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Review article

Phototherapy and photochemotherapy of sclerosing skin diseases

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The treatment of sclerosing skin diseases [systemic sclerosis, localized scleroderma, lichen sclerosus et atrophicus, sclerodermoid graft-vs.-host disease, scleredema adultorum (Buschke), scleromyxedema and necrobiosis lipoidica] is difficult and remains a great challenge. Numerous treatments, some with potentially hazardous side effects, are currently used with only limited success. The introduction of phototherapy and photochemotherapy for sclerosing skin diseases has considerably enriched the therapeutic panel and proven useful in a number of sclerosing skin diseases especially in localized scleroderma. Two phototherapeutic modalitites are used for the treatment of sclerosing skin diseases, long-wave ultraviolet A and psoralen plus ultraviolet A (PUVA). This article reviews current knowledge about the application of phototherapy and photochemotherapy to various sclerosing skin disorders.

Key words: **photochemotherapy; phototherapy; PUVA; sclerosing skin diseases; UVA_1.**

Dermal sclerosis is a manifestation of many skin disorders. It is most frequently caused by systemic sclerosis or localized scleroderma, but is also found in lichen sclerosus et atrophicus, sclerodermoid graft-vs.-host disease (GvHD), scleredema adultorum (Buschke), scleromyxedema, or necrobiosis lipoidica. Therapy of cutaneous sclerosis is often unrewarding. The introduction of phototherapy and photochemotherapy for sclerosing skin diseases has considerably improved therapeutic options. Two phototherapeutic modalitites have been used for the treatment of sclerosing skin diseases: In 1994, psoralen plus ultraviolet A (PUVA) (1) and in 1995, long-wave ultraviolet A (UVA_1) (2) were proposed as effective and safe treatments for localized scleroderma. This article reviews reports about the application of phototherapy and photochemotherapy to various sclerosing skin disorders.

Methods

Reports were identified that assess the efficacy of UVA_1 and PUVA in the management of cutaneous sclerosis. Identification was carried out by searching the computerized bibliographic databases, MEDLINE (covering the period from January 1973 to August 2003) and the Cochrane library. Additionally, reference lists of retrieved articles were screened for further relevant articles. Retrieved reports included small-scale open clinical trials, case series and case reports. No randomized controlled trials were identified. Studies were analyzed for the therapeutic modalities used, the number of patients included, the doses applied per individual treatment, the total number of treatments given and the therapeutic outcome.

Irradiation modalities

UVA_1 comprises the electromagnetic spectrum from 340 to 400 nm. Frequently used lamps have an emission peak at 370 nm and wavelengths below 340 nm are filtered (3, 4). Although no definite guidelines exist, UVA_1 therapy is applied three to five times per week with gradual increments up to a maximum dose that is then kept until the end of treatment. Regimens with a range of daily dosages have been developed that are termed low-dose UVA_1 (10–20 J/cm^2), medium-dose UVA_1 (30–50 J/cm^2), or high-dose UVA_1 (up to 130 J/cm^2). Radiation sources are fluorescent lamp cubicles or high-output metal halide sources (5). Generally, a dose of 30 J/cm^2 is well tolerated by patients. In order to avoid possible phototoxic reactions, a gradual increase, e.g., 1, 3, 5, 10, 20 and 30 J/cm^2 UVA_1 is recommended. UVA_1 lamps are relatively costly, however, conventional broad-band UVA lamps may also be used for the treatment of sclerodermoid connective tissue diseases (e.g., morphea) (6).

In PUVA therapy, the photosensitizing psoralen can be administered orally (systemic PUVA) or topically, either by application of a psoralen-containing oil-in-water emulsion (cream PUVA) or by immersion in an aqueous psoralen solution (bath PUVA). Different psoralens are therapeutically utilized (8-methoxypsoralene (8-MOP), also termed methoxsalene, 5-methoxypsoralene, 4,5′,8-trimethoxypsoralene), 8-MOP being the most widely applied component.

