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High-Dose-UVA1 Phototherapy: A Novel and Highly Effective Approach for the Treatment of Acute Exacerbation of Atopic Dermatitis

JEAN KRUTMANN and ERWIN SCHÖPF

Department of Dermatology, University of Freiburg, Freiburg, FRG

High-Dose-UVA1 irradiation has recently been found to be a new, prompt-acting and highly effective phototherapeutic approach to the treatment of patients with acute exacerbation of atopic dermatitis. This therapeutic efficacy was demonstrated by a marked improvement of clinical symptoms as well as of laboratory parameters, which were found to reflect disease activity in atopic dermatits. Investigation of the photoimmunological mechanisms responsible for the therapeutic effectiveness of this modality indicates that eosinophils and epidermal Langerhans cells may be targets for High-Dose-UVA1. ***Key words: Atopic dermatitis; Phototherapy; High-Dose-UVA1; Eosinophils; Langerhans cells.***

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Jean Krutmann, M.D., Department of Dermatology, University of Freiburg, Hauptstrasse 7, W-7800 Freiburg i. Br., Germany.

INTRODUCTION

Exposure to sunlight has been known for years to be of benefit for most patients with atopic dermatitis (AD). This observation has stimulated the interest of dermatologists in phototherapeutic approaches to the management of AD (1). Accordingly, photochemotherapy with psoralen plus UVA (320–400 nm) light (PUVA) was reported to be effective in the treatment of patients with AD (2). However, in contrast to PUVA therapy of psoriasis and cutaneous T cell lymphoma, photochemotherapy of AD is associated with a number of disadvantages. In particular, the number of PUVA treatments necessary to achieve clearing of eczema is comparatively high, which may be of major relevance in view of very recent results from long-term follow-up studies on PUVA-treated patients, who apparently run an increased risk of developing certain types of skin tumours (3).

Moreover, PUVA therapy without the simultaneous use of glucocorticosteroids is frequently associated with an immediate flare-up of the disease shortly after cessation of PUVA therapy (2). In consequence, PUVA therapy is not used as a standard treatment for AD.

In contrast to PUVA, UVB (295–315 nm) treatment of AD is not associated with major side effects. The therapeutic efficacy of UVB therapy, however, is clearly limited. In particular, UVB irradiation is not used as a monotherapy, but rather in combination with topical corticosteroids to treat patients with acute exacerbation of AD (1). Recent studies indicate that in addition to UVB, UVA irradiation may also be effectively used in the treatment of patients with AD (4). Accordingly, extension of the action spectrum towards longer wavelengths (UVA-UVB; 300–400 nm) was found to significantly improve the therapeutic effectiveness, as compared with conventional UVB therapy. However, the UVA doses used in UVA-UVB therapy are rather low. The fact that UVA irradiation was of some benefit in the management of AD prompted us to examine the efficacy of a phototherapy with very high doses of UVA1 (340–400 nm) light for the treatment of patients with acute exacerbation of AD (5). The UVA doses used were selected because previous studies strongly indicated that UVA1 irradiation employed in this dose range may be capable of affecting epidermal Langerhans cells, a cell population which is thought to play a crucial role in the pathogenesis of AD (6, 7).

The present paper reviews a pilot study examining the therapeutic effectiveness of High-Dose-UVA1 irradiation in the management of patients with acute exacerbation of AD (5). In addition, preliminary studies on the photoimmunological mechanisms responsible for the therapeutic effectiveness of this new modality will be summarized (5, 17).

High-Dose-UVA1 therapy of patients with acute AD

In a pilot study conducted at the Department of Dermatology at the University of Freiburg, 15 patients with acute exacerbation of AD were treated with High-Dose-UVA1 irradiation (5). High-Dose-UVA1 therapy consisted of daily exposures to 130 J/cm^2 UVA1. The total number of treatments was limited to 15. The control group consisted of 10 patients with AD, who were treated with UVA-UVB therapy in a MED-dependent fashion, as previously described (4). The two groups did not differ significantly with regard to sex, age, or clinical severity before phototherapy (5). All patients were treated under indoor conditions and additional therapy was restricted to the unlimited use of emollients. Using an established clinical scoring system, High-Dose-UVA1 therapy was found to induce a significant clinical improvement of AD. Moreover, as compared with patients treated with UVA-UVB irradiation, significant differences in favour of High-Dose-UVA1 irradiated patients could be observed.

