Phototherapy for Atopic Eczema 58

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58.1 Introduction

In the past few years, several new phototherapeutic modalities including UVA/UVB [1], 311-nm UVB [2] and UVA1 phototherapy [3] have been developed to treat atopic dermatitis (eczema). As a consequence, dermatologists now have a diverse spectrum of phototherapeutic modalities from which to choose to tailor their treatment to the individual needs of a particular patient. Treatment decisions can now be based on the effectiveness of a given form of phototherapy for a specific stage of atopic dermatitis, i.e., acute and severe vs chronic and moderate disease activity. We have therefore developed a phototherapeutic approach to atopic dermatitis [3] which should result in phototherapy of eczema that is both as effective and as safe as possible. In general, phototherapy of an acute, severe exacerbation of atopic dermatitis may be achieved with high- or medium-dose UVA1 therapy, whereas conventional UVA, UVA/UVB, 311-nm UVB, and low-dose UVA1 phototherapy are phototherapeutic modalities that are primarily suited for treatment of chronic stages of this disease.

58.2 UVA1 Phototherapy for Acute, Severe Atopic Eczema

UVA1 phototherapy is a highly effective modality that can be used as monotherapy for a limited period of time (10–15 exposures). It is most effective for the treatment of patients with severe, acute exacerbation of atopic dermatitis. Potential long-term risks of UVA1 phototherapy are not known; therefore patients should not be treated over extended periods of time, e.g., for maintenance therapy. For the same reasons, its use is not recommended for patients younger than 18 years of age. The therapeutic effectiveness of UVA1 irradiation in the management of patients with atopic dermatitis was first evaluated in an open study in patients with acute, severe exacerbations of eczema [4]. They were exposed to 130 J/cm^2 UVA1 daily for 15 consecutive days. Its therapeutic effectiveness was assessed by means of a clinical scoring system as well as by monitoring serum levels of eosinophil cationic protein (ECP), a laboratory parameter that can be measured objectively and has been shown to correlate well with disease activity in eczema. In that study, UVA1 phototherapy was found to be highly efficient in promptly inducing clinical improvement and reducing elevated serum ECP levels. Patients treated with UVA1 were compared with subjects who had been treated with UVA/UVB phototherapy. Significant differences in favor of UVA1 therapy were observed [4]. These results were corroborated and extended in a randomized, controlled multicenter trial in which UVA1 therapy, as compared with glucocorticoid treatment, was significantly better at day 10 in reducing the clinical score [5].

The therapeutic effectiveness of UVA1 therapy is dose-dependent. Low-dose UVA1 (30 J/cm^2) is less effective than UVA/UVB therapy [6], whereas high-dose UVA1 therapy (130 J/cm^2) is superior to UVA/UVB phototherapy [4, 5]. In addition, a medium-UVA1 dosage schedule (50 J/cm^2) was superior to a low-dose UVA1 regimen (10 J/cm^2), whereas no significant difference was detected in a bilateral comparison study between a medium- and a high-dose regimen. [7, 8].

High-dose UVA1 phototherapy may not be given to patients with UVA-sensitive atopic dermatitis or photodermatosis. It is necessary to exclude these diseases prior to initiation of high-dose UVA1 therapy. This can easily be accomplished by photoprovocation testing.

Except for eczema herpeticum, no acute side effects have been observed in any of the patients treated with high-dose UVA1 therapy. No other side effects have occured, although its potential carcinogenic risk is a theoretical concern. It is important to note that exposure of hairless albino Skh-hr1 mice to high doses of UVA1 radiation has been shown to induce squamous cell carcinoma [9]. The actual contribution of UVA radiation to the development of malignant melanoma in humans is currently being debated and at this point cannot be excluded [10]. Until more is known about high-dose UVA1 therapy, its use should be limited to periods of acute exacerbation of atopic dermatitis and, in general, one treatment cycle should not exceed 10 – 15 continuously applied exposures and should not be repeated more than once per year [3].

58.3 Phototherapy of Chronic, Moderate Atopic Eczema

Broad-band UVB [11], combined UVA/UVB [1, 12 – 14], broad-band UVA [15], low-dose UVA1 [6, 7] and, in particular, 311-nm UVB phototherapy [2, 15] are effective treatments in mild and moderate atopic dermatitis. They are not particularly effective in patients with acute, severe exacerbations of their disease. In contrast to UVA1 therapy, these forms of UV therapy are usually not employed as monotherapy. Rather, they are used in combination regimens together with topical glucocorticoids in order to reduce the need for glucocorticoid application. All of these therapies are considered to be relatively safe, even if applied over extended periods of time, and they should thus be used to induce long-term improvement. Patients do best if severe disease is initially controlled by more potent but also more aggressive modalities. For example, 311-nm UVB phototherapy has proved to be an ideal modality for maintenance therapy once high-dose UVA1 has been used in the initial phase of management of an acute, severe exacerbation of atopic dermatitis [3]. If high-dose UVA1 therapy is not available, severe atopic dermatitis should be controlled prior to start of phototherapy by aggressive topical glucocorticoid therapy or systemic immunosuppressive modalities such as glucocorticoids or cyclosporin A.

