. 2000;43(4):675–8.

77. Hofer A, Soyer HP. Oral psoralen-UV-A for systemic scleroderma. Arch Dermatol. 1999;135(5):603–4.

78. Karrer S, Abels C, Landthaler M, Szeimies RM. Topical photodynamic therapy for localized scleroderma. Acta Derm Venereol. 2000;80(1):26–7.

79. Rose RF, Turner D, Goodfield MJ, Goulden V. Low-dose UVA1 phototherapy for proximal and acral scleroderma in systemic sclerosis. Photodermatol Photoimmunol Photomed. 2009;25(3):153–5.

80. Pereira N, Santiago F, Oliveira H, Figueiredo A. Low-dose UVA(1) phototherapy for scleroderma: what benefit can we expect? J Eur Acad Dermatol Venereol. 2012;26(5):619–26.

81. von Kobyletzki G, Uhle A, Pieck C, Hoffmann K, Altmeyer P. Acrosclerosis in patients with systemic sclerosis responds to low-dose UV-A1 phototherapy. Arch Dermatol. 2000;136(2):275–6.

82. Oikarinen A, Knuutinen A. Ultraviolet A sunbed used for the treatment of scleroderma. Acta Derm Venereol. 2001;81(6):432–3.

83. Rombold S, Lobisch K, Katzer K, Grazziotin TC, Ring J, Eberlein B. Efficacy of UVA1 phototherapy in 230 patients with various skin diseases. Photodermatol Photoimmunol Photomed. 2008;24(1):19–23.

84. Kreuter A, Hyun J, Skrygan M, Sommer A, Tomi NS, Breuckmann F, Altmeyer P, Gambichler T. Ultraviolet A1 phototherapy decreases inhibitory SMAD7 gene expression in localized scleroderma. Arch Dermatol Res. 2006;298(6):265–72.

85. Tuchinda C, Kerr HA, Taylor CR, Jacobe H, Bergamo BM, Elmets C, Rivard J, Lim HW. UVA1 phototherapy for cutaneous diseases: an experience of 92 cases in the United States. Photodermatol Photoimmunol Photomed. 2006;22(5):247–53.

86. Ozdemir M, Engin B, Toy H, Mevlitoglu I. Treatment of plaque-type localized scleroderma with retinoic acid and ultraviolet A plus the photosensitizer psoralen: a case series. J Eur Acad Dermatol Venereol. 2008;22(4):519–21.

87. Pavlotsky F, Sakka N, Lozinski A, Barzilai A. Bath psoralen-UVA photochemotherapy for localized scleroderma: experience from a single institute. Photodermatol Photoimmunol Photomed. 2013;29(5):247–52.

88. Morison WL. Psoralen UVA therapy for linear and generalized morphea. J Am Acad Dermatol. 1997;37(4):657–9.

89. Pasic A, Ceovic R, Lipozencic J, Husar K, Susic SM, Skerlev M, Hrsan D. Phototherapy in pediatric patients. Pediatr Dermatol. 2003;20(1):71–7.

90. von Felbert V, Kernland-Lang K, Hoffmann G, Wienert V, Simon D, Hunziker T. Irradiation with water-filtered infrared A plus visible light improves cutaneous scleroderma lesions in a series of cases. Dermatology. 2011;222(4):347–57.

91. Kauer F, Simon JC, Sticherling M. Nodular morphea. Dermatology. 2009;218(1):63–6.

92. Uchiyama M, Okubo Y, Kawashima H, Yamamoto K, Mitsuhashi Y, Tsuboi R. Case of localized scleroderma successfully treated with bath psoralen and ultraviolet A therapy. J Dermatol. 2010;37(1):75–80.

93. Morita A, Sakakibara S, Sakakibara N, Yamauchi R, Tsuji T. Successful treatment of systemic sclerosis with topical PUVA. J Rheumatol. 1995;22(12):2361–5.

94. Mohanna M, Distler O, Sprott H, Kündig T, French LE, Hofbauer G. Skin lesions in anti-Pm-Scl-70 positive systemic sclerosis-dermatomyositis overlap syndrome improve during local PUVA phototherapy. Eur J Dermatol. 2013;23(5):730–1.

