Phototherapy: a promising treatment option for skin sclerosis in scleroderma?

C. Sunderkötter, A. Kuhn¹, N. Hunzelmann² and S. Beissert

In systemic sclerosis (SSc; scleroderma) fibrosis of the skin can lead to considerable morbidity. No significant improvement has been reported from studies investigating antifibrotic therapies so far. In dermatology, phototherapy with ultraviolet (UV) irradiation is successfully used for treatment of several diseases because of its anti-inflammatory as well as immunosuppressive mechanisms, and its low-risk profile. In addition, the UVA spectrum in particular exerts antifibrotic effects as it leads to reduction of procollagen synthesis and expression of collagenase-1 in vitro. Accordingly, treatment with long-wavelength UVA-1 irradiation or photochemotherapy with UVA plus the photosensitizer psoralen (PUVA) have been successfully used to reduce skin fibrosis in localized scleroderma (morphea). There are only in particular few reports on treatment of skin sclerosis in SSc, but the results are in concordance with the good experience that have been observed at our and other dermatological centres. Phototherapy is able to stop or inhibit the fibrotic processes and to induce softening of sclerotic skin, especially in limited SSc. Phototherapy thus represents a therapeutic alternative for antifibrotic treatment with a low rate of adverse effects, which should be applied before the sclerotic process has proceeded too far.

Introduction

Scleroderma is a connective tissue disease characterized by deposition of large amounts of collagen. Localized scleroderma (morphea) affects only the skin, whereas systemic sclerosis (SSc; scleroderma) can additionally involve the lungs, gastrointestinal tract, kidneys and heart. Fibrosis of the skin is sometimes marked and leads to considerable morbidity with loss of flexibility, joint contractures and disfigurement. It even contributes to life-threatening complications by limiting and impeding thoracic excursion for breathing.

Although different antifibrotic treatments have been evaluated, there is still no satisfying solution to this problem as none of these approaches has been sufficiently effective and most of the treatments, such as immunosuppressives, have major adverse effects.

Phototherapy using ultraviolet (UV) irradiation has been a mainstay of dermatological treatment for a large number of especially inflammatory dermatoses. Accordingly, phototherapy using defined wavelengths alone or in combination with psoralens has been successfully used to control psoriasis, atopic dermatitis, prurigo (especially in renal prurigo), graft-versus-host disease (GvHD) and skin malignancies, such as cutaneous T-cell lymphoma (CTCL).

UV irradiation is able to suppress cellular immunity. Analysis of UV-irradiated lesional skin showed selective elimination of infiltrating T-cells via induction of apoptosis, impairment of cell proliferation via interference with cell-cycle-regulating proteins and induction of inhibitory cytokines such as IL-10. The immunosuppressive effects of UV irradiation have been studied extensively in vitro especially in mice, which cannot be sensitized to contact allergens via UV-irradiated skin. Using higher UV doses, these immunosuppressive effects are not locally restricted but are also effective at distant non-irradiated sites. In humans, UV irradiation was able to suppress T-cell-mediated contact hypersensitivity responses (challenge phase), indicating that UV irradiation inhibits the immune reactions at various levels.

Antifibrotic effects of phototherapy: clinical and experimental evidence

UV irradiation also has antifibrotic effects. It has been associated with a reduction of dermal decorin levels and of connective tissue growth factor, and with reduced synthesis of procollagen [1, 2]. In addition, UVA irradiation induced the expression of collagenase-1 matrix metalloproteinase-1), an enzyme involved in cleaving collagen bundles in cultured fibroblasts derived from morphea patients [3]. The combination of the immunosuppressive and the antifibrotic effects may account for the therapeutic effects of phototherapy in SSc. The acute risks of phototherapy include dermatitis solaris. Although high and chronic UV exposure leads to the development of epithelial skin cancer (squamous and basal cell carcinoma), retrospective evaluation of patient data has shown that the carcinogenic risk of phototherapy is low as it mostly encompasses a selected and narrow range of wavelengths.

While UVB (290–320 nm) only penetrates into the epidermis and upper papillary dermis, longer-wavelength UVA (320–400 nm) can reach the subcutis to induce biological effects. Therefore, UVA irradiation appears to be more suitable for treatment of sclerotic disorders. In order to achieve higher therapeutically effective UVA doses in deeper skin layers, special irradiation devices emitting UVA-1 have been developed, which is the long UVA wavelengths (340–400 nm). They minimize UV-induced erythema caused by shorter wavelengths. Because of some scattered infrared irradiation (above 780 nm), UVA-1 phototherapy generates considerable heat and thus requires
ventilation, cooling and insertion of filters designed to absorb infrared irradiation.