Studies directly comparing all the different forms of UV therapy for chronic, moderate atopic eczema have not been conducted, but some trials indicate that either UVA/UVB [6, 12] combination therapy or narrow-band 311-nm UVB therapy [2, 15] is superior to conventional broadband UVB, broadband UVA, or low-dose UVA1 therapy. Also, narrow-band UVB appears to be equivalent to bath-PUVA for this indication [16]. The actual choice made for a particular patient also depends on what irradiation devices are available. At the moment, UVA/UVB is more widely available than 311-nm UVB therapy. Jekler and Larkö, in a paired comparison study, observed significant differences in favor of UVA/UVB therapy over broadband UVB therapy [6]. In this trial, patients were allowed to continue the use of topical glucocorticoids and were irradiated three times per week for a maximum of 8 weeks in a UVB MED-dependent manner.

The therapeutic effectiveness of 311-nm UVB therapy for chronic, moderate atopic dermatitis was first shown in an open trial conducted by George et al. [2] and has been confirmed more recently in a randomized controlled study [15]. In their well-designed study, George et al. irradiated patients with chronic, moderate eczema with 50 100-W TL-01 lamps equipped with reflectors, resulting in a UVB output of 5 mW/cm^2 and maximum treatment times of less than 10 min [2]. The irradiation regimen used with 50 lamps was identical to that previously described for 311-nm therapy of psoriasis. Patients were monitored for severity of clinical symptoms as well as glucocorticoid use 12 weeks prior to phototherapy, during the 12 weeks of phototherapy, and for another 24 weeks after cessation of phototherapy. The 311-nm UVB phototherapy not only decreased the clinical severity but also significantly reduced the use of glucocorticoids. These beneficial effects were still present in the majority of patients 6 months after cessation of 311-nm UVB therapy. In this study, a specially constructed air-conditioned irradiation unit was used for 311-nm UVB phototherapy. Equivalent therapeutic results could also be achieved if TL-01 lamps were fitted into a conventional PUVA irradiation device, indicating that higher temperatures during 311-nm UVB phototherapy did not lead to heat-induced irritation of eczema [17]. The 311-nm UVB therapy may be associated with a reduced risk of skin cancer compared to broadband UVB or to PUVA therapy [18]. The demonstration of 311-nm UVB therapy's effectiveness for treating childhood atopic eczema is therefore of particular interest [19].

If neither a UVA/UVB nor a 311-nm UVB irradiation device is available, broadband low-dose (0.5-MED) UVB therapy can be used. Placebo-controlled studies have shown it to be effective for this disease [11].

58.4 Phototherapy of Atopic Hand and Foot Eczema

Local UVA-1 phototherapy appears to be an interesting option in the management of patients with chronic vesicular dyshidrotic hand eczema. In an open pilot study, palms and backs of hands of 12 patients with an acute exacerbation of their disease were exposed to 15 UVA-1 irradiations with a dose of 40 J/cm^2 per day over a period of 3 weeks. After 1 week, all but one patient reported a marked relief of itch. After the 3rd week, significant clinical improvement was noted in ten out of 12 patients [20].

Alternatively, cream-PUVA therapy can be used. Eczematous skin lesions are topically treated with a cream containing 0.0006 % – 0.001 % 8-methoxypsoralen and 1 h later, treated skin areas are exposed to UVA radiation [21]. This highly effective and easy-to-perform variant of local PUVA therapy has meanwhile been standardized and found to be equivalent to local UVA-1 phototherapy for this indication [22].

58.5 Mechanism of Action

Through the induction of DNA photoproducts, UVB radiation transiently inhibits cell proliferation. It has therefore been thought that the therapeutic effectiveness of UVB phototherapy in psoriasis is due mainly to its antiproliferative effects. Since the introduction of UVB radiation into dermatologic therapy, however, the number of skin diseases showing a favorable response to phototherapy has grown substantially. The vast majority are immunologic in nature. Studies on the role of UV radiation-induced immunosuppression in photocarcinogenesis and on the effects of UV radiation on the function of epidermal Langerhans cells have provided increasing evidence that UVB but also UVA (and in particular UVA1) radiation exert profound effects on the skin's immune system (reviewed in [22]). As a consequence, UVB and UVA phototherapy are currently regarded as modalities whose mechanism of action depends upon the immune system. Most of the immunomodulatory effects that have been described are not specific for a single type of light source. The in vivo relevance of these immunomodulatory effects is dependent on the physical properties of the UV radiation employed. On a per photon basis, wavelengths within the UVB spectrum possess greater energy than UVA radiation, but because of their shorter wavelength, they have a more superficial depth of penetration within the skin. As a result, UVB phototherapy primarily affects the function of epidermal keratinocytes and Langerhans cells, whereas UVA1 radiation additionally affects dermal fibroblasts, dermal dendritic cells, endothelial cells, T lymphocytes within the dermis, mast cells, and granulocytes. The photoimmunological effects induced by UVB and UVA1 radiation fall into three major categories: (a) effects on soluble mediators, (b) modulation of the expression of cell surface-associated molecules, and (c) induction of apoptosis in pathogenetically relevant cells.