The therapeutic effectiveness of High-Dose-UVA1 irradiation was corroborated by laboratory findings. Accordingly, we showed previously that serum levels of eosinophil cationic protein (ECP) are elevated in patients with AD (8) and that this serum parameter may be used as a sensitive measure to monitor disease activity in AD (9). High-Dose-UVA1 therapy was found to markedly decrease elevated serum ECP levels, whereas no such decrease could be observed in patients with UVA-UVB therapy.

In contrast to conventional phototherapies, High-Dose-UVA1 irradiation was found to induce an almost immediate improvement in symptoms of acute AD.

Accordingly, as few as six High-Dose-UVA1 exposures reduced the clinical severity score by about 50% (Fig. 1). These data strongly indicate that High-Dose-UVA1 exposure may constitute a novel phototherapeutic approach to the effective treatment of acutely exacerbated AD. The prompt onset of clinical improvement strongly resembled that which may be achieved with a topical glucocorticoid treatment. Moreover, High-Dose-UVA1 irradiation induced complete clearing of eczematous lesions on the patients' face, a skin area which is extremely susceptible to the adverse effects of a topical glucocorticosteroid therapy. High-Dose-UVA1 therapy may therefore represent an effective alternative to glucocorticoid therapy for the inital treatment of patients with acute exacerbation of AD.

No serious side effects have been observed in patients treated with High-Dose-UVA1 irradiation. Due to limited experience with this new modality, one may only speculate on potential long-term side effects. There is, however, increasing evidence from animal studies that High-Dose-UVA1 irradiation may contribute considerably to photoageing of skin (10). Moreover, it is not possible at present to exclude that High-Dose-UVA1 irradiation may increase the risk of developing skin tumours (11). Further clinical trials are therefore necessary to define precisely the actual therapeutic effectiveness of High-Dose-UVA1 therapy. Accordingly, we have recently initiated a multicentre trial including a total of 90 patients, in order to compare directly the therapeutic effectiveness of High-Dose-UVA1 irradiation versus a conventional glucocorticosteroid therapy.

Photoimmunological mechanisms

Ultraviolet radiation is a well known modulator of immune responses in the skin (12). Extensive work has been done to investigate the effects of UVB and PUVA on the skin's immune system, whereas little is known about the photoimmunological effects associated with High-Dose-UVA1 irradiation. The observation that High-Dose-UVA1 therapy may be effectively used to treat AD should stimulate photoimmunologists to examine this issue more closely. The importance of these studies is further emphasized by the fact that the pathogenesis of AD is still poorly understood and that High-Dose-UVA1 irradiation may be used as a tool with which to analyse the mechanisms contributing to acute exacerbation of AD.

There is increasing evidence that eosinophils may be of pathogenetic importance in AD (13). Acute exacerbation of AD may be mimicked by patch testing AD patients with inhalant allergens. Immunhistochemical studies clearly indicate that one of the earliest pathogenetic events in these patch