For systemic PUVA therapy, 8-MOP, e.g., is taken orally at a dose of 0.6 mg/kg body weight. UVA irradiation follows 2 h later. For bath PUVA therapy, a 20 min bath at 30–37 °C in 8-MOP at a concentration of 0.5–1.0 mg/l water is taken, UVA is applied immediately after the bath because photosensitivity rapidly decreases when psoralen is topically applied (7–9). For cream PUVA therapy, the psoralen is applied evenly to the skin for 15 min to 1 h in an oil-in water formulation (e.g., 0.001% 8-MOP) prior to UVA irradiation (10). Guidelines for topical PUVA have been defined by the British Photodermatology Group (11).

UVA-irradiation is delivered with broad-band fluorescent UVA-lamps with an emission peak at 355 nm and a small proportion of UVB. The initial UVA dose is either given on an empirical scheme according to the Fitzpatrick skin type (12) or according to the individual minimal phototoxic dose (MPD). PUVA treatment should be initiated following the MPD assessment at 72 h, because the maximum intensity of PUVA erythema occurs only 48–96 h after irradiation (13). For systemic PUVA therapy, an initial UVA dose of 50–70% of the MPD is recommended, while for bath and cream PUVA therapy, an initial dose of 30% of the MPD is recommended because of the higher phototoxic potential. Bath PUVA therapy may be associated with logistic drawbacks because of the requirements of bathing facilities. Bathing does not seem to be appropriate for patients presenting with single lesions only. In these cases, the application of psoralens by creme or gel may be preferable.

Side effects of phototherapy and photochemotherapy

PUVA therapy has phototoxic side effects: erythema, diffuse hyperpigmentation and lentigines, pruritus and bullous phototoxic reactions. All are more common with topical PUVA application because of higher tissue concentrations. With systemic administration additional side effects may occur like UV-independent drug intolerance including nausea (especially with 8-MOP), headache, and possibly phototoxic cataract. Possible long-term effects of UVA_1 phototherapy are skin aging and induction of skin tumors (14, 15). PUVA therapy may increase the risk of skin cancer, especially of squamous cell carcinoma and melanoma (16–18). The combination of PUVA, chemotherapy and immunosuppression increases the risk for skin cancer.

Generally, when treating sclerosing skin diseases, long-term adverse effects are not of great concern, if treatment courses are of short duration.

Localized scleroderma (morphea)

The clinical manifestation of morphea is livid erythema with centrifugal expansion and yellowish-white hardening in the center of the lesion. Subsequently, atrophy, hypo- or hyperpigmentation can be observed. Disseminated lesions (widespread morphea, pansclerotic morphea) and linear lesions, e.g., frontoparietal (en coup de sabre) occur. Rarely, generalized pansclerotic lesions develop.

Phototherapy and photochemotherapy have become important treatment options for patients with morphea. Different treatment protocols have been used: UVA_1 therapy (340–400 nm) as well as broad-band UVA at low dose, bath PUVA, cream PUVA and oral PUVA therapy were applied (Table 1). Several studies concerning the effect of UVA_1 on localized scleroderma were performed. The study groups differed in size (maximum 20 patients), localization of plaques, dose of UVA_1 (high/medium/low dose), number of treatments, evaluation methods (clinical criteria, cutaneous elastometry, thickness of sclerotic plaques measured by 20 MHz ultrasound and histopathologic analysis) and intraindividual control (unirradiated plaques). High-dose UVA_1 therapy was found to be superior to low-dose UVA_1 although there was no complete clearance, but softening of sclerotic plaques (3). However, medium- and low-dose UVA_1 therapy also induced significant clinical improvement (4, 19–24). A further phototherapeutic option for localized scleroderma is PUVA (bath, cream or oral) therapy that was used with good results (25–29).

