

Original Article

Efficacy and persistence of UVA (320-400 nm) therapy on clinical condition and serum IL-4 level in atopic dermatitis patients.

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Abstract

The benefits of ultraviolet (UV) radiation on atopic dermatitis (AD) have been appreciated for years. The most efficacious wavelengths of UV radiation therapy for AD is still not well defined, but recent studies suggest increased benefit with UVA therapy.

Aim of Work: To evaluate the efficacy and persistence of UVA (320-400 nm) therapy for severe AD and to determine if serum IL-4 levels correlate with disease severity before and after therapy.

Subjects and Methods: Thirty patients with severe AD received 30 UVA sessions; 3 sessions per week with an initial dose of 1.0 J/cm² and increasing 0.2 J/cm² each session thereafter. Disease severity (by SCORAD score) and serum IL-4 level were measured pre- and post- UVA therapy.

Results: All 30 patients completed the study, and a decrease in mean SCORAD score of 58% ($p < 0.0001$) and in mean serum IL-4 level of 70% ($p < 0.0001$) was observed.

Conclusion: UVA therapy is an effective and relatively safe treatment for severe AD. Its clinical benefit persisted, in part, during a 6-month follow-up period. Serum IL-4 reflected clinical improvement produced by UVA therapy and, therefore, it represents a potential peripheral blood biomarker for AD severity.

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder that occurs in up to 20% of infants. It runs a variable course but frequently persists into adult life and can result in significant morbidity. Pruritis is the cardinal

Key words: Atopic dermatitis, phototherapy, UVA, IL4.

symptom of AD, which can lead to widespread excoriation and lichenification⁽¹⁾. The pathogenesis of AD is one of stage-related imbalance of the T helper 2 (Th2) to Th1 cell ratio, and cytokines produced by these Th cells in situ induce and maintain AD skin lesions, often in response to exogenous allergens. The cytokine profile expressed in patients' skin depends critically on the stage of disease, with an initial Th2-like inflammatory phase (IL-4, IL-5, and IL-13 production) in acute lesions followed by a switch to a second, chronic phase dominated by the Th1-like cytokine interferon- γ . These elicit an immune response resulting in the up-regulation of IgE and the recruitment and activation of mast cells, basophils, and eosinophils⁽²⁾. It has been suggested that the initial imbalance favoring increased numbers of Th2 cells, which mainly produce IL-4, is one of the most important pathogenic mechanisms⁽³⁾.

There are different therapeutic protocols and approaches for treating AD depending on factors such as the age of the patient and the severity, extent, and distribution of skin lesions. Pharmacological therapy is the mainstay of treatment. Emollients, topical corticosteroids and immunomodulators, and oral antihistamines are most commonly used. Systemic medications such as cyclosporin A can be used, but unfortunately most of these treatments, can have marked side effects. Moreover, severe AD, especially when it involves the face, does not respond well to conventional therapy⁽⁴⁾. Thus, for severe and recalcitrant AD patients, alternative treatments often need to be considered.

Phototherapy mediates pleiotropic responses directed to the skin as well as blood and systemic immune responses in man⁽⁵⁾. Its multiple effects include its therapeutic actions by a direct antimicrobial effect against staphylococcus aureus^(5,6,7) and by induction of immunocyte apoptosis through generation of free oxygen radicals that cause irreparable damage to these inflammatory cells. In part, UV radiation shifts the Th cell ratio and changes Th cell morphology,

which alters the cytokine production of inflammatory cells in AD and other dermatologic diseases. The number and activity of both Langerhans cells and natural killer cells in skin lesions also decrease after phototherapy^(8,9).

Ultraviolet radiation therapy has been shown to be an effective modality in the treatment of chronic recalcitrant AD in several clinical trials. Combined UVA-UVB phototherapy proved to be more effective than UVB alone^(12,13,14). So we did this study to assess the efficacy and persistence of UVA (320-400 nm) therapy on AD. Moreover, to evaluate the role of serum IL-4 before and after phototherapy as an immunologic and serologic parameter of disease severity.