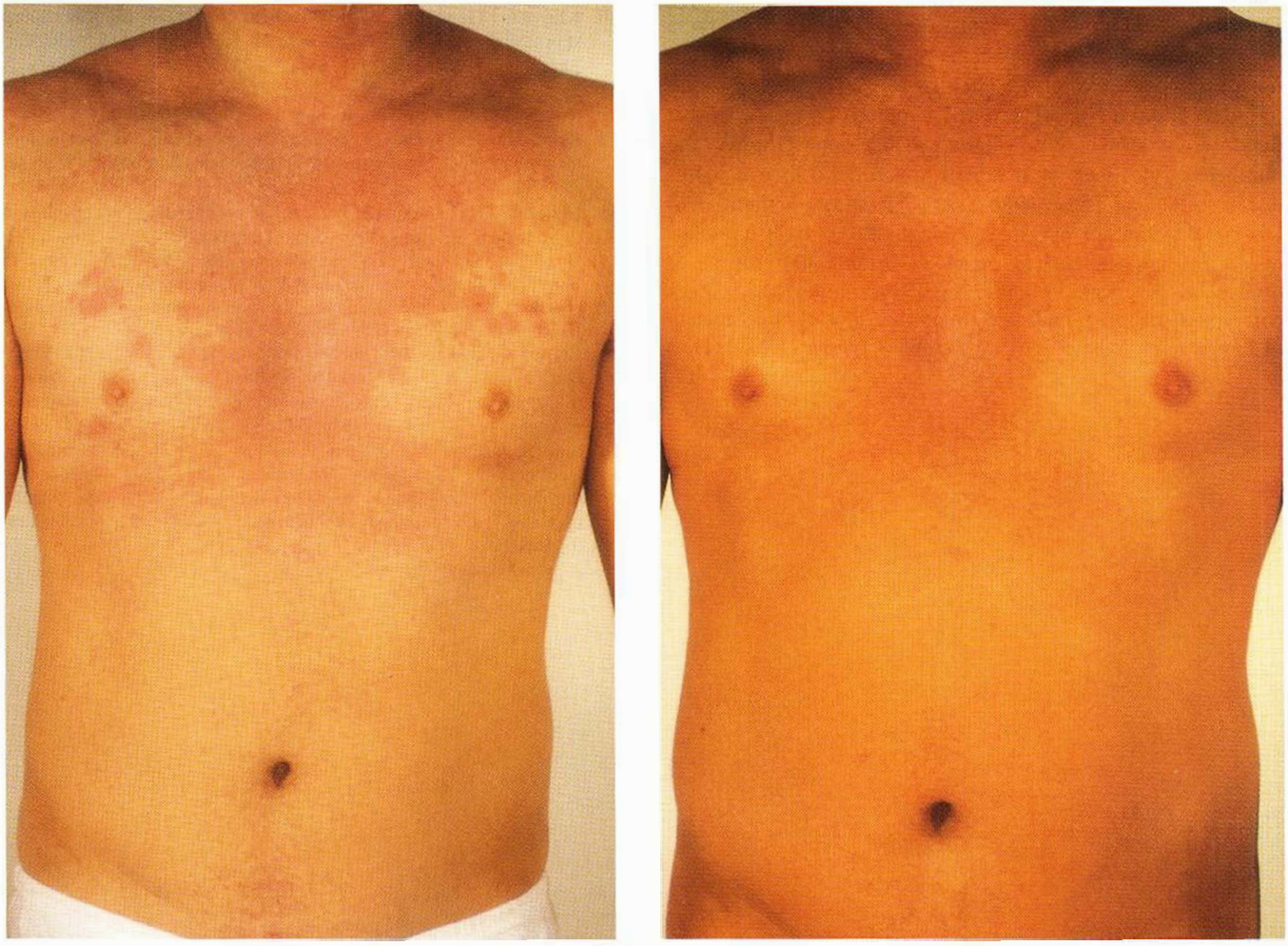

Fig. 1. A patient with acute exacerbation of atopic dermatitis before the first *(a)* and after the 6th *(b)* exposure to High-Dose-UVA1 irradiation.

test reactions is an influx of activated eosinophils into the dermis (14, 15). This finding is corroborated and extended by the observation that sera of patients with AD contain increased levels of ECP, which may reflect the activation state of eosinophils in these patients (8). Since eosinophils are believed to participate in the acute inflammatory reaction and since High-Dose-UVA1 therapy apparently worked best during the acute phase of the disease, it is tempting to speculate that High-Dose-UVA1 therapy may act by modulating eosinophil function. This hypothesis is strongly supported by the recent demonstration that elevated ECP levels in patients with AD fell markedly following High-Dose-UVA1 treatment. However, serum ECP was found to be a disease severity marker (9). Further studies examining the effects of High-Dose-UVA1 irradiation on serum levels of eosinophil granule derived proteins distinct from ECP (13), such as major basic protein, eosinophil-derived neurotoxin and eosinophil peroxidase, are therefore required to determine whether decreased serum ECP may indeed reflect an effect of High-Dose-UVA1 on eosinophil function or simply clinical improvement in High-Dose-UVA1 treated patients.

The demonstration of IgE-bearing Langerhans cells has prompted several investigators to hypothesize that Langerhans cells may be of pathogenetic relevance in AD (7). In order to determine whether Langerhans cells may be affected by High-Dose-UVA1 therapy, the expression of cell surface markers present on epidermal Langerhans cells was examined by immunohistochemistry (16). High-Dose-UVA1 therapy was found to markedly upregulate the number of $CD1a^+$, $CD1c^+$ dendritic epidermal cells, whereas in the same biopsies, the number of IgE^+ positive dendritic epidermal cells was significantly reduced. These studies strongly indicate that High-Dose-UVA1 therapy may be capable of differentially modulating Langerhans cell surface marker expression. It will be of interest to determine whether these morphological changes correspond to functional alterations that modify the capacity of Langerhans cells to activate distinct T helper cell subsets.

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