In summary, both UVA_1 and PUVA therapy can be used whereas no superiority of either treatment can be acknowledged. Our own experience is positive with either modality. Often times, lesions can be stopped from growing, are softened and less erythematous. However, we regularly observe postinflammatory hyperpigmentation as residues. Generally, one cannot expect to revert sclerotic lesions to normal skin. Rather, clearance of early inflammatory lesions back to normal appearing skin and softening of sclerotic lesions is the goal. Concerning recurrence rates, there are only few data available (3, 22, 25). In our

Table 1. Phototherapy of morphea

Therapy	Number of patients	Dose (J/cm^2)	Number of treatments	Results/Comments	Reference
High-dose UVA_1 vs. low-dose UVA_1	10	130	30	10/10 Reduction of plaques size 4/10 Complete clearance, no reduction in control plaques (covered)	(3)
	7	20	30	2/7 Reduction or softening of plaques 0/7 Complete clearance Effectiveness of treatment evaluated by clinical criteria, ultrasonography, cutaneous elastometry	
UVA_1	20	20	30	18/20 Clearance of lesions (>80%) All patients remarkable softening, documented by clinical score, ultrasonography and histopathologic analysis	(4)
UVA_1	8	48	20	8/8 Softening of sclerotic plaques Improvement confirmed by skin score and cutometer measurements, no reduction in control plaques (covered)	(19)
UVA_1	7	30	30	7/7 Decrease of induration and increased joint mobility	(20)
UVA_1+calcipotriol	19 children	20	40	19/19 Remarkable softening and repigmentation, ultrasound confirms clinical improvement No control group of UVA_1 only or calcipotriol only	(21)
UVA_1	2	20	30	2/2 Sclerotic plaques completely resolved, histologically less thickness of dermis, no entrapped adnexi or blood vessels	(22)
	1 with overlying LSA	20	30	Plaques resolved, residual slight discoloration	
UVA_1	1	20	32	Resolution of sclerotic skin lesions, impressive improvement of the ectropion of the right eyelid, healing of limb ulcers, rapid improvement of joint mobility, substantial decrease of skin thickness in ultrasonography	(23)
UVA_1	1	20	30	Morphea of the eyelid lesion softened, eye lid retraction reversed	(24)
Broad-band UVA	12	20	20	12/12 Remarkable softening, histological significant reduction of collagen in plaques, no reduction in control plaque (covered)	(6)
Bath PUVA 1 mg/l 8-MOP	17	1.2–3.5	35	13/17 Clinical and ultrasound improvement 4/7 Histological reduction of collagen	(25)
Bath PUVA 1 mg/l 8-MOP	6 children	18.0–108.5 (cumulative dose)	14–39	6/6 Improvement in terms of softening of sclerotic plaques	(26)
Cream PUVA 0.001% (skin type I+II) 0.0025% (skin type III+IV)	4	67.5–121 (cumulative dose)	30	4/4 Sclerotic plaques disappeared or remarkably improved, thickness of skin decreased in ultrasonography, dermal collagen reduced histologically	(27)
Oral PUVA	1	18	127	Complete clearance	(28)
Oral PUVA	4	358–838.5 (cumulative dose)	44–88	Progression of morphea stopped Recent lesions cleared No reversement of scarring and atrophy, but loss of induration	(29)

UVA_1, long-wave ultraviolet A; PUVA, psoralen plus ultraviolet A; 8-MOP, 8-methoxypsoralene.

experience, new lesions are not uncommon in treated patients and these patients require repeated therapy.

Systemic sclerosis

Systemic sclerosis can affect skin, gastrointestinal tract, lungs and kidneys. According to the degree of skin involvement, systemic sclerosis is subdivided into a limited acral variant that progresses slowly and a more aggressive diffuse variant including the trunk (30).

Currently, the efficacy of phototherapy and photochemotherapy in the treatment of systemic sclerosis relies on uncontrolled studies and case reports including only a limited number of patients (Table 2). Controlled studies are hampered because there are no generally accepted objective endpoints to measure the activity of the disease. Spontaneous stabilization or improvement of the condition are not uncommon, making it even more difficult to judge the efficacy of