Aim of Work:

To evaluate the efficacy and persistence of UVA (320-400 nm) therapy for severe AD and to determine its effect on serum IL-4 levels before and after therapy.

Subjects and Methods

Patients:

Thirty patients with chronic severe AD were enrolled. All patients gave their informed consent after receiving full information about the purpose and design of the study. Diagnosis of AD was based on the UK modifications of Hanifin and Rajka diagnostic criteria. Exclusion criteria were: < 4 years of age, bacterial or viral superinfection, pregnancy or lactation, photosensitivity, ongoing oral antibiotic treatment, any systemic immunomodulating therapy or corticosteroid therapy within the last 6 weeks, topical corticosteroid or oral antihistamine therapy within the last two weeks, phototherapy within the last 9 weeks, and a history of melanoma or non-melanoma skin cancer.

Patient Assessment:

Patients were assessed using SCORAD

scoring⁽¹¹⁾, which was developed by the European Task Force on Atopic Dermatitis. It includes the extent of affected body surface, the intensity of 6 clinical signs (erythema, infiltration, exudation, excoriation, lichenification, and dryness), and the degree of two subjective symptoms (itching and insomnia). The intensity items are graded from 0 to 3 and the subjective symptoms from 0 to 10 on a visual analog scale⁽¹¹⁾. SCORAD score was determined at the point of entry in the study, every week during UVA treatment, and monthly for six months after completion of therapy. All clinical assessments were performed by the same investigator. Clinical improvement was designated “complete remission” “marked”, “moderate”, “mild”, and “insignificant” response, respectively, for 95% or greater, 94% to 75%, 74% to 50%, 49% to 25%, and less than 25% reduction in SCORAD score.

UVA Therapy:

The UVA equipment consisted of 20 fluorescent tubes emitting 320 to 400 nm wavelength radiation (UVA, Waldmann F85/100-PUVA) and evenly arranged in a cubicle (Waldmann, Villingen-Schwenningen, Germany) in an air-conditioned room.

Patients were treated with whole body UVA therapy at an initial dose of 1.0 J/cm² and increasing 0.2 J/cm² each session thereafter. UVA therapy was administered three times a week (every other day with Friday off) for 30 exposures on an outpatient basis. The maximum single dose was 6.8 J/cm² and the average cumulative dose was 108 ± 9 J/cm². Patients were not allowed to use any form of medication two weeks before, during, or after the study. However, patients were permitted to use emollients as needed.

Discontinuation of UVA therapy and reporting any adverse events occurred for any patient experiencing less than 5% improvement, deterioration of skin status based on SCORAD score after 3 weeks, developing bacterial superinfection, herpes simplex infection, or any other

serious complications. None of the patients required cessation of UVA therapy.

Serum IL-4 Measurements

Serum IL-4 levels were measured with the specific enzyme-linked immunosorbent assay kit, Quantikine human IL-4 Immunoassay Kit (R and D Systems, Minneapolis, MN), according to the manufacturer’s protocol. Serum IL-4 level was measured for all 30 AD patients both before and after UVA therapy.

Statistics:

Results are expressed as mean ± standard deviation. Paired t-test was used to assess the significance of differences between pre-therapy and post-therapy SCORAD scores and serum IL-4 levels. Probability (P) values of less than 0.05 were considered significant. In order to determine a possible association between the serum level of IL-4 and the severity of AD,

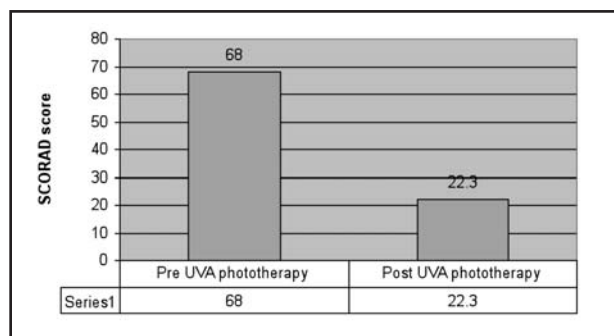


FIG.1. The effect of UVA phototherapy on SCORAD score of AD patients.