The latter one is currently thought to be of key importance for phototherapy [22]. Both UVB and UVA (in particular UVA1) radiation are highly efficient in inducing apoptosis in human cells. T cells, as compared with monocytes or keratinocytes, have an increased susceptibility to UV radiation-induced apoptosis; this mechanism is therefore of particular importance for phototherapy of T cell-mediated skin diseases such as atopic dermatitis. For example, UVA1 phototherapy of patients with atopic dermatitis was shown to induce apoptosis in skin-infiltrating T helper cells, thereby leading to a gradual reduction of the inflammatory infiltrate and concomitant improvement of patients' skin disease. A very detailed, up-to-date review of photoimmunological mechanisms that are responsible for the efficacy of phototherapy has been provided in [22].

58.6 Concluding Remarks

Great progress has been made within recent years to define the mode of action of UV therapy. Continuation of these research efforts will be important for further progress in the development of new modalities based on a scientific rationale rather than on empiricism. In this regard, it has recently been shown that wave-

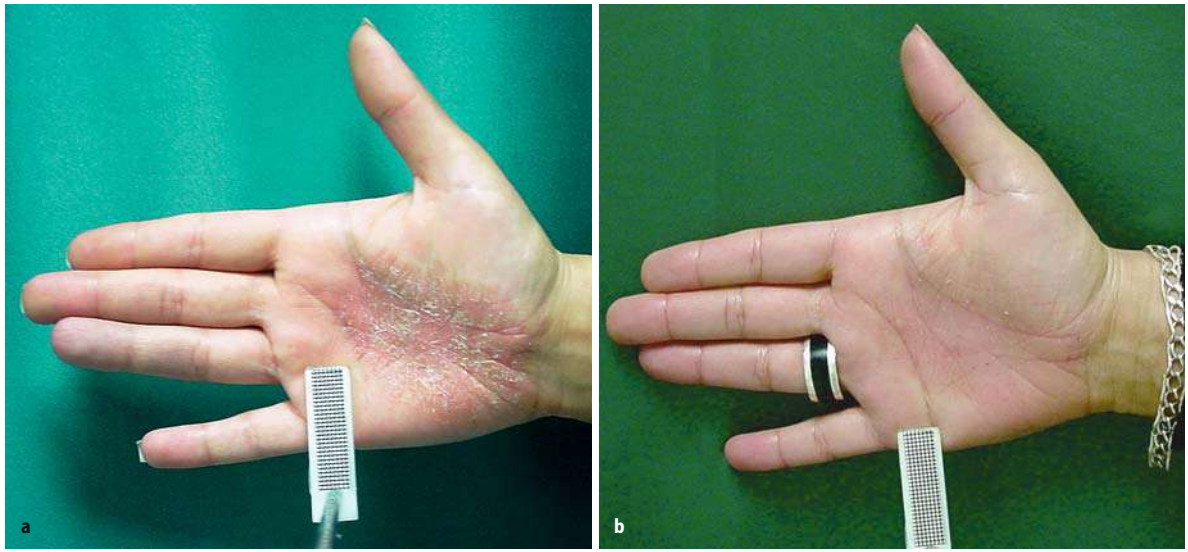

Fig. 58.1a, b. Patient with atopic hand eczema before (**a**) and after (**b**) UV-free phototherapy

lengths within the visible range can be effectively used to treat patients with atopic hand and foot eczema [23]. This development was prompted by the observation that UVA1 phototherapy-induced apoptosis in house dust mite-specific T cells, which had been cloned from lesional skin of patients with atopic eczema, is mediated through the generation of singlet oxygen. This reactive oxygen species, however, cannot only be generated by wavelengths in the UV but in particular by radiation in the near visible range (Soiret band, 405 nm). A UV-free partial body irradiation device with an emission maximum between 400 and 450 nm has therefore been developed and found to induce prompt and long-lasting improvement in patients with atopic hand and foot eczema (Fig. 58.1). In marked contrast to UV radiation, which is a complete carcinogen, visible radiation does not increase the risk for skin cancer and UV-free phototherapy might therefore be well suited for the treatment of children and young adults, who make up the vast majority of patients with atopic dermatitis. It will be interesting to see whether these preliminary results can be confirmed in independent studies.

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