Table 2. Phototherapy of systemic sclerosis

Therapy	Number of patients	Dose (J/cm^2)	Number of treatments	Results/Comments	Reference
UVA_1	8	30	50	1/8 Slight improvement 7/8 Clearly reduced sclerosis, marked softening of the skin, improvement of finger mobility 5/8 Improvement of Raynaud phenomenon 1/8 Nearly complete healing of acral necrosis	(31)
UVA_1	4	60	9–29	4/4 Marked softening of the skin, increase in joint mobility, increase in acral skin temperature, increase in cutaneous elasticity Histology revealed loosening of collagen bundles	(32)
Bath PUVA	12	98 (cumulative dose) 0.5 g 8-MOP/l	38	9/12 Marked softening increased mobility of fingers 1/12 Complete disappearance of sclerosis 2/12 No amelioration	(33)
Topical PUVA	3	5.2 (average cumulative dose)	14–20	3/3 Improvement of joint mobility and skin induration Histologically collagen more spaced and delicate	(34)
Oral PUVA	4	70.5 (mean cumulative dose), 0.6 mg/kg body weight 8-MOP	30	4/4 No change in skin thickness (ultrasound) and clinical assessment of sclerosis and joint mobility Histologically skin score improved	(35)

UVA_1, long-wave ultraviolet A; PUVA, psoralen plus ultraviolet A; 8-MOP, 8-methoxypsoralene.

medical intervention. The reports available so far all suggest a beneficial effect of phototherapy or photochemotherapy on the symptoms of the disease in the majority of patients (31–34) with the exception of one study using oral PUVA (35). In our experience many patients favorably respond with softening of acral skin and an increase in the mobility of small joints. This effect, however, is often not long-lasting, and patients that respond well to phototherapy or photochemotherapy frequently require a repeated course after 6–12 months. The recommended treatment protocols are as in localized scleroderma.

Lichen sclerosus et atrophicus

Lichen sclerosus et atrophicus is a rare chronic inflammatory skin disease characterized by white, flat, well-defined, indurated papules or atrophic plaques. Whereas extragenital lesions can be found in only 15–20% of the patients and are often asymptomatic, the anogenital region is most often affected which frequently causes great discomfort to the patient (36, 37).

At present, phototherapy (low-dose UVA_1) and photochemotherapy (PUVA bath) of extragenital lichen sclerosus et atrophicus have been tried in a limited number of patients (38–41), with encouraging results (Table 3). If lesions respond insufficiently to glucocorticoids, we consider phototherapy and photochemotherapy as a valid alternative in the treatment of extragenital lichen sclerosus et atrophicus. For genital lichen sclerosus et atrophicus there is currently not enough evidence to support the use of phototherapy or photochemotherapy. There is only one report (42) on the use of photochemotherapy for genital LSA. Therefore, high-potency glucocorticoids are considered as the treatment of choice or, alternatively, therapy with topical T-cell inhibitors (tacrolimus, pimecrolimus) may be considered.

Sclerodermoid GvHD

Chronic GvHD develops after allogeneic bone marrow transplantation and is mediated by donor T lymphocytes activated by human lymphocyte antigen incompatibility with the host. It starts, by definition, 100 days after transplantation and is preceded in most, although not in all, cases by acute GvHD. The affected target organs are skin, gastrointestinal tract and liver. The mucocutaneous manifestations of chronic GvHD characteristically mimic those of lichen planus or scleroderma. For the treatment of chronic cutaneous sclerodermoid GvHD, UVA_1 (43–45), oral (46, 47) and bath PUVA (48), have been used (Table 4). Improved joint mobility and regression of sclerosis were observed with UVA_1 (43–45), while reduction of skin thickness was reported with PUVA therapy (48). Since published experience is limited to few patients with any of the phototherapeutic modalities and other treatments were simultaneously applied, the observations need confirmation in larger studies. In summary, phototherapy and photochemotherapy are useful therapeutic options, particularly in cases where GvHD is restricted to the skin. In principal, phototherapy can be combined with sys-

Table 3. Phototherapy of lichen sclerosus et atrophicus

Therapy	Number of patients	Dose (J/cm^2)	Number of treatments	Results	Reference
UVA_1	2	20	40	2/2 Nearly complete clearance of lesions, thickness of skin decreased and density of skin increased in ultrasound	(38)
UVA_1	10	20	40	10/10 Remarkable softening and repigmentation, corium thickness decreased, histologically normal structure of skin	(39)
UVA_1	1	20	40	Complete clearance of lesions Results confirmed by ultrasonography	(40)
Bath PUVA	1	31.7 (mean cumulative dose)	24	Decreased itching, complete clearance of lesions (confirmed by histopathology and ultrasound)	(41)
Cream PUVA	5	44.2 (mean dose)	25.6 (average)	Genital LSA 2/5 Markedly improved 2/5 Improved 1/5 Unchanged	(42)

UVA_1, long-wave ultraviolet A; PUVA, psoralen plus ultraviolet A.