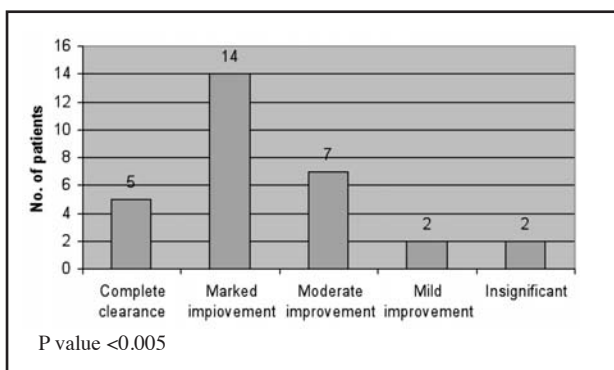


FIG.2. The degrees of improvement of AD patients following UVA phototherapy.

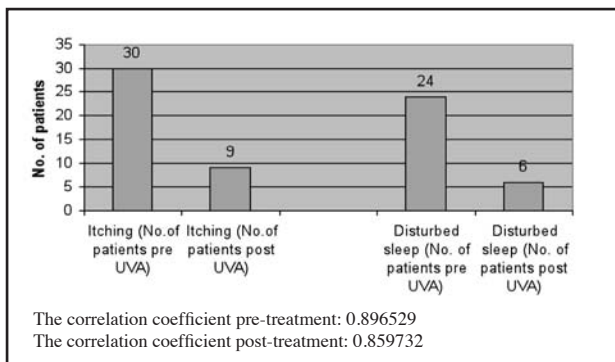


FIG.3. The effect of UVA phototherapy on itching and sleep in AD patients.

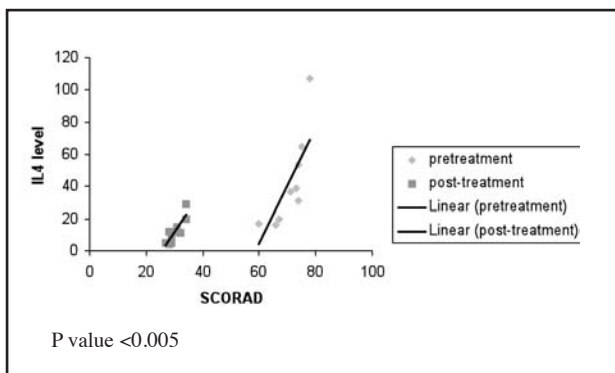


FIG.4. The correlation between serum IL-4 levels and SCORAD scores in AD patients.

correlation analyses (Pearson) were performed for AD patients based on the differences of serum IL-4 level and SCORAD score⁽¹⁰⁾.

Results

All 30 patients completed the study, and none of them experienced any complications (e.g. severe phototoxic erythema or eczema herpeticum) or unpleasant side effects during the course of UVA therapy.

Following UVA therapy, almost all patients (28 patients) improved during treatment as indicated by a significant decrease of the SCORAD score from an initial pre-therapy score of 68 ± 6 to a post-therapy score of 22.3 ± 11.3 Fig, 1. This represents a 58% improvement in mean SCORAD score at the end of UVA therapy (p value < 0.001). Individually, UVA

therapy induced complete remission (clearing) in 5 patients (17%), marked improvement in 14 patients (46%), moderate improvement in 7 patients (23%), mild improvement in 2 patients (7%), and insignificant improvement in 2 patients (7%) Fig, 2.

Clinical improvement mainly occurred within the first 10 exposures (initial 2 to 3 weeks) and relief of pruritus always preceded lesion resolution. Eighteen patients (60%) of the study group reported improvement in sleep, and 21 patients (70%) reported reduction in itch at the end of UVA therapy Fig, 3.