95. Kanekura T, Fukumaru S, Matsushita S, Terasaki K, Mizoguchi S, Kanzaki T. Successful treatment of scleroderma with PUVA therapy. J Dermatol. 1996;23(7):455–9.

96. García-Bustínduy M, Noda A, Sánchez R, González de Mesa MJ, Guimerá F, García-Montelongo R. PUVA therapy in localized scleroderma. J Eur Acad Dermatol Venereol. 1998;10(3):283–4.

97. Todd DJ, Askari A, Ektaish E. PUVA therapy for disabling pansclerotic morphoea of children. Br J Dermatol. 1998;138(1):201–2.

98. Baum S, Pavlotsky F, Shpiro D, Trau H. PUVA treatment in sclerodermatoid spectrum of dermatologic diseases: our initial experience. Isr Med Assoc J. 2004;6(9):563–4.

99. Rose RF, Goodfield MJ. Combining PUVA therapy with systemic immunosuppression to treat progressive diffuse morphoea. Clin Exp Dermatol. 2005;30(3):226–8.

100. Gambichler T, Kreuter A, Rotterdam S, Altmeyer P, Hoffmann K. Linear scleroderma 'en coup de sabre'

treated with topical calcipotriol and cream psoralen plus ultraviolet A. J Eur Acad Dermatol Venereol. 2003;17(5):601–2.

101. Aragane Y, Kawada A, Maeda A, Isogai R, Isogai N, Tezuka T. Disseminated scleroderma of a Japanese patient successfully treated with bath PUVA photochemotherapy. J Cutan Med Surg. 2001;5(2):135–9.

102. Yamaguchi K, Takeuchi I, Yoshii N, Gushi A, Kanekura T, Kanzaki T. The discrepancy in hardness between clinical and histopathological findings in localized scleroderma treated with PUVA. J Dermatol. 1998;25(8):544–6.

103. Wollina U, Looks A, Uhlemann C, Wollina K. Pansclerotic morphea of childhood-follow-up over 6 years. Pediatr Dermatol. 1999;16(3):245–7.

104. Lim D, Johnston S, Novakovic L, Fearfield L. Radiation-induced morphoea treated with UVA-1 phototherapy. Clin Exp Dermatol. 2014;39(5):612–5.

105. Scharffetter-Kochanek K, Goldermann R, Lehmann P, Holzle E, Goerz G. PUVA therapy in disabling pansclerotic morphoea of children. Br J Dermatol. 1995;132(5):830–1.

106. Yildirim M, Baysal V, Aridogan BC, Kesici D, Erturan I. Pansclerotic morphea treated with UVA: a case report. J Dermatol. 2003;30(8):625–7.

107. Tewari A, Garibaldinos T, Lai-Cheong J, Groves R, Sarkany R, Branislav Novakovic L. Successful treatment of microstomia with UVA1 phototherapy in systemic sclerosis. Photodermatol Photoimmunol Photomed. 2011;27(2):113–4.

108. Forsea AM, Cretu AN, Ionescu R, Giurcaneanu C. Disabling pansclerotic morphea of childhood–unusual case and management challenges. J Med Life. 2008;1(3):348–54.

109. Herzinger T, Prinz JC, Röcken M. Pansclerotic morphea of the head. Arch Dermatol. 2008;144(1):125–6.

110. Gruss C, Stucker M, Kobyletzki G, Schreiber D, Altmeyer P, Kerscher M. Low dose UVA1 phototherapy in disabling pansclerotic morphoea of childhood. Br J Dermatol. 1997;136(2):293–4.

111. Steger JW, Matthews JH. UVA therapy for scleroderma. J Am Acad Dermatol. 1999;40(5 Pt 1):787–8.

112. Brownell I, Soter NA, Franks AG Jr. Familial linear scleroderma (en coup de sabre) responsive to antimalarials and narrowband ultraviolet B therapy. Dermatol Online J. 2007;13(1):11.

113. Cho S, Choi MJ, Zheng Z, Goo B, Kim DY, Cho SB. Clinical effects of non-ablative and ablative fractional lasers on various hair disorders: a case series of 17 patients. J Cosmet Laser Ther. 2013;15(2):74–9.

114. Eisen D, Alster TS. Use of a 585 nm pulsed dye laser for the treatment of morphea. Dermatol Surg. 2002;28(7):615–6.