Table 4. Phototherapy and photochemotherapy of sclerodermoid graft-vs.-host disease

Therapy	Number of patients	Dose (J/cm^2)	Number of treatments	Results	Reference
UVA_1	5	50	30	6/6 Improved joint mobility, softening of sclerotic lesions, clearance of erosions	(43)
	1 child	20	30		
UVA_1	4 localized 1 generalized	50	15–33	3/4 Complete response 1/4 Partial response No change in unirradiated control lesions 2/5 Relapse after 5 months but response to another treatment	(44)
UVA_1	1	20	30	Improved joint mobility Regression of sclerosis Histologically reduction of cellular infiltrate and sclerotic changes Ultrasound: nearly normal skin thickness	(45)
UVA_1+bath PUVA	1	667 UVA_1+64 UVA (cumulative dose)	34	Complete clearance (>80% reduction of skin thickness and density, pleating in sclerodermic skin lesions up to levels of normal skin)	(48)
Bath PUVA	1	14.2	25	Partial remission (20–80% reduction of skin thickness and density, improved pleating of sclerodermic lesions)	(48)
Oral PUVA	2	1094 (cumulative dose)	24	1/2 Short complete response 1/2 Partial respond; both patients rapidly relapse, symptoms of severe phototoxicity	(47)
	1	190 (cumulative dose)	24	PUVA well tolerated, but no improvement	
Oral PUVA	1	0.5–7.0	37	Lessened infiltrations, improved mobility	(46)
UVB	1	5 (cumulative dose)	48	Reduction of dryness and pruritus	(72)
	1	10 (cumulative dose)	37	No clearance of lesions	

UVA_1, long-wave ultraviolet A; PUVA, psoralen plus ultraviolet A.

temic immunosuppressive drugs, but the combination of phototherapy and ciclosporin A must be avoided because of an increased risk for cutaneous neoplasms. If a UVA_1 irradiation device is available, UVA_1 may be preferred to oral or topical PUVA because of a lower risk of phototoxic reactions and the absence of side effects resulting form the oral intake of psoralens such as nausea, headache, vertigo, cataract, lentigines, or elevated liver enzymes.

Other sclerosing skin diseases

Scleredema adultorum, lichen myxoedematosus, scleromyxedema and necrobiosis lipoidica

Scleredema adultorum is characterized by rapidly progressive non-pitting cutanous-subcutaneous indurations. It is usually a self-limited disease that regresses in 50% of patients within two years after onset (49). There are reports on the use of bath and cream PUVA in scleredema adultorum (50, 51).

Table 5. Phototherapy of necrobiosis lipoidica

Therapy	Number of patients	Dose (J/cm^2)	Number of treatments	Results	Reference
Topical PUVA	30	3.6–207.9 (cumulative dose) 0.005% 8-MOP gel	5–42	5/30 Complete clearing 11/30 Improvement 10/30 No effect 4/30 Worsening	(57)
Topical PUVA	10	19.7–108.2 (cumulative dose) 0.15% 8-MOP emulsion	12–65	2/10 Complete clearance 4/10 Substantial clinical improvement 4/10 No effect	(58)
Topical PUVA	7	ND 0.05% 8-MOP gel	9–62	5/7 Lesions paler and flatter Return to normal skin texture 2/7 No effect	(59)

UVA_1, long-wave ultraviolet A; PUVA, psoralen plus ultraviolet A; 8-MOP, 8-methoxypsoralene; ND, not documented.

In the reported patients and in our experience, treatment of scleredema required higher cumulative doses of PUVA than other sclerodermoid diseases. In analogy to other sclerotic skin conditions, UVA_1 may also pose a promising therapeutic option, although at present the use of UVA_1 in scleredema has not been reported.