The mean serum IL-4 level in AD patients was 34.1 ± 14.5 pg/ml and 10.4 ± 4.3 pg/ml pre- and post- UVA therapy, respectively (p value < 0.001). Serum IL-4 tended to be elevated in patients with high SCORAD scores, and serum IL-4 levels were moderately correlated with pre-therapy SCORAD scores ($r=0.37$, P value=0.04). However, no correlation was observed between serum IL-4 and SCORAD score after UVA therapy ($r=0.02$, P value 0.41) Fig, 4.

After the 10-week therapy period, 17 patients (5 with complete clearing and 12 with marked improvement) were able to discontinue all treatments and declined any further therapy, 6 patients (2 with marked improvement and 4 with moderate improvement) continued on emollients and avoidance of any provocative factors, while the remaining 7 patients (3 patients with moderate improvement and 4 patients with mild or insignificant improvement) initiated topical corticosteroid therapy along with emollients.

For follow up of the clinical severity of AD following UVA therapy, we arbitrarily classified relapses as mild (less than 40% of the pre-therapy score), moderate (40-70% of the pre-therapy score), and severe (greater than 70 % of the pre-therapy score). At 1 month after therapy, 5 patients had a mild relapse and none had moderate or severe relapses; mean SCORAD score was 31.6 ± 3.4 . After 3 months, 7 had a mild relapse, 5 had a moderate relapse, and 2 patients had a severe relapse; mean SCORAD score was 38.3 ± 6.4 . After 6 months, 9 patients had a mild relapse,

8 patients had a moderate relapse, and 5 patients had a severe relapse; mean SCORAD score was 45.9 ± 7.3 .

Discussion

In previous studies, combined UVA-UVB phototherapy proved to be more effective than UVB alone⁽¹²⁻¹⁴⁾. This suggested that UVA irradiation may have an effective therapeutic role either in combination or even alone. In this study, UVA therapy alone decreased the mean SCORAD score by 58% in severe AD patients, with more than 75% improvement seen in 21 of the 30 study patients. Mean serum IL-4 levels reflected the observed clinical improvement. This improvement that we observed is comparable to the UVA-induced improvement reported by other investigators^(21,22,15) with ratios of 72%, 67%, 67% respectively. They reported that UVA was superior to UVB in efficacy.

As previously reported⁽³⁾ we observed a rapid and substantial therapeutic response within the first 3 weeks of treatment (≤ 10 sessions). Specific symptom relief during this period included a reduction in pruritus that preceded cutaneous lesion resolution.

None of patients in our trial experienced any serious complications (e.g. severe phototoxic erythema or eczema herpeticum) or notable side effects during the course of UVA therapy, which is similar to the short-term safety profile reported by Jekler and colleagues¹²

UVA therapy also induced a significant decrease in mean IL-4 serum level of about 70% from its pre-therapy level. This substantial decrease in serum IL-4 suggests that successful UVA therapy may influence the cytokine expression of pathogenic Th2 cells a finding supported by other studies⁽²³⁾. The moderately significant correlation between SCORAD score and serum IL4 level in atopic patients, which is compatible with that reported by others⁽²⁴⁾, that serum IL-4 reflects AD disease severity. This is in agreement with some investigators⁽¹⁵⁾ who documented that IL-4 was significantly increased

in AD patients and improved with UVA-1 therapy, and who reported that IL-4 could be one of the activation markers used for monitoring clinical improvement of AD.

conclusion

In conclusion, UVA proved to be an effective, accessible, convenient and relatively safe treatment for severe AD. And, although, disease inevitably re-occurs, some level of clinical benefit persisted on average for at least 6 months following completion of UVA therapy. Serum IL-4 level appears to be a qualitatively reliable marker for monitoring pre- to post-therapy improvement in AD disease. Serum IL-4 reflected clinical improvement produced by UVA therapy and, therefore, it represents a potential peripheral blood biomarker for AD severity.

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