The effects of broadband UVA can be increased by local or systemic application of a photosensitizing agent (phototherapy). The photosensitizer, i.e. 8- or 5-methoxypsoralen (8-MOP, 5-MOP), is applied orally 2 h prior to UVA irradiation or locally by immersing the patient in diluted 8-MOP or by application of 8-MOP-containing cream immediately prior to UVA irradiation (PUVA). For sclerosis, bath-PUVA appears to be sufficient, thus avoiding side effects of oral PUVA such as nausea or the necessity of eye protection in sunlight. UVA-1 and bath-PUVA can both be directed to a specific lesional area such as the hands or feet. Phototherapy is individually adjusted according to skin type as well as to disease activity.

The idea that phototherapy could be used for the treatment of skin sclerosis in patients with SSc has been derived from the observation that dermatologists could ameliorate a widespread range of sclerotic skin diseases including localized scleroderma (morphea) by phototherapy. This cutaneous disease is characterized by circumscribed fibrotic plaques, which may form at any skin area and result in long-lasting induration of the dermis and subcutaneous tissue with the risk of muscle atrophy, contractures and slow-healing ulcers.

For treatment of morphea most reports have focused on the use of bath-PUVA, which induced improvement or even clearance of fibrotic plaques [4]. However, broadband UVA was also able to soften areas of localized scleroderma and to reduce the mean concentration of tissue collagen (n = 12, doses of 10 to 20 J/cm² broadband UVA 3 x a week, cumulative doses 200–400 J/cm²) [5]. UVA-1 was effective to a similar extent in reducing skin thickness and stiffness or in increasing elasticity of plaques, given at high doses of 130 J/cm² per irradiation (n = 10, cumulative dose 3900 J/cm² UVA-1) [6] or at low doses of 20 J/cm² (n = 20, cumulative dose 600 J/cm²) [4] or even a medium dose of 30 J/cm² UVA-1 per treatment (n = 7) [7]. In these studies, the majority of patients, except for those with deep, subcutaneously localized scleroderma, responded well to phototherapy, which was probably due to a lack of photon penetration required for the induction of biological processes into these areas. For topical PUVA therapy, an 8-MOP-containing cream is applied onto the affected skin area prior to irradiation. This treatment was reported to have achieved remarkable improvement of skin sclerosis with reduced stiffness of fingers, hands and knees (n = 3, 0.25–0.40 J/cm² UVA, cumulative dosage 3.5–9.6 J/cm²) [8]. In another smaller uncontrolled study, oral PUVA therapy resulted in a histologically visible reduction of fibrosis, although post-therapeutic skin severity scores did not improve significantly (n = 4; 0.5–4 J/cm², cumulative dose 70.5 J/cm² UVA) [9].

These reports indicate that phototherapy could be an effective therapeutic option for treatment of sclerotic skin in patients with SSc. However, the number of studies or case series so far is low, partially due to the rarity of SSc and perhaps also due to unawareness or unavailability of this treatment in centres treating those patients.

The beneficial effects of UVA-1 phototherapy for patients with SSc are still under investigation. Due to its deep penetration, UVA-1 may also exert systemic effects contributing to treatment/ control of disease. Since UV irradiation is known to induce cutaneous cytokines with immunosuppressive properties such as IL-10, which can get access to the circulation, it might be possible that these UV-induced factors contribute to systemic immunomodulation of phototherapy. Certainly additional systemic immunosuppressive treatment is needed for patients with visceral disease since phototherapy alone is insufficient to control internal organ involvement in SSc. Local UVA-1 irradiation administered to the hands or forearms has been shown to be also effective in the treatment of acral sclerotic skin lesions in patients with SSc. Such treatment resulted in softening of stiffness, increases of total skin distensions, reduction of skin thickness and an increase in dermal collagenase activity (n = 18, 30 J/cm² UVA-1 4×/week, cumulative dose of 1500 J/cm²; n = 8, 30 J/cm² UVA-1 4×/week, cumulative dose of 1500 J/cm²; n = 3, 60 J/cm² UVA-1 cumulative dose 510–1740 J/cm²) [9–11].

In summary, phototherapy appears to be a promising antifibrotic treatment for skin sclerosis in SSc. However, one cannot expect that it will completely reverse sclerosis, but the published studies in morphea and SSc so far, as well as our own experience, have demonstrated that it could stop or inhibit the fibrotic processes. Additionally, phototherapy induces softening of already existing sclerosis, although it may not be effective once joint contractures and atrophy in fingers have already occurred. Therefore, it is important to start phototherapy at an early stage of disease. Larger controlled multicentre studies would be welcome and could now be facilitated by established networks such as the German Scleroderma Network (DNSS) or EUSTAR.

### Key messages

- Phototherapy induces softening of scleroderma skin lesions.
- UV irradiation is able to activate matrix metalloproteinases.
- Exposure to UV irradiation suppresses cutaneous and systemic immune responses.

### References

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