Lichen myxoedematosus and its generalized variant, scleromyxedema, are characterized by thickened skin and symmetric eruptions of firm, waxy, closely spaced papules. Typically, the skin on the trunk seems 'too wide', reminiscent of an elephant's skin (52). Lichen myxoedematosus and scleromyxedema are associated with abnormal levels of immunoglobulin type IgG (monoclonal gammopathy). PUVA therapy (53, 54) seems to be a possible option in the management of these diseases. There is no information available about its long-term efficacy. Interestingly, accidental exposure to UVB was reported to have exacerbated lichen myxoedematosus in one patient (55). In a patient with scleromyxedema, PUVA therapy was complicated by the rapid appearance of multiple keratoakanthomas and the development of squamous cell carcinoma (56).

Necrobiosis lipoidica is a rare skin disease that affects predominantly the legs and is frequently associated with diabetes mellitus. Clinical findings are slowly growing oval plaques that initially are erythematous and have a raised irregular border, and then develop yellow-brown, waxy central atrophic areas. There are few reports (57–59) about partially successful treatment with topical PUVA in necrobiosis lipoidica (Table 5). In summary, complete remission of lesions cannot be expected. One study involving 30 subjects showed improvement in about half of patients. In our experience softening of sclerotic lesions can be achieved, but hyperpigmentations remain.

Effects of phototherapy and photochemotherapy in sclerosing skin diseases

The mechanisms of phototherapy and photochemotherapy in sclerosing skin diseases are only partially understood. As an anti-inflammatory effect, UVA_1 decreases the number of infiltrating T cells by triggering different apoptotic pathways: Immediate and delayed apoptosis (60). Both apoptotic pathways result in cell death of T and B lymphocytes. Induction of apoptosis by UVA was also observed in fibroblasts in reconstructed skin equivalents, a mechanism that may diminish dermal production of collagen (61). Furthermore, in cultured fibroblasts UVA can dose-dependently increase the expression of matrix metalloproteinases that show a proteolytic specificity for interstitial collagen, whose enhanced degradation may soften the sclerotic tissue (62–65). UVA decreases the activity of prolyl-hydroxylase, an enzyme that stabilizes the triple helix structure of collagen (66, 67). Moreover, UV radiation may impair cross-linking of collagen fibres (68). It appears that DNA-alterations play an important role in the therapeutic effect of PUVA. Psoralens intercalate DNA; UV radiation induces covalent psoralen-DNA photoadducts that lead to cross-linking of the DNA resulting in inhibition of DNA replication and, subsequently, cell cycle checkpoint arrest (69, 70). Like UVA_1, PUVA induces T cell apoptosis (71).

Conclusions

Most of the small-scale clinical trials and the case reports reviewed in this article suggest that phototherapy and photochemotherapy is a rewarding therapeutic option in the treatment of several sclerosing skin diseases. However, the wide variability and the lack of standardization of treatment protocols

and evaluation criteria used by different researchers hamper the evaluation of published data. The beneficial effects of phototherapy and photochemotherapy on morphea have been reported most frequently. We consider UVA_1 or PUVA therapy as a primary therapeutic option for this disease. In cases with very limited disease, topical corticosteroids may be tried first. Although the effects of phototherapy and photochemotherapy on systemic scleroderma have been studied only in a small number of patients, its adjunctive use should be encouraged for its beneficial effect on sclerosis. In the treatment of lichen sclerosus et atrophicus, high potency topical steroids (e.g., clobetasol proprionate) are effective in most cases and, therefore, are a therapeutic mainstay. However, if lesions are numerous and scattered, making topical steroid therapy tedious or even impractical, early use of phototherapy and photochemotherapy may be indicated. The cutaneous manifestations of sclerodermoid GvHD are only poorly responsive to immunosuppressive chemotherapy. Phototherapy and photochemotherapy may alleviate cutaneous symptoms and may be useful especially in those patients without involvement of internal organs. In several other sclerosing skin diseases (genital LSA, scleredema adultorum (Buschke), scleromyxedema, or necrobiosis lipoidica), because of the paucity of valid therapeutic alternatives, phototherapy and photochemotherapy with UVA_1 or PUVA may also be warranted. It is hoped and anticipated that the beneficial effect of phototherapy in sclerosing skin disease will be confirmed in future